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Review

Carbapenem-alternative strategies for complicated urinary tract infections: A systematic review of randomized controlled trials

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Introduction

Urinary Tract Infections (UTI) are the most common bacterial infections requiring antibiotic treatment in the western world.[1,2] The clinical spectrum of UTI includes urethritis, cystitis, prostatitis and pyelonephritis. Most UTIs have a rapid and favorable response to antibiotic treatment.[3] Complicated UTI (cUTI) is defined by the presence of systemic symptoms or susceptibility of the host for a complicated course, for example pregnancy or functional deficits of the urinary tract.[4] Most guidelines recommend treating cUTI with a 7–14 day course of antibiotics.[5,6] In cases of febrile-UTI (i.e. pyelonephritis, sepsis or acute prostatitis) empiric intravenous antibiotic therapy is mostly advised, with stepdown to pathogen-directed antibiotics when possible. The empirical antibiotic treatment should cover most prevalent causative pathogens. Appropriate empirical treatment options that cover the unknown causing pathogen are therefore especially critical in severe infections and vulnerable patients.[7] Pathogen-directed adjustments should be made as soon as antibiotic susceptibility patterns are known.[5,6,8]

The emergence of *Enterobacterales* carrying Extended-Spectrum β-Lactamase (ESBL) enzymes has limited the antimicrobial arsenal available for both empiric and pathogen-directed treatment of cUTI.[9] Distribution of ESBL-carriage varies greatly worldwide, with a reported prevalence up to 70% in the Asia-Pacific region.[2,10] Rates of co-resistance to fluoroquinolones, aminoglycosides and trimethoprim-sulfamethoxazole are high, further limiting treatment options.[11]

Until recently, carbapenems were considered the last resort treatment for infections caused by ESBL-producing *Enterobacterales*. Unfortunately, carbapenem use is highly associated with the emergence of Carbapenem Resistant *Enterobacterales* (CRE).[10,12,13] Patients that have cUTI with CRE bacteraemia are at increased risk of receiving inappropriate antimicrobial therapy and are more likely to die from the infection, compared to patients with carbapenem-susceptible *Enterobacterales*.[14]

To find alternative treatment options for – and to reduce the incidence of CRE – carbapenem-alternative antimicrobial strategies for the empirical and pathogen-directed therapy for cUTI have been widely advocated. Several classes of carbapenem-saving antimicrobials have been developed or re-explored, including β -Lactam/β -lactamase inhibitor combinations (BL/BLIs), tigecycline, colistin and fosfomycin.[15,16,25,26,17–24]

The aim of this systematic review was to identify carbapenem-alternative antimicrobial strategies with comparable efficacy and safety as carbapenems that could be used for the empirical or pathogen-directed treatment of cUTI.

Methods

Protocol

This systematic review was conducted following the Cochrane handbook.[27] Prior to the search the protocol was published at PROSPERO, the international prospective register of systematic reviews, available from: https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017054102. Two amendments were made prior to conducting the search. Microbiological cure was added as a co-primary outcome. In the fourth version the third re-

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viewer was added (CW). We deviated from the original protocol by also including randomized controlled trials (RCTs) investigating the empirical treatment if the participant had a complicated urinary tract infection with any pathogen, whereas the protocol was restricted to infections caused by Enterobacterales. Next, the co-primary endpoint 'clinical cure with microbiological success' was included if data for the separate endpoints was not available. The study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[28] Finally, instead of the Dutch www.trialregister.nl, the European clinical trial register was searched to find more eligible trials.

Search strategy

MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and PSYCHINFO were searched on 4 March 2020 combining search terms for carbapenem and UTI and their synonyms. The search was limited to RCTs, using the RCT search filters as recommended by Cochrane.[29] The full search strategy is reported in the Supplementary material S1.

Reference lists of eligible studies and systematic reviews, abstracts from the ECCMID and IDSA conferences from 2016 to 2020, and the top 20 infectious diseases journals in 2017 (Supplementary material S2) were manually searched for eligible studies using the search terms 'randomized controlled trial' and 'urinary tract infection'. Additionally, www.clinicaltrials.gov and www.clinicaltrialsregister.eu were searched using the term 'urinary tract infection' (Supplementary material S2).

Study selection

Titles and abstracts were independently screened by two reviewers (TD and TV), using the Cochrane recommended tool available at http://www.covidence.org. Articles were included for full-text screening if at least one of the researchers deemed a study suitable. Full text-articles were assessed for eligibility independently by the two reviewers. Conflicts were resolved by a third reviewer (CW).

Eligibility criteria

We included RCTs in adult patients (≥18 years, men or women) with a cUTI, including acute pyelonephritis, in which carbapenem-saving antimicrobials with in vitro activity against ESBL-producing *Enterobacterales* were compared to carbapenem therapy for either the empirical or pathogen-directed therapy. Both intravenous and oral antimicrobials were allowed, and pre-considered carbapenem-saving antimicrobials included the following: piperacillin–tazobactam, ampicillin–sulbactam, amikacin, plazomicin, gentamicin, tobramycin, ceftazidime–avibactam, ceftolozane–tazobactam, tigecycline, colistin, fosfomycin, levofloxacin, moxifloxacin, ciprofloxacin, sitafloxacin, cefepime, nitrofurantoin, trimethoprim–sulfamethoxazole. RCT's required at least one of the following outcomes: clinical cure, mortality, microbiological cure, length of hospital stay, readmission, recurrence/relapse, Intensive Care admission, and (serious) adverse event. Studies not written in English, Dutch, French, German or Spanish were excluded. A full description of the study selection could be found in Supplementary material S1.

Quality assessment

Risk of bias was assessed independently by TD and TV using the Cochrane Risk of Bias Tool, in which sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and, if applicable, other sources of bias were judged.[29] Pre-considered other sources of bias were: (1) the study was not published in a peer reviewed journal, (2) in case of pharmacy sponsored trials, the pharmaceutical company had a role in the conduct, analysis or reporting of the RCT or this was not well described. Discrepancies were resolved by discussion. Risk of bias was categorized as high, intermediate, or low if ≥4, 2–3, or ≤1 sources of bias were scored as high or unknown.

Data extraction

Data was extracted independently by two reviewers (TD and TV). Discrepancies were resolved by discussion. For each study, information was collected about methodology, design, UTI case definition, population, intervention and comparison characteristics, and the following outcomes were extracted: primary outcomes: clinical cure, microbiological cure and mortality; secondary outcomes: length of hospital stay, readmission rate, recurrence/relapse rate, intensive care unit readmission rate, or (serious) adverse event rate. Results were reported for the intention-to-treat analysis, or, if not available (in order of preference) from the modified intention to treat analysis or the reported primary analysis. Corresponding authors were contacted to retrieve missing data. For studies identified via registration libraries (marked as completed or recruiting) but not yet published, we contacted the authors for outcome data.

Definitions

In data extraction, a distinction was made between trials investigating empirical and pathogen-directed treatment. Empirical treatment was defined as treatment initiated without knowledge of the causative pathogen. Pathogen-directed treatment was defined as treatment directed against the causative pathogen taking into account the antibiotic susceptibility pattern. Definitions of clinical or microbiological failure used in the original studies were collected and are described. For studies not reporting clinical or microbiological failure, it was calculated as the inverse of clinical or microbiological cure, respectively. We distinguished early clinical or microbiological failure, if measured within 14 days post-end-of-treatment, from late clinical or microbiological failure, if measured between 14 and 60 days post-end-of-treatment.

Analysis

Clinical heterogeneity was assessed by comparing the interventions (antimicrobial, dose), comparators (antimicrobial, dose of carbapenem) and study populations, i.e. cUTI, acute pyelonephritis (AP), bacteraemia, community or health-care acquired infection. Meta-analysis was planned if more than one RCT was available for one intervention, provided that the clinical heterogeneity between these trials was small.

Results

A total of 1950 unique records were identified through database screening supplemented with non-database sources. After screening titles and abstracts, 67 references were selected for full-text reading, of which 51 were excluded, leaving 16 studies in 16 articles (Fig. 1).

