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Clinical cure rate and cost-effectiveness of carbapenem-sparing beta-lactams vs. meropenem for Gram-negative infections: A systematic review, meta-analysis, and cost-effectiveness analysis

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ABSTRACT

The increasing incidence of infections caused by extended-spectrum beta-lactamase (ESBL)/AmpC-producing bacteria leads to increasing use of carbapenems and risk of carbapenem resistance. Treatment success of carbapenem-sparing beta-lactams (CSBs) for ESBL infections is unclear. The aim of this study was to appraise the clinical cure rate and estimate the cost-effectiveness of meropenem vs. CSBs (piperacillin-tazobactam, temocillin, ceftazidime-avibactam, and ceftolozane-tazobactam) for urinary tract infections (UTIs) or intra-abdominal infections (IAIs) due to ESBL/AmpC-producing bacteria. A systematic literature search of the Cochrane library, EMBASE, PubMed, and Web of Science was conducted to identify studies assessing the clinical cure rate of the antibiotics. To assess the cost-effectiveness of CSBs vs. meropenem, a combined decision analytic and Markov model was probabilistically analysed over a 5-year period. The main outcome was presented as the incremental cost-effectiveness ratio and evaluated with a threshold of €20 000 per life year gained (LYG).

From 656 identified articles, 17 and 14 studies were included in the qualitative synthesis and quantitative synthesis, respectively. A clinical cure of ceftazidime-avibactam and ceftolozane-tazobactam was comparable to meropenem in patients with complicated IAIs (cIAIs) due to ESBL (Risk ratio [RR]=1·04, 95% confidence interval [CI]=0·95-1·13). Both temocillin and ceftolozane-tazobactam were deemed cost-effective compared to meropenem with €157·58 and €13 398·34 per LYG, respectively, in patients with UTIs due to ESBL. However, only ceftazidime-avibactam (plus metronidazole) was cost-effective for the treatment of IAIs, with €16 916·77 per LYG. These results show that several CSBs can be considered as viable candidates for the treatment of UTIs and IAIs caused by ESBL.

1. Introduction

Urinary tract infections (UTIs) and intra-abdominal infections (IAIs) are the most common infectious diseases in hospital practice. Gram-negative pathogens that produce extended-spectrum beta-lactamase (ESBL)/AmpC limit the selection of antibiotic therapy, with few available options. Meropenem, a carbapenem, is considered first-line therapy for (suspected) infections due to ESBL/AmpC-producing Gram-negative pathogens. The global epidemic of Gram-negative resistance has dramatically increased the use of carbapenems, with the risk of developing carbapenem resistance increasing in parallel. Resistance to carbapenems is associated with poor patient outcomes and has a high economic burden [1], particularly in hospitalized patients with bloodstream infections (BSIs) [2]. In the Netherlands, a country with one of the lowest rates of bacterial resistance, ESBL-producing Gram-negative bacteria are found in clinical specimens in nearly 10% of patients. The Dutch national antibiotic use surveillance system reported that the Defined Daily Dose per 100 patient-days for meropenem had a four-fold increase from 2006 to 2015 [3].