Three studies were judged as having high risk of bias (Seo 2017, Malaisri 2017, Merli 2016), eight had intermediate risk of bias (Jaspers 1998, Carmeli 2016, Naber 2002, Naber 2009, Portsmouth 2018, Wagenlehner 2019, Tetraphase 2018, Cerexa 2018) and five studies had low risk of bias (Kaye 2018, Wagenlehner 2016,

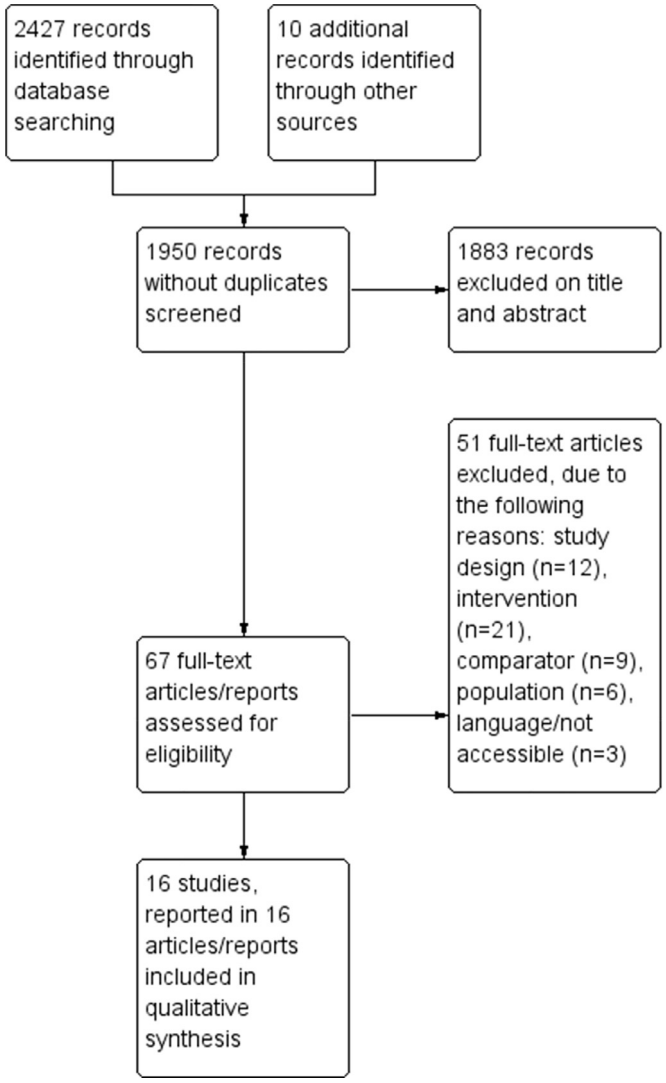
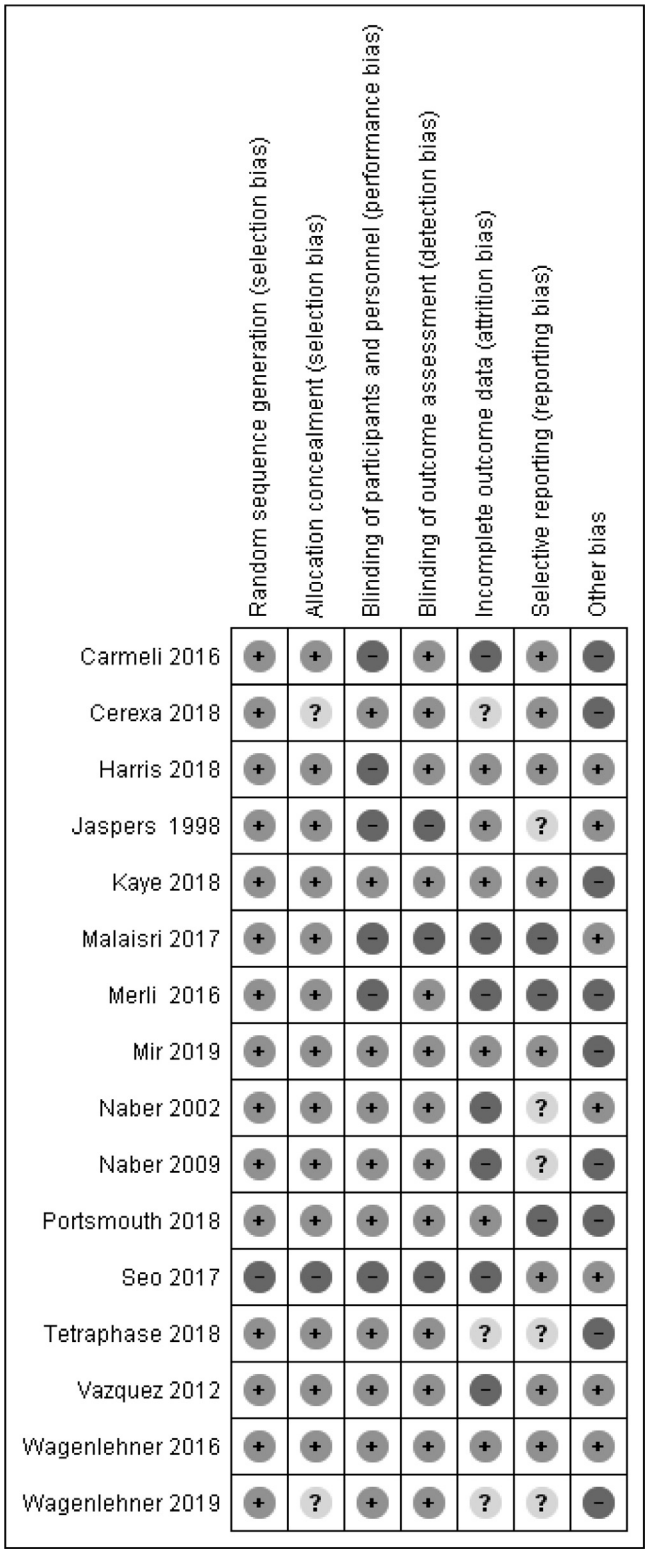


Fig. 1. Study flow diagram.

Table 1
Risk of bias table.



Vazquez 2012, Harris 2018, Mir 2019). The risk of bias for all studies is described in Table 1, motivation for classification is provided in the Supplementary material S3. Three were phase 2 studies (Portsmouth 2018, Cerexa 2018, Vazquez 2012), six were phase three studies (Wagenlehner 2019, Tetraphase 2018, Mir 2019, Kaye 2018, Wagenlehner 2016, Carmeli 2016), six were post registry studies (Merli 2016, Naber 2002, Naber 2009, Jaspers 1998, Harris 2018, Seo 2017). One study was a pilot study of a non-registered drug (Malaisri 2017).

Characteristics of studies investigating the empirical or pathogen-directed treatment are described in Tables 2 and 3. Definitions of the primary and secondary outcome measures, follow-up period and analysis population of each study are provided in the Supplementary material S4. High clinical heterogeneity between the studies was found in study populations, interventions, comparators and outcomes. For that reason, a meta-analysis was not conducted.

Empirical treatment

For the RCTs that investigated the empirical treatment of cUTI, clinical and microbiological cure are reported in Figs. 2 and 3, respectively, and other outcomes in Table 4. A phase II RCT (Vazquez 2012) reported no differences between ceftazidime–avibactam and imipenem–cilastatin regarding clinical failure, microbiological failure or mortality.[30] In a subsequent phase III RCT (Wagenlehner 2016), significantly less early (RR 0.78, 95%CI: 0.62–0.99) and late microbiological failures (RR 0.81, 95%CI: 0.67–0.98) were reported in patients receiving ceftazidime–avibactam compared to doripenem, with no differences in clinical outcomes.[18,31], A phase III trial (Wagenlehner 2019) compared plazomicin to meropenem

Table 2
Study characteristics of studies evaluating the empirical treatment.

Study	UTI type@	Population characteristics	Population comorbidity	Intervention	Comparison	Analysis population size (of which AP)#	Treatment duration (mean/range, days)
Cerexa 2018[33]	Adults ≥ 18 years with cUTI or AP	60 years (mean), bacteremia: 6%	Mean BMI 28.5 kg/m^2	CXL 600mg-600 mg every 8 h, CXL every 12 h,	Doripenem 500 mg every 8 h	51 vs. 42 vs. 51	7–10 days (range) 8 days (mean)
Jaspers 1998*[37]	Adults ≥65 years with cUTI or AP with systemic symptoms	76 years (mean), bacteremia: 23%	Diabetes Mellitus: 14% Mean APACHE II score: 19	Cefuroxim 1500 mg/8 h + gentamicin 4 mg/kg body weight /24 h $	Meropenem 1000 mg / 8 h $	6 vs. 5	7.5 days (mean)
Kaye 2018[35]	Adults with cUTI or AP	53 years (mean), female: 66%, bacteremia: 5%	Mean BMI: 26.4 kg/m^2 Diabetes Mellitus: 16% CCI≥3: 52% GFR ≤50 mL/min: 12%	Piperacillin–tazobactam 4000–500 mg/8 h $$	Meropenem–vaborbactam 2000–2000 mg/8 h $$	273 vs. 272 (161 vs. 161)	10 days (of which 8 days IV)
Merli 2016*[45]	Adults with liver cirrhosis with health-care associated UTI	58 years (mean)	Diabetes Mellitus: 36% MELD score: 15 Chronic kidney disease: 12%	Amoxicillin-clavulanic acid 2200 mg/8 h IV or ciprofloxacin 500 mg/12 h PO	Imipenem-cilastatin 500 mg/6 h (IV)	22 vs. 21	Not reported
Mir 2019[32]	Adults with cUTI or AP	≥ 65 years: 8%%, female: 57%	Mean BMI: 23 kg/m^2 Diabetes Mellitus: 13% GFR 30–50 mL/min: 6%	CSE 1000 mg/500 mg/ 37 mg/12 h	Meropenem 1000 mg/8 h	74 vs. 69 (26 vs. 26)	5–14 days (range), 6.5 days (mean)
Naber 2002[34]	Adults with cUTI or AP	59 years (mean), female: 43%	Diabetes Mellitus: 29% Cardiopulmonary disease: 33%	Piperacillin–tazobactam 2000–500 mg /8 h	Imipenem–cilastatin 500–500 mg /8 h	166 vs. 171 (22 vs. 18)	5–14 days (range)
Naber 2009[36]	Adults with cUTI or AP	51 years (mean), female: 62%, bacteremia: 8%	Mean BMI: 26.5 kg/m^2 GFR <50 mL/min: 14%	Levofloxacin IV 250 mg /24 h $$$	Doripenem 500 mg/8 h $$$	376 vs. 377 (198 vs. 194)	10 days (incl. PO)
Portsmouth 2018[60]	Adults with cUTI or AP	62 years (mean), female: 57%, bacteremia: 7%	Mean BMI: 27.3 kg/m^2 GFR ≤50 mL/min: 21%	Cefiderocol 2000 mg/8 h &	Imipenem–cilastatin &	252 vs. 119 (130 vs. 64)	9 days (median)
Tetraphase 2018[61]	Adults with cUTI or AP	NA	NA	Eravacycline 1500 mg/kg/24 h &&	Ertapenem 1000 mg/24 h &&	428 vs. 403	7–10 days (range, incl. PO)
Vazquez 2012[31]	Adults with cUTI or AP due to Gram-negative bacteria	47 years (mean), female: 74%, bacteremia: 5%	Mean BMI: 27.0 kg/m2	Ceftazidime–avibactam 500–125 mg/8 h &&&	Imipenem–cilastatin 500–500 mg / 6 h &&&	27 vs. 35 (13 vs. 14)	7–14 days (incl. PO)
Wagenlehner 2016[18]	Adults with cUTI or AP	52 years (mean), female: 70%%, bacteremia: 8%	Mean BMI: 26.3 kg/m^2 GFR <50 mL/min: 10%	Ceftazidime–avibactam 2000–500 mg/8 h	Doripenem 500 mg/8 h	393 vs. 417 (287 vs. 296)	10 days or 14 days for bacteremia (incl. PO)
Wagenlehner 2019[31]	Adults with cUTI or AP	59 years (mean), female: 53%, bacteremia: 12%	BMI ≥25 kg/m^2: 6% GFR 30–60 mL/min: 34%	Plazomicin 15 mg/kg/24 h &&&&	Meropenem 1000 mg/8 h &&&&	191 vs. 197 (84 vs. 78)	7–10 days (incl. PO)

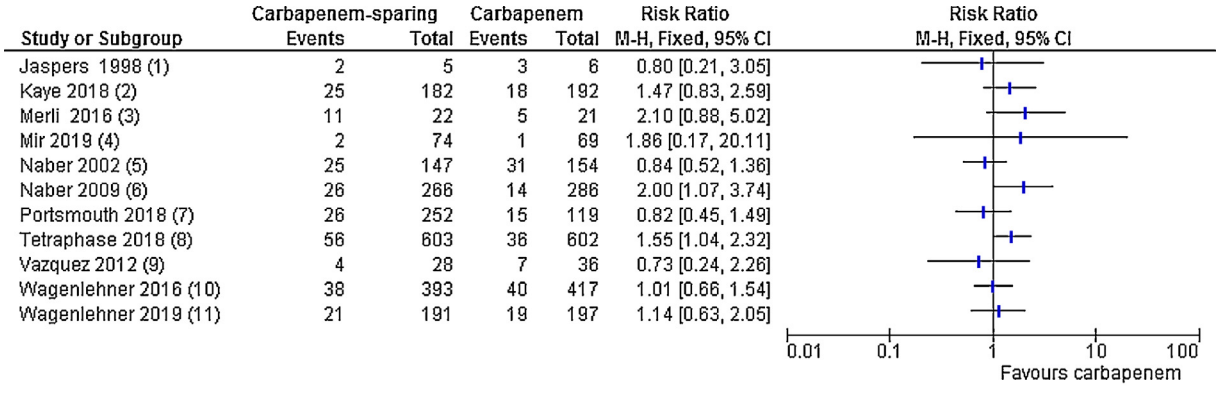
NA = Not available, cUTI = complicated urinary tract infection, AP = acute pyelonephritis, CCI = Charlson comorbidity index, BMI = body mass index, IV = intravenous, PO = per Oral, MELD = Model of End-Stage Liver Disease, CXL = Ceftaroline fosamil/Avibactam, CSE = Ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid (EDTA)
@ If not reported health-care related infection, it is considered community-acquired infection.
* Population characteristics and comorbidity are only available for the total study population including non-urinary source infections.
$ Adapted dosage in case of renal insufficiency.
$$ If patients met pre-specified criteria for improvement, they could be switched to oral levofloxacin (500 mg/24 h).
$$$ Switch to oral levofloxacin (250 mg administered once daily) if no fever were present for at least 24 h, if signs and symptoms of cUTI were absent or improved from baseline levels, and if at least one follow-up urine culture showed no growth or a colony count of <10^{4}CFU/ml and no subsequent cultures yield an uropathogen at ≥10^4 CFU/ml.
& No oral antibiotic (step-down) therapy was allowed.
&& Eravacycline or ertapenem was given for a minimum of 5 days followed by an optional stepdown treatment to oral levofloxacin (750 mg/24 h).
&&& Switch to oral ciprofloxacin 500 mg/12 h was allowed for the remaining treatment course, or alternative oral therapy if the patient was intolerant to ciprofloxacin or had a ciprofloxacin-resistant pathogen at baseline.
&&&& Switch to optional oral antibiotics after 4 days of empirical treatment (levofloxacin 500 mg/24 h or any other approved oral therapy).
# The number of randomized patients (and the size of the safety population) could be higher than the analysis population.

for the treatment of cUTI or AP. No differences were found in early clinical failure, whereas significantly less early microbiological failures (RR 0.45, 95%CI: 0.29–0.70), less late microbiological failure (RR: 0.45, 95%CI: 0.31–0.66) and less clinical relapses (RR: 0.22, 95%CI: 0.07–0.77) occurred in the plazomicin arm.[31] A phase III trial (Mir 2019) compared the efficacy of ceftriaxone–sulbactam-Disodium EDTA to doripenem for the treatment of cUTI or AP and found no differences in clinical or microbiological efficacy.[32] A phase II trial (Cerexa 2018) that compared the efficacy of ceftaroline fosamil–avibactam, administered every 8 or 12 h, to doripenem found no significant differences in microbiological failure. The results regarding the clinical endpoints were not publically available.[33] A phase II trial (Portsmouth 2018) evaluated the efficacy of cefiderocol vs. high dose imipenem–cilastatin (1000–

Table 3
Study characteristics of studies evaluating the pathogen-directed treatment.