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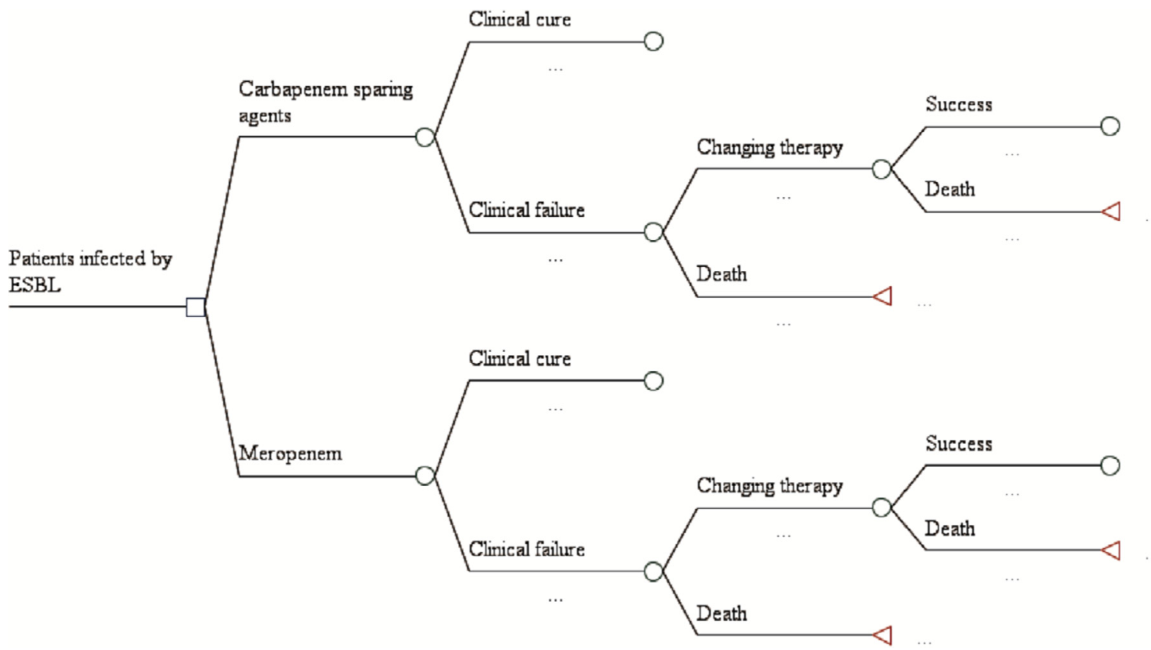

Fig. 1. Decision analytic model structure.

Alternative antibiotics to carbapenems are considered to minimize the emergence of carbapenem resistance [4]. Some beta-lactam/beta-lactamase inhibitors (BL/BLIs) are active against ESBL/AmpC-producing bacteria [5,6]. Also, temocillin, a narrow-spectrum penicillin antibiotic, is stable against ESBL/AmpC produced by Enterobacteriaceae [7]. This study was conducted to: 1, appraise the clinical cure rate of meropenem compared to four carbapenem sparing beta-lactams (CSBs), temocillin, piperacillin-tazobactam, ceftolozane-tazobactam, and ceftazidime-avibactam, for UTIs and IAIs due to ESBL/AmpC-producing bacteria; and 2, estimate the cost-effectiveness of CSBs (temocillin, ceftolozane-tazobactam, and ceftazidime-avibactam) vs. meropenem for ESBL infections from a Dutch healthcare perspective.

2. Material and methods

2.1. Clinical cure rate: systematic review and meta-analysis

2.1.1. Search strategy and selection criteria

Cochrane library, EMBASE, MEDLINE/ PubMed, and Web of Science were searched to identify relevant articles on January 15th, 2018 (Appendix A). A manual search was conducted in the reference lists of included full-text articles or relevant systematic review studies to capture additional studies. An additional search was conducted to find recent relevant papers in the above-mentioned databases from January 15th to May 15th, 2018. We also searched for relevant unpublished studies using trial registries.

Papers were included if they reported clinical outcomes (clinical cure, microbiological response, and mortality) of at least one of five antibiotics of interest (meropenem, temocillin, piperacillin-tazobactam, ceftolozane-tazobactam, ceftazidime-avibactam) for the treatment of UTI or IAI due to ESBL/AmpC-producing Gram-negative bacteria. Studies were excluded if they met the following criteria: 1, patients aged <18 years; 2, not published in English language; 3, year of publication before 2000; 4, not based on original data; 5, conference abstracts; or 6, a case report.

Two independent reviewers (CPN and TNDD) screened the title and abstract of records to evaluate the potentially eligible articles. After initial screening, all full-text articles were reviewed independently for inclusion eligibility. Reviewer discrepancies were resolved by consensus. If there was no agreement, a third reviewer (HW) decided whether the article should be included.