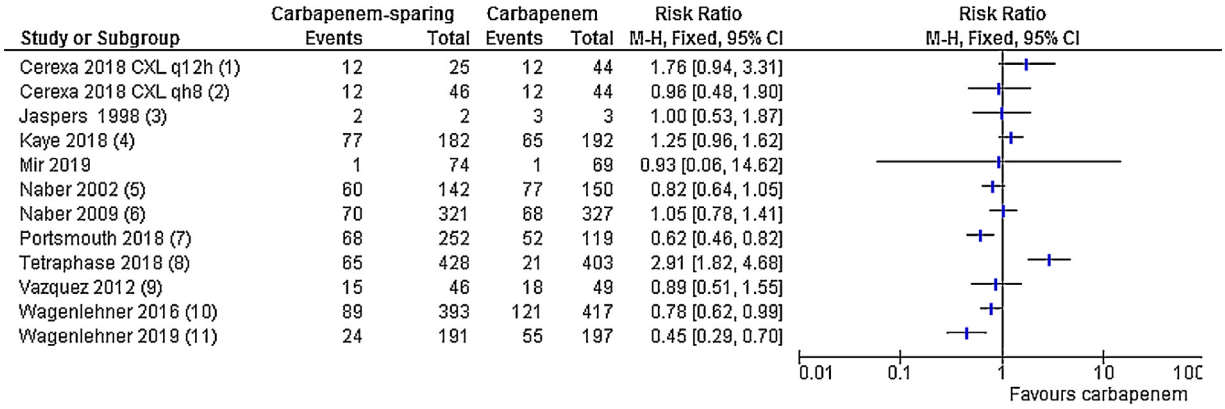
Study	UTI type@	Population characteristics@@	Population comorbidity@@	Intervention	Comparison	Total population size (of which pyelonephritis)#	Treatment duration (mean)
Carmeli 2016[39]	Adults with cUTI or AP caused by ceftazidime-resistant Enterobacterales or Pseudomonas aeruginosa. *	63 years (mean), female: 45%, bacteremia: 4%	Mean BMI: 28.1 kg/m^2 GFR ≤50 mL/min: 22%	Ceftazidime–avibactam 2000–500 mg/8 h $	Imipenem ($n=76$) meropenem ($n=57$) ertapenem ($n=3$) doripenem ($n=11$) non-carbapenem-class (6)	144 vs. 137 (57 vs. 70)	10 days
Harris 2018[40]	Adults with 3-GC resistant *Escherichia coli* or Klebsiella *pneumonia* bloodstream infection	70 years (mean), female: 52%, bacteremia: 100%	Weight: 67.8 kg, renal dysfunction: 20% Diabetes Mellitus: 36%, mean CCI: 2.7	Piperacillin–tazobactam 4500 mg/6 h $	Meropenem 1000 mg/8 h $	103 vs. 128 (NA)	7 days
Malaisri 2017[42]	Adults with AP with ESBL-positive *E. coli* **	69 years (mean), female: 67%	Diabetes Mellitus: 28%, chronic kidney disease: 14%	Sitafloxacin 100 mg/12 h PO $	Ertapenem 1000 mg/24 h $	19 vs. 17 (19 vs. 17)	10 days (of which 3 days IV)
Seo (1) 2017[41]	Adults with healthcare-associated ESBL-positive *E. coli* UTI***	67 years (mean), female: 85%, bacteremia: 30%	Diabetes Mellitus: 41%, mean CCI: 4.6	Piperacillin–tazobactam 4000–500 mg/6 h $	Ertapenem 1000 mg/24 h $	33 vs. 33	14 days
Seo (2) 2017[41]	Adults with healthcare-associated ESBL-positive *E. coli* UTI***	70 years (mean), female: 85%, bacteremia: 23%	Diabetes Mellitus: 41%, mean CCI: 4.5	Cefepime 2000 mg/12 h $	Ertapenem 1000 mg/24 h $	6 vs. 33	14 days

NA = not available, cUTI = complicated urinary tract infection, AP = acute pyelonephritis, CCI: Charlson comorbidity index, BMI = body mass index, 3-GC = third-generation cephalosporin, IV = intravenous, PO = per Oral
@ If not reported else, the study population consists of community-acquired infection.
@@ For the population with cUTI, unless otherwise stated.
* Regardless of previous antibiotic therapy.
** Adults needed to use at least 3 days of iv intravenous carbapenems and the results of urine culture needed to be available. Carbapenems included meropenem 1 mg/8 h, imipenem 500 mg/6 h, doripenem 500 mg/8 h, and ertapenem 1 mg/24 h.
*** The ESBL-EC needed to be detected and required susceptibility to the study medicines, regardless of the susceptibility to other antibiotics.
$ Adapted dosage in case of renal insufficiency.
# The number of randomized patients and the size of the safety population could be higher than the analysis population.



Footnotes
(1) Cefuroxim-gentamicin vs. meropenem (late clinical failure)
(2) Piperacillin-tazobactam vs. meropenem-vaborbactam
(3) Amoxicillin/clavulanic acid IV or ciprofloxacin po vs. imipenem/cilastin
(4) CSE vs. meropenem
(5) Piperacillin -tazobactam vs. imipenem-cilastatin
(6) Levofloxacin iv vs doripenem
(7) Cefiderocol vs. Imipenem-cilastatin
(8) Eravacycline vs. ertapenem
(9) Ceftazidime- avibactam vs. imipenem-cilastin
(10) Ceftazidime-avibactam vs. doripenem
(11) Plazomicin vs. meropenem

Fig. 2. Early clinical failure (empirical treatment).



Footnotes
(1) Ceftaroline fosamil and avibactam every 12 hours vs. doripenem
(2) Ceftaroline fosamil and avibactam every 8 hours vs. doripenem
(3) Cefuroxim-gentamicin vs. meropenem (late microbiological failure)
(4) Piperacillin-tazobactam vs. meropenem-vaborbactam
(5) Piperacillin-tazobactam vs. imipenem-cilastatin
(6) Levofloxacin iv vs. doripenem
(7) Cefiderocol vs. Imipenem-cilastatin
(8) Eravacyline vs. ertapenem
(9) Ceftazidime-avibactam vs. Imipenem-cilastin
(10) Ceftazidime-avibactam vs. doripenem
(11) Plazomicin vs. meropenem

Fig. 3. Early microbiological failure (empirical treatment).

Table 4
Late clinical and microbiological failure, mortality and (serious) adverse events for studies evaluating the empirical treatment.

Study	Comparison	Late clinical failure	Late microbiological failure	Mortality	Adverse events	Serious adverse event rate
Cerexa 2018[33]	CXL^ every 8 h, CXL every 12 h, Doripenem 500 mg every 8 h	NA	27/34 vs. 22/25 vs. 19/32	1/72 vs 0/73 vs. 2/73	27/72 vs. 27/73 vs. 29/73	9/145* vs. 3/73
Jaspers 1998[37]	Cefuroxim-gentamicin vs. meropenem	2/5 vs. 3/6	2/2 vs. 3/3	NA	NA	NA
Kaye 2018[35]	Piperacillin–tazobactam vs. meropenem–vaborbactam	**39/182 vs. 26/192**	NA	2/273 vs. 2/272	97/273 vs. 106/272	13/273 vs. 7/272
Merli 2016[45]	Amoxicillin/clavulanic acid iv or ciprofloxacin po vs. imipenem/cilastin	NA	NA	**5/22 vs. 0/21**	NA	NA
Mir 2019[32]	CSE^^ vs. meropenem	71/74 vs. 62/69	70/72 vs. 61/68	1/117 vs. 0/113	13/117 vs. 14/113	1/117 vs. 0/113
Naber 2002[34]	Piperacillin–tazobactam vs. Imipenem–cilastatin	40/115 vs. 39/118	72/142 vs. 81/150	2/166 vs. 2/171	28/166 vs. 28/171	2/166 vs.2/171
Naber 2009[36]	Levofloxacin iv vs doripenem	11/229 vs. 23/251	NA	0/372 vs. 1/376	222/372 vs. 240/376	**15/372 vs 0.28/376**
Portsmouth 2018[62]	Cefiderocol vs. imipenem–cilastatin	**47/252 vs. 33/119**	**108/252 vs. 67/119**	1/300 vs. 0/148	**122/300 vs. 76/148**	14/300 vs. 12/148
Tetraphase 2018	Eravacyline vs. ertapenem	NA	NA	3/601 vs. 2/600	**174/601 vs. 52/600**	11/601 vs. 6/600
Vazquez 2012[31]	Ceftazidime–avibactam vs. imipenem–cilastin	7/28 vs. 12/36	23/46 vs. 26/49	0/68 vs. 0/67	46/68 vs. 51/67	6/68 vs. 2/67
Wagenlehner 2016[18]	Ceftazidime–avibactam vs. doripenem	58/393 vs. 67/417	**125/393 vs. 163/417**	0/511 vs. 0/509	185/511 vs. 158/509	21/511 vs. 12/509
Wagenlehner 2019[31]	Plazomicin vs. meropenem	22/191 vs. 29/197	**30/191 vs. 69/197**	1/303 vs. 0/301	59/303 vs. 65/301	5/303 vs. 5/301

CXL = Ceftaroline fosamil and avibactam, CSE = Ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid EDTA
^^ Ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid (EDTA).
*Combined groups of CXL^ every 8 h, CXL every 12 h.
Results that are statistically different ($p<0.05$) are highlighted. Outcome definitions and analysis populations for all studies are reported in the Supplementary material S4. Secondary endpoints are reported in the Supplementary material S5, if available.

1000 mg every 8 h) for cUTI. Cefiderocol resulted in significantly less early (RR: 0.62, 95%CI: 0.46–0.82) and late microbiological failures (RR: 0.76, 95%CI: 0.62–0.94) and less late clinical failures (RR: 0.60, 95%CI: 0.36–0.99). In a phase III trial (Tetraphase 2018) eravacycline, a novel tetracycline, was found inferior to ertapenem for the treatment of cUTI or acute pyelonephritis, with regard to the co-primary endpoint clinical cure and microbiological success at the end of infusion visit (363/428 vs. 382/403, RR: 0.89, 95%CI: 0.85–0.94), whereas the results at 5 −10 days post-end of treatment were not significantly different (293/428 vs. 302/403, RR: 0.91, 95%CI: 0.84–1.00). A RCT (Naber 2002) compared piperacillin–tazobactam to imipenem–cilastatin for cUTI. No differences were

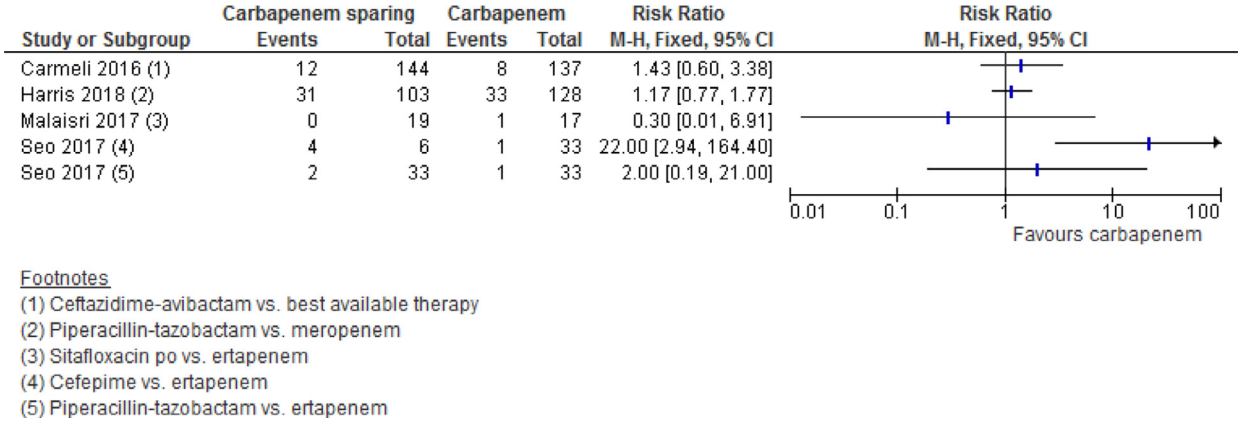


Fig. 4. Early clinical failure (pathogen-directed treatment).

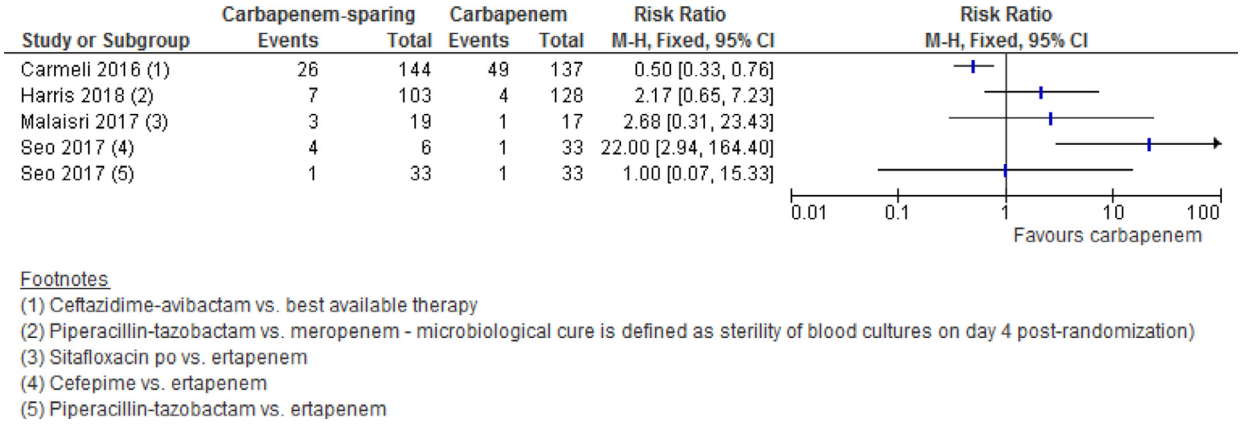


Fig. 5. Early microbiological failure (pathogen-directed treatment).

observed in clinical failure or microbiological failure.[34] In a phase III registry RCT (Kaye 2018) piperacillin–tazobactam was compared against meropenem–vaborbactam. More late clinical failure was found in the piperacillin–tazobactam arm (RR 1.58, 95%CI: 1.01–2.49) with no differences in early clinical or microbiological failure.[35] A pharmacy sponsored RCT (Naber 2009) evaluated low dose intravenous levofloxacin (250 mg/24 h) with doripenem as a comparator and found more early clinical failures in the levofloxacin arm (RR: 2.00, 95%CI: 1.07–3.74), with no differences in early microbiological or late clinical cure.[36] In a non-pharmacy sponsored RCT (Jaspers 1998), cefuroxime-gentamicin combination therapy was compared to meropenem for the treatment of serious bacterial infections in patients >65 years. Of 79 participants, only 11 suffered urinary tract infection, impeding a valuable comparison.[37] An investigator initiated RCT (Merli 2016) compared a standard antimicrobial strategy, consisting of oral amoxicillin-clavulanic acid or intravenous ciprofloxacin with a broad spectrum strategy consisting of imipenem/cilastatin in patients with hepatic cirrhosis and health-care associated infection.[63] In 43 included patients with cUTI a significant higher mortality rate was found in the 'standard' arm than in the imipenem/cilastin arm (5/22 vs. 0/21, RR 0.23, 95%CI: 0.04–0.41), which was the primary outcome.[38,64] In no other of the RCTs significant differences were reported in mortality for the population with cUTI.

Pathogen-directed treatment

Results for RCTs that investigated the pathogen-directed treatment of cUTI are reported in Fig. 4 and 5 and Table 5. In a RCT from 2016 ceftazidime–avibactam was compared to best-available therapy pathogen-directed to ceftazidime-resistant pathogens in patients with cUTI ($n = 333$) or abdominal infection ($n = 28$). Best-available therapy consisted of carbapenem in all except 6 cUTI patients. Lower early and late microbiological failure rates were found in the ceftazidime–avibactam arm, with risk ratios of respectively 0.50 (95%CI: 0.33–0.76) and 0.67 (95%CI: 0.50–0.90), with no differences in clinical failure or mortality.[39] A recent RCT from 2018 compared piperacillin–tazobactam to meropenem for the pathogen-directed treatment of third-generation cephalosporin resistant *K. pneumoniae* or *E. coli* bacteraemia, with mortality as a primary outcome. Microbiological cure 4 days post-end of treatment was defined as sterilization of blood and did not include urine cultures.[40] In an interim analysis after enrolling 378 patients, piperacillin–tazobactam was inferior regarding the endpoint mortality, which led to premature termination of the study. However, in the subpopulation of patients with cUTI, consisting of 231 patients, a non-significant difference was found in mortality, clinical and microbiological failure. In a smaller RCT from 2017 with 66 enrolled patients consisting of three treatment arms, piperacillin–tazobactam, ertapenem and cefepime were evaluated for the pathogen-directed treatment of healthcare-associated UTI, caused by ESBL producing *E. coli*.[41] No differences were found regarding clinical failure, microbiological failure or mortality between piperacillin–tazobactam and ertapenem. The cefepime arm was terminated after only six enrolled patients due to unexpectedly high rates of early clinical ($n = 4$, 67%) and microbiological failure ($n = 4$, 67%).[41] A study from 2017 with 33 enrolled patients compared oral sitafloxacin to ertapenem for acute pyelonephritis caused by ESBL-positive *E. coli*. No differences were found regarding early clinical and microbiological failure.[42] No significant dif-

Table 5
Late clinical and microbiological failure, mortality and (serious) adverse events for studies evaluating the pathogen-directed treatment.

Study	Comparison	Late clinical failure*	Late microbiological failure	Mortality	Adverse events	Serious adverse event rate
Carmeli 2016[39]	Ceftazidime–avibactam vs. best available therapy (97% carbapenem)	21/144 vs. 19/137	**45/144 vs. 64/137**	3/164 vs. 3/168	**34/152 vs. 54/153**	4/152 vs. 7/153
Harris 2018[40]	Piperacillin–tazobactam vs. meropenem	NA	NA	7/103 vs. 4/128	NA	2/103 vs. 3/128
Malaisri 2017[42]	Sitafloxacin vs. ertapenem	NA	NA	0/19 vs. 1/17	1/19 vs. 0/17	0/19 vs. 0/17
Seo 2017 (1)[41]	Piperacillin–tazobactam vs. ertapenem	NA	NA	2/33 vs. 2/33	NA	NA
Seo 2017 (2)[41]	Cefepime vs. ertapenem	NA	NA	2/6 vs. 2/33	NA	NA

Results that are statistically different ($p<0.05$) are highlighted. Outcome definitions and analysis populations for all studies are reported in the Supplementary material S4. Secondary endpoints are reported in the Supplementary material S5, if available.

ferences in mortality were observed in the populations in which the pathogen-directed treatment of cUTI was evaluated.