The following data were extracted: study design, setting, patient characteristics, total number of subjects, antibiotic use, definition of clinical outcome, and clinical outcome of the drugs. The type of infection (i.e., UTI, IAI, complicated UTI [cUTI], and complicated IAI [cIAI]) was determined according to a definition of each study and described in detail elsewhere [8–10]. The primary outcome was clinical cure rate. Clinical cure was defined as resolution or significant improvement in symptoms of infection without additional antibiotics. Other outcomes were microbiological response, and mortality rate of the study drugs.

The Cochrane Risk of Bias Tool was used to assess the risk of bias of randomized controlled trials (RCTs) in this systematic review [11]. The Newcastle-Ottawa Scale (NOS) [12] and the National Institutes of Health Quality Assessment Tool [13] were used for the quality assessment of cohort studies and case series studies, respectively.

2.1.2. Data analysis

A fixed-effects model with an inverse variance was performed to get a pooled clinical outcome rate with a 95% confidence interval (CI). If there was moderate or high heterogeneity between studies (I^2 values from 50%), a random-effects model was more suitable. The random-effects model was also used if researchers assessed variation between studies regardless of statistical heterogeneity. Sensitivity analyses were performed to assess the pooled rate or pooled risk ratio (RR) of antibiotic clinical cure for UTIs/IAIs only due to ESBL, or due to ESBL/AmpC and ceftazidime resistance. All statistical analyses were performed using Review Manager 5·3 and R 3·4·2 software.

2.2. Cost-effectiveness analysis

2.2.1. Model structure and assumptions

A combined decision analytic Markov model was used to probabilistically analyse the cost-effectiveness of the CSBs compared to meropenem for cIAIs and cUTIs due to ESBL. In the decision analytic model, total costs and life year gained (LYG) were estimated for alternatives as definitive therapy in inpatients diagnosed with

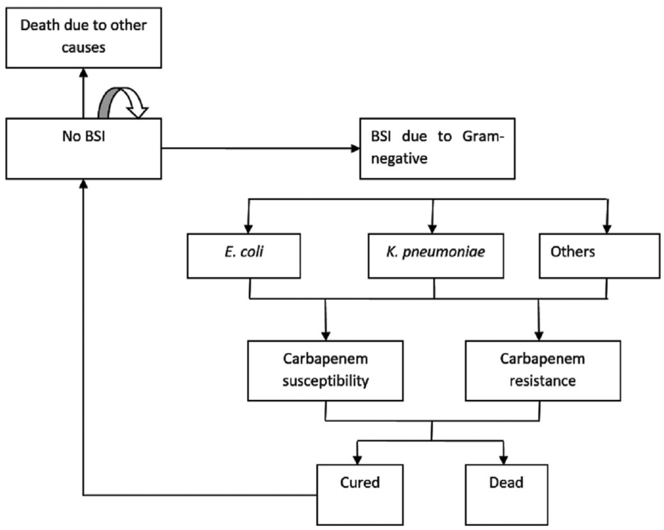

Fig. 2. Markov model structure.

cIAIs or cUTI caused by ESBL (Fig. 1). Patients entered the model if: 1, microbiological results become available and showed presence of ESBL; or 2, there was clinical failure of initial therapy. If there was clinical failure of the study drugs, salvage therapy with the combination of meropenem and colistin was used for cost purposes [14].

Patients with clinical cure entered a 5-year Markov model (Fig. 2) linked to the decision-analytic model to estimate the effect and costs due to carbapenem resistance in serious infectious disease, i.e., BSI. Due to the lack of data, we only considered 5-year consequences of carbapenem resistance in BSI patients who previously suffered from cUTI or cIAI in the Markov model. Four states in the Markov model are: 1, no BSI; 2, BSI; 3, death due to BSI; and 4, death due to other causes. In the first cycle, a patient could enter “no BSI”, “BSI” or “death due to other causes” state. In each one-year-cycle, a patient in “no BSI” state could remain there or make a transition to “BSI” or “death due to other causes”. Patients in “BSI” state could be treated successfully, or death caused by BSI. If patients were cured, they entered “no BSI” state. In this model, the treatment success rate depended on whether patients were still susceptible to carbapenem, and other risk factors of clinical failure were assumed to be the same between these groups. The probability of carbapenem resistance would be higher in patients who had previous meropenem exposure.