Adverse and serious adverse events

Less adverse events were found when using pathogen-directed ceftazidime–avibactam compared to best available therapy, consisting of 97% carbapenems (RR: 0.63, 95%CI:0.44–0.91).[39] In contrary, another study that evaluated its empirical use revealed no difference in adverse events, although there was a trend towards a relevant increase in the ceftazidime–avibactam group, compared to doripenem.[43] Empiric levofloxacin (250 mg/24 h) resulted in less serious adverse events compared to doripenem (RR:0.54, 95%CI: 0.29–1.00).[36] Less adverse events were reported in the cefiderocol arm versus high dose imipenem–cilastin (RR: 0.79, 95%CI: 0.64–0.98). More non-severe adverse events were found after using eravacycline than ertapenem (RR: 3.34 95%CI: 2.50-4.46). In the other studies, no significant differences were reported regarding adverse or serious adverse events between the treatment arms.

Other secondary outcomes

Significantly less relapses were found after using plazomicin, compared to meropenem for empirical treatment of cUTI (RR: 0.22, 95%CI: 0.06–0.75).[44] The following secondary outcomes were infrequently measured and, if measured, revealed no difference between the carbapenem and non-carbapenem regimens: hospital stay, readmission, recurrence/relapse and intensive care unit readmission. These are reported in Supplementary material S5.

Discussion

In this systematic review we identified 16 RCTs that evaluated the efficacy and safety of alternatives to carbapenem-class antibiotics for the empirical or pathogen-directed treatment of complicated urinary tract infections, including acute pyelonephritis. In order to provide a comprehensive overview of current and future carbapenem-alternative antimicrobials, we made no restrictions in inclusion based on the completeness of the trial, the sample size, or the phase of the trial. As a consequence, the clinical heterogeneity between the studies was large concerning both the patient populations, the intervention and comparator, and outcomes. This prohibited a meaningful meta-analysis. Conclusions can therefore be drawn on the level of the individual studies and drugs tested. In order to facilitate the interpretation we reported detailed characteristics of each RCT and attempted to retrieve additional data for each study. Analysis populations varied between RCTs; several studies reported no (modified) intention-to-treat analysis or did not specify the analysis population, impeding generalization of the results to clinical practice.

Overall, well conducted trials for alternatives to carbapenems were rare. Eleven out of sixteen studies had an intermediate or high risk of bias. Most studies had small sample sizes as a result of early termination of the trial or from being a phase II trial, with resulting low precision of these studies.[30,33,37,41,42,45] Some of these studies included patients with a wider range of infections,[37,40,45] with the sub-populations of patients with cUTI being too small to provide meaningful interpretation of the results.[37,45] Furthermore, three studies that evaluated the empirical treatment and enrolled patients before 2010 can be considered outdated, as resistance rates to the investigated antibiotics have changed.[36,37,46] Next, in seven out of ten studies that were pharmacy sponsored, the independence of the investigators was not guaranteed: either the sponsor was responsible for the conduct of the study or one or more of the authors were employed by the sponsor, see Supplementary material S3. Last, percentages of participants with bacteraemia were low in most included RCTs (Tables 2 and 3), and results are not automatically generalizable to patients with bacteremic cUTI.

For the empirical treatment of cUTI, ceftazidime–avibactam, plazomicin, cefiderocol and ceftriaxon–sulbactam disodium-EDTA emerged as reasonable alternatives to carbapenem with at least comparable safety and efficacy. All four are FDA and EMA registered for the treatment of cUTI or pyelonephritis. Remarkably, no phase III trial could be found that evaluates the efficacy of cefiderocol. Eravacycline did not receive FDA approval for the treatment of complicated urinary tract infections, as it did not reach the non-inferiority threshold compared to ertapenem regarding the co-primary endpoint clinical cure and microbiological success. Ceftaroline fosamil-avibactam is not currently registered for the treatment of cUTI. The phase 2 trial results were not published in a peer-reviewed journal and the drug development process seems to be discontinued for unknown reasons. The two studies evaluating the empirical treatment with piperacillin–tazobactam delivered conflicting results, with more late clinical failures compared to meropenem–vaborbactam, but not compared to imipenem–cilastatin. In the meropenem–vaborbactam study, only 3 out of 545 patients had CRE infection, making it unlikely that the vaborbactam was responsible for the difference in efficacy.[34] Levofloxacin proved inferior to doripenem, which is potentially explained by the low dose of 250 mg levofloxacin used in the study. A dose of 750 mg per day may be more appropriate for cUTI.[4,19,36,47] A standard therapy with oral ciprofloxacin or intravenous amoxicillin-clavulanic acid resulted in a higher mortality than when using imipenem–cilastatin for health-care related infections in patients with hepatic cirrhosis, although results should be interpreted with caution, as risk of bias was high.[45]

The generalizability of the RCTs that evaluate the empirical treatment is difficult to establish as susceptibility rates of the

causative pathogens against the carbapenem and non-carbapenem antimicrobials in the study populations were not reported. Presumably, the efficacy of empirical treatment regimens depends on the baseline antimicrobial resistance of uropathogen in the population of interest. Based on expert opinion, guidelines proposed a minimal coverage threshold of 90% for the empirical antibiotic treatment of cUTI.[5,6] Of the reviewed carbapenem-alternative options, ceftazidime–avibactam, plazomicin, cefiderocol and ceftriaxone–sulbactam disodium-EDTA reach this threshold throughout most regions and populations and could be used empirically for cUTI, even if an ESBL-producing pathogen is suspected.[48–50] Except for ceftriaxone–sulbactam disodium-EDTA, these antimicrobials possess in vitro activity to CRE.[51–53] However, the development of resistance and the sustainability of these carbapenem-alternative drugs remains unknown, as these are currently used to a lesser extent than carbapenems. Susceptibility to piperacillin–tazobactam, cefuroxime-gentamicin, levofloxacin, ciprofloxacin, and amoxicillin-clavulanic acid among uropathogens varies strongly, but is often below 90% among Enterobacterales, with even lower susceptibility rates in case of ESBL-carrying *Enterobacterales*, limiting their applicability as empirical therapy in most regions.[10,54–56]

For the pathogen-directed treatment, ceftazidime–avibactam was found to be as efficacious as carbapenem therapy in one open label, pharmacy driven trial. Interestingly, recruitment in this trial was ended prematurely by the sponsor after inclusion of 278 patients of the pre-planned 400 based on the amount and variety of cultured species. Since this is the only RCT on ceftazidime–avibactam as pathogen-directed treatment, caution may be warranted before implementation in clinical practice. Piperacillin–tazobactam was evaluated as pathogen-directed treatment in two RCTs. Both studies were underpowered for the treatment of cUTI. The larger, well-conducted open label trial found a significant increase in mortality when piperacillin–tazobactam compared to meropenem was used to treat bacteremia from all sources. The difference in mortality between the two arms was smaller when only looking at urinary-source bacteraemia, possibly because of the overall better prognosis in contrast to non-urinary-source bacteraemia. The other study on pathogen-directed piperacillin–tazobactam only included 66 patients in three arms and had methodological flaws, which severely impedes the interpretability. The third treatment arm consisted of cefepime and was stopped prematurely for safety reasons after inclusion of 6 participants. For ethical reasons it is not likely that cefepime will be evaluated in future trials for the treatment of cUTI. In a 'pilot' RCT comparing sitafloxacin to ertapenem for the pathogen-directed treatment of cUTI caused by ESBL positive E. *coli* only 36 participants were enrolled and this trial has a high risk of bias. Consequently, no conclusions could be drawn on the efficacy and safety of sitafloxacin, which is also not registered for this indication.

This review restricted to RCTs that directly compared carbapenem-alternative antimicrobials to carbapenems. Three RCTs worth mentioning, were excluded that evaluated two carbapenem-saving antimicrobials: The ASPECT-cUTI trial found that ceftolozane–tazobactam was non-inferior to levofloxacin (750 mg daily) for the empirical treatment of cUTI regarding clinical cure with superiority of ceftolozane–tazobactam regarding microbiological cure,[19] the ZEUS trial found that intravenous fosfomycin was non-inferior to piperacillin–tazobactam for the empirical treatment of cUTI regarding clinical and microbiological cure.[57] The question remains how the efficacy of fosfomycin and ceftolozane–tazobactam compares to that of carbapenem, as the results from this review suggest that levofloxacin and piperacillin–tazobactam are less efficacious than carbapenem.

Various RCTs are currently ongoing or completed but not yet published that evaluate the efficacy of carbapenem-alternatives to carbapenem for the treatment of cUTI, which are listed in Supplementary material S2, e.g. intravenous fosfomycin, temecollin, Tebipenem Pivoxil Hydrobromide, sitafloxacin, polymixin B, cefepime-Tazobactam. Some carbapenem-saving antimicrobials with *in vitro* activity to ESBL producing *Enterobacterales* are, to our knowledge, not yet being evaluated in a RCT for the treatment of cUTI; the most important being tigecycline as empirical treatment option for cUTI and oral fosfomycin as stepdown treatment for cUTI caused by ESBL.

Based on this review, ceftazidime–avibactam, plazomicin, cefiderocol and ceftriaxon–sulbactam disodium-EDTA for the empirical treatment and ceftazidime–avibactam for the pathogen-directed treatment for cUTI are potential alternatives to carbapenem. Results for empiric piperacillin–tazobactam, ceftaroline fosamil-avibactam, eravacycline, cefuroxime-gentamicin, amoxicillin-clavulanic acid, ciprofloxacin and low dose levofloxacin and pathogen-directed piperacillin–tazobactam, sitafloxacin and cefepime were either inconclusive or suggested inferiority.

Contributors

TD, TV and MB designed and registered the study. TD, TV, CW and JD performed the review activities, including searches, all phases of study selection (including inclusion and exclusion of abstracts) and data extraction, quality assessment and data interpretation. TD wrote the initial draft and TV, CW, JD and MB contributed writing to subsequent versions of the manuscript. All authors reviewed the study findings and read and approved the final version before submission.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.08.008.

References

1. Tobudic S, Matzneller P, Stoiser B, Wenisch JM, Zeitlinger M, Vychytil A, et al. Pharmacokinetics of intraperitoneal and intravenous fosfomycin in automated peritoneal dialysis patients without peritonitis. *Antimicrob Agents Chemother* 2012;**56**:3992–5. doi:10.1128/AAC.00126-12.
2. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol* 2015;**13**:269–84. doi:10.1038/nrmicro3432.
3. Geerlings SE. Clinical presentations and epidemiology of urinary tract infections. *Microbiol Spectr* 2016;**4**. doi:10.1128/microbiolspec.UTI-0002-2012.
4. Dutch Working Party on Antibiotic Policy (Stichting Werkgroep Antibiotica Beleid). SWAB guidelines for antimicrobial therapy of complicated urinary tract infections in adults [Internet]. SWAB; 2013. (Clinical Guideline). Available from https://swab.nl/en/swab-guidelines.
5. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011;**52**:103–20. doi:10.1093/cid/ciq257.
6. Stichting Werkgroep Antibioticabeleid. SWAB Guidelines for Antimicrobial Therapy of Complicated Urinary Tract Infections in Adults 2013:1–94.
7. Bader MS, Loeb M, Brooks A. An update on the management of urinary tract infections in the era of antimicrobial resistance. *Postgrad Med* 2016:1–17. doi:10.1080/00325481.2017.1246055.
8. Dutch Working Party on Antibiotic Policy (Stichting Werkgroep Antibiotica Beleid). SWAB Guidelines for Antimicrobial Stewardship SWAB; 2016. (Clinical Guideline). Available from https://swab.nl/en/swab-guidelines.

9. Pitout JD, Laupland KB. Extended-spectrum β-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis* 2008;**8**:159–66. doi:10.1016/S1473-3099(08)70041-0.
10. Harris PNA, Tambyah PA, Paterson DL. β-lactam and β-lactamase inhibitor combinations in the treatment of extended-spectrum β-lactamase producing Enterobacteriaceae: time for a reappraisal in the era of few antibiotic options? *Lancet Infect Dis* 2015;**15**:475–85. doi:10.1016/S1473-3099(14)70950-8.
11. Frakking F.N.L., Rottier W.C., Dorigo-Zetsma JW. Appropriateness of empirical treatment and outcome in bacteremia caused by extended-spectrum-β-lactamase-producing bacteria 2013;57:3092–9. https://doi.org/10.1128/AAC.01523-12.
12. Chang H-J, Hsu P-C, Yang C-C, Kuo A-J, Chia J-H, Wu T-L, et al. Risk factors and outcomes of carbapenem-nonsusceptible Escherichia coli bacteremia: a matched case-control study. *J Microbiol Immunol Infect* 2011;**44**:125–30. doi:10.1016/j.jmii.2010.06.001.
13. van Loon K, Voor in 't holt AF. Vos MC. Clinical epidemiology of carbapenem-resistant Enterobacteriaceae: a systematic review and meta-analyses. *Antimicrob Agents Chemother* 2017 AAC.01730-17. doi:10.1128/AAC.01730-17.
14. Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis. *BMC Infect Dis* 2017;**17**. doi:10.1186/s12879-017-2383-z.
15. D'Angelo RG, Johnson JK, Bork JT, Heil EL. Treatment options for extended-spectrum beta-lactamase (ESBL) and AmpC-producing bacteria. *Exp Opin Pharmacother* 2016;**17**:953–67. doi:10.1517/14656566.2016.1154538.
16. Karaiskos I, Souli M, Giamarellou H. Plazomicin: an investigational therapy for the treatment of urinary tract infections. *Exp Opin Investig Drugs* 2015;**24**:1501–11. doi:10.1517/13543784.2015.1095180.
17. Brust K, Evans A, Plemmons R. Tigecycline in treatment of multidrug-resistant Gram-negative bacillus urinary tract infections: a systematic review. *J Antimicrob Chemother* 2014;**69**:2606–10. doi:10.1093/jac/dku189.
18. Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone G, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. *Clin Infect Dis* 2016;**61**:e5–12. doi:10.1093/cid/ciw378.
19. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet* 2015;**385**:1949–56. doi:10.1016/S0140-6736(14)62220-0.
20. Boucher HW, Talbot GH, Benjamin DK, Bradley J, Guidos RJ, Jones RN, et al. 10 x '20 progress – development of new drugs active against gram-negative bacilli: an update from the infectious diseases society of America. *Clin Infect Dis* 2013;**56**:1685–94. doi:10.1093/cid/cit152.
21. Pilmis B, Scemla A, Join-Lambert O, Mamzer M-F, Lortholary O, Legendre C, et al. ESBL-producing enterobacteriaceae-related urinary tract infections in kidney transplant recipients: incidence and risk factors for recurrence. *Infect Dis* 2015;**47**:718–22. doi:10.3109/23744235.2015.1051107.
22. Fournier D, Chirouze C, Leroy J, Cholley P, Talon D, Plésiat P, et al. Alternatives to carbapenems in ESBL-producing Escherichia coli infections. *Med Mal Infect* 2013;**43**:62–6. doi:10.1016/j.medmal.2013.01.006.
23. Vardakas KZ, Legakis NJ, Triarides N, Falagas ME. Susceptibility of contemporary isolates to fosfomycin: a systematic review of the literature. *Int J Antimicrob Agents* 2016;**47**:269–85. doi:10.1016/j.ijantimicag.2016.02.001.
24. Edwards SJ, Clarke MJ, Wordsworth S, Emmas CE. Carbapenems versus other beta-lactams in treating severe infections in intensive care: a systematic review of randomised controlled trials. *Eur J Clin Microbiol Infect Dis* 2008;**27**:531–43. doi:10.1007/s10096-008-0472-z.
25. Golan Y. Empiric therapy for hospital-acquired, Gram-negative complicated intra-abdominal infection and complicated urinary tract infections: a systematic literature review of current and emerging treatment options. *BMC Infect Dis* 2015;**15**:313. doi:10.1186/s12879-015-1054-1.
26. Bader MS, Loeb M, Brooks A. An update on the management of urinary tract infections in the era of antimicrobial resistance. *Postgrad Med* 2016;**00**:1–17. doi:10.1080/00325481.2017.1246055.
27. Chandler J, Higgins J, Deeks J, Davenport C, Clarke M Cochrane handbook for systematic reviews of interventions version 5.2.0. *Chapter 1: Introduction*. Cochrane; 2017. (updated February2017.
28. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;**349**:g7647. doi:10.1136/bmj.g7647.
29. Higgins J.P.T., Green S. Cochrane handbook for systematic reviews of interventions Version 5.1. 0. [updated March 2011]. The Cochrane Collaboration, 2011, Available from www.cochrane-handbook.org. vol. 4. 2014.
30. Vazquez JA, González Patzán LD, Stricklin D, Duttaroy DD, Kreidly Z, Lipka J, et al. Efficacy and safety of ceftazidime–avibactam versus imipenem–cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. *Curr Med Res Opin* 2012;**28**:1921–31. doi:10.1185/03007995.2012.748653.
31. Wagenlehner FME, Cloutier DJ, Komirenko AS, Cebrik DS, Krause KM, Keepers TR, et al. Once-daily plazomicin for complicated urinary tract infections. *N Engl J Med* 2019. doi:10.1056/NEJMoa1801467.
32. Mir MA, Chaudhary S, Payasi A, Sood R, Mavuduru RS, Shameem M. Ceftriaxone+Sulbactam+Disodium EDTA versus meropenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: PLEA, a double-blind, randomized noninferiority trial. *Open Forum Infect Dis* 2019. doi:10.1093/ofid/ofz373.
33. European clinical trials database (EudraCT) [Internet]. Identifier 2010-022487-12. A phase 2, multicenter, randomized, double-blind, comparative study to evaluate the efficacy and safety of intravenous coadministered ceftaroline fosamil and NXL104 versus intravenous doripenem in adult subjects with complicated urinary tract infection. 2018 01 Aug [cited 2019 Nov 12]; [8 pages]; Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-022487-12/results.
34. Naber KG, Savov O, Salmen HC. Piperacillin 2 g/tazobactam 0.5 g is as effective as imipenem 0.5 g/cilastatin 0.5 g for the treatment of acute uncomplicated pyelonephritis and complicated urinary tract infections. *Int J Antimicrob Agents* 2002;**19**:95–103. doi:10.1016/S0924-8579(01)00481-2.
35. Kaye KS, Bhowmick T, Metallidis S, Bleasdale SC, Sagan OS, Stus V, et al. Effect of meropenem-vaborbactam vs piperacillin-Tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection the TANGO I randomized clinical trial. *JAMA – J Am Med Assoc* 2018;**319**:788–99. doi:10.1001/jama.2018.0438.
36. Naber KG, Llorens L, Kaniga K, Kotey P, Hedrich D, Redman R. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. *Antimicrob Agents Chemother* 2009;**53**:3782–92. doi:10.1128/AAC.00837-08.
37. Jaspers CAJJ, Kieft H, Speelberg B, Buiting A, Van Marwijk Kooij M, Ruys GJHM, et al. Meropenem versus cefuroxime plus gentamicin for treatment of serious infections in elderly patients. *Antimicrob Agents Chemother* 1998;**42**:1233–8.
38. Merli M, Lucidi C, Di Gregorio V, Lattanzi B, Giannelli V, Giusto M, et al. An empirical broad spectrum antibiotic therapy in health-care-associated infections improves survival in patients with cirrhosis: a randomized trial. *Hepatology* 2016;**63**:1632–9. doi:10.1002/hep.28332.
39. Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed. *Lancet Infect Dis* 2016;**16**:661–73. doi:10.1016/S1473-3099(16)30004-4.
40. Harris PNA, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with e coli or Klebsiella pneumoniae bloodstream infection and ceftriaxone resistance. *JAMA – J Am Med Assoc* 2018;**320**:984–94. doi:10.1001/jama.2018.12163.
41. Seo YB, Lee J, Kim YK, Lee SS, Lee JA, Kim HY, et al. Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum beta-lactamase-producing Escherichia coli. *BMC Infect Dis* 2017;**17**. doi:10.1186/s12879-017-2502-x.
42. Malaisri C, Phuphuakrat A, Wibulpolprasert A, Santanirand P, Kiertiburanakul S. A randomized controlled trial of sitafloxacin vs. ertapenem as a switch therapy after treatment for acute pyelonephritis caused by extended-spectrum β-lactamase-producing Escherichia coli: a pilot study. *J Infect Chemother* 2017;**23**. doi:10.1016/j.jiac.2017.05.005.
43. Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone GG, et al. Ceftazidime-avibactam versus Doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. *Clin Infect Dis* 2016;**63**:754–62. doi:10.1093/cid/ciw378.
44. Cloutier DJ, Miller LG, Komirenko AS CD, Krause KM, Keepers TR C LE, Wagenlehner FME. Evaluating once-daily plazomicin versus meropenem for the treatment of complicated urinary tract infection and acute pyelonephritis: results from a phase 3 study (EPIC). *Am. Soc. Microbiol.* 2017 June 1-5New Orleans, LA, USA, 2017.
45. Merli M, Lucidi C, Di Gregorio V, Lattanzi B, Giannelli V, Giusto M, et al. An empirical broad spectrum antibiotic therapy in health-care-associated infections improves survival in patients with cirrhosis: a randomized trial. *Hepatology* 2016;**63**:1632–9. doi:10.1002/hep.28332.
46. Naber K.G., Savov O., Salmen H.C. Piperacillin 2 g/tazobactam 0.5 g is as effective as imipenem 0.5 g/cilastatin 0.5 g for the treatment of acute uncomplicated pyelonephritis and complicated urinary tract infections. Int J Antimicrob Agents. 2002;19:95–103. https://doi.org/10.1016/s0924-8579(01)00481-2, https://doi.org/.
47. Koningstein M, Van Der Bij AK, De Kraker ME a, Monen JC, Muilwijk J, De Greeff SC, et al. Recommendations for the empirical treatment of complicated urinary tract infections using surveillance data on antimicrobial resistance in the Netherlands. *PLoS One* 2014;**9**. doi:10.1371/journal.pone.0086634.
48. Sader HS, Castanheira M, Mendes RE, Flamm RK, Farrell DJ, Jones RN. Ceftazidime-avibactam activity against multidrug-resistant Pseudomonas aeruginosa isolated in U.S. Medical Centers in 2012 and 2013. *Antimicrob Agents Chemother* 2015;**59**:3656–9. doi:10.1128/AAC.05024-14.
49. López-Diaz MDC, Culebras E, Rodríguez-Avial I, Rios E, Viñuela-Prieto JM, Picazo JJ, et al. Plazomicin activity against 346 extended-spectrum-β-lactamase/AmpC-producing Escherichia coli urinary isolates in relation to aminoglycoside-modifying enzymes. *Antimicrob Agents Chemother* 2017;**61**. doi:10.1128/AAC.02454-16.
50. Kohira N, West J, Ito A, Ito-Horiyama T, Nakamura R, Sato T, et al. In vitro antimicrobial activity of a siderophore cephalosporin, S-649266, against Enterobacteriaceae clinical isolates, including carbapenem-resistant strains. *Antimicrob Agents Chemother* 2016;**60**:729–34. doi:10.1128/AAC.01695-15.

51. Zhanel GG, Golden AR, Zelenitsky S, Wiebe K, Lawrence CK, Adam HJ, et al. Cefiderocol: a siderophore cephalosporin with activity against carbapenem-resistant and multidrug-resistant gram-negative bacilli. *Drugs* 2019. doi:10.1007/s40265-019-1055-2.
52. McKinnell JA, Dwyer JP, Talbot GH, Connolly LE, Friedland I, Smith A, et al. Plazomicin for infections caused by carbapenem-resistant Enterobacteriaceae. *N Engl J Med* 2019. doi:10.1056/NEJMc1807634.
53. Van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to Carbapenem-resistant Enterobacteriaceae. *Clin Infect Dis* 2018. doi:10.1093/cid/cix783.
54. Kristo I, Pitiriga V, Poulou A, Zarkotou O, Kimouli M, Pournaras S, et al. Susceptibility patterns to extended-spectrum cephalosporins among Enterobacteriaceae harbouring extended-spectrum β-lactamases using the updated Clinical and Laboratory Standards Institute interpretive criteria. *Int J Antimicrob Agents* 2013;**41**:383–7. doi:10.1016/j.ijantimicag.2012.12.003.
55. Tiengrim S, Phiboonbanakit D, Thunyaharn S, Tantisiriwat W, Santiwatanakul S, Susaengrat W, et al. Comparative in vitro activity of sitafloxacin against bacteria isolated from Thai patients with urinary tract infections and lower respiratory tract infections. *J Med Assoc Thai* 2012 95 Suppl 2.
56. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2016. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). 2017. https://doi.org/10.2900/296939.
57. Kaye K.S., Rice LB D.A. et al. Intravenous Fosfomycin (ZTI-01) for the Treatment of Complicated Urinary Tract Infections (cUTI) Including Acute Pyelonephritis (AP). IDSA, IDweek 2017, Poster 845, n.d.
58. Tetraphase Pharmaceuticals, Watertown, MA. Data File 2018. https://ir.tphase.com/press-releases.
59. Harris PNA, Peleg AY, Iredell J, Ingram PR, Miyakis S, Stewardson AJ, et al. Meropenem versus piperacillin-tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible Escherichia coli and Klebsiella spp (the MERINO trial): study protocol for a randomised controlled trial. *Trials* 2015;**16**. doi:10.1186/s13063-014-0541-9.
60. Portsmouth S, van Veenhuyzen D, Echols R, Machida M, Camilo J, Ferreira A, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind non-inferiority trial. *Lancet Infect Dis* 2018;**3099**:1–10. doi:10.1016/S1473-3099(18)30554-1.
61. Tetraphase Pharmaceuticals, Watertown, MA. Data File 2018.
62. Portsmouth S, van Veenhuyzen D, Echols R, Machida M, Camilo J, Ferreira A, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind non-inferiority trial. *Lancet Infect Dis* 2018;**3099**:1–10. doi:10.1016/S1473-3099(18)30554-1.
63. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;**36**:309–32. doi:10.1016/j.ajic.2008.03.002.
64. Bennett JE, John E, Dolin R, Mandell GL. *Mandell, Douglas, and Bennett's Principles and practice of infectious diseases*, 1. Philadelphia, PA: Elsevier/Saunders; 2010.