2.2.2. Study drugs in the model

Non-carbapenem therapies used in patients with cUTIs are: 1, temocillin; 2, ceftazidime-avibactam; and 3, ceftolozane-tazobactam. In cIAI patients, two non-carbapenem therapies were considered as follows: 1, ceftazidime-avibactam plus metronidazole, and 2, ceftolozane-tazobactam plus metronidazole [15,16].

2.2.3. Input parameters

The key input parameters are summarized in the S2 file. Clinical cure rate was derived from the systematic review and meta-analysis of this study. In these models, only long-term effects of carbapenem resistance in BSI were estimated. Hospital costs per day and hospital administration costs were obtained from the Dutch reference costs list [17]. All costs were calculated in 2017 indexed euros (€).

2.2.4. Outcomes

Total costs and LYG were estimated for different treatment strategies. The strategy was considered cost-effective if an incremental cost-effectiveness ratio (ICER) was below a given willingness-to-pay (WTP) of €20 000 per LYG [18]. Annual discount rates of 4% and 1·5% were applied to costs and effects, respectively, according to the Dutch guidelines [19]. All analyses were conducted using the TreeAge Pro 2011 and R·3·4·2 software.

2.2.5. Sensitivity analyses

One-way sensitivity analyses were conducted to evaluate the robustness of the model outcomes due to an uncertainty of input parameters (Appendix B). A probabilistic sensitivity analysis (PSA) was performed to estimate parameter uncertainty using the available evidence from the previously published literature. The PSA was executed using Monte Carlo simulation with 10 000 iterations from the stochastic input parameters.

2.2.6. Scenario analyses

Carbapenem exposure was assumed to increase the risk of carbapenem resistance in a five-year period after treatment. To further explore the effect of carbapenem exposure over time, a three-year Markov model was performed in scenario analyses. In the base case analysis, the clinical cure rate of the study drugs was obtained from the systematic review with different cohorts. Therefore, scenario analyses were conducted using the clinical cure rate derived from RCTs that compared ceftolozane-tazobactam vs. meropenem and ceftazidime-avibactam vs. meropenem for cIAIs due to ESBL. The price of temocillin is not available in the Netherlands; therefore, the Belgian list price was used to calculate the daily cost of temocillin. In the scenario analysis, the cost-effectiveness of temocillin was estimated using the recommended retail price from the manufacturer (Appendix B).

3. Results

3.1. Clinical cure rate of antibiotics

The initial literature search retrieved 656 studies (Fig. 3). Of these articles, 17 studies [5,9,15,16,20–25,26–30] were included in a qualitative synthesis and 14 studies [5,9,15,16,22–26,28–30] were used in a meta-analysis. (note: two articles were considered to be four studies [16,24]). Reasons for study exclusion are presented in Appendix C. All studies were published after 2005, with nine RCTs, three retrospective cohort studies, and five retrospective case series studies (Appendix D). All RCTs recruited patients with cIAIs and cUTIs. Cohort studies recruited acute pyelonephritis and UTIs; and case series studies had diverse patient populations. All studies focused on IAIs and UTIs due to ESBLs and two articles also included infections caused by AmpC. Temocillin was studied in only one article, whereas the other drugs were each investigated in at least three articles. Regarding quality assessment within studies, most studies were assessed as a satisfactory or low risk of bias (Appendix E).

Fig. 4 indicates that the clinical treatment success rate of meropenem from seven studies was 85% (95%CI=77-90%). Kim et al. reported 100% clinical cure with meropenem, but 7% of patients experienced relapse within 30 days in the carbapenem group, including ertapenem, imipenem, and meropenem (this study was not included in the meta-analysis) [27]. The single study investigating temocillin reported a clinical cure rate of 93% in patients with UTIs caused by ESBL [20]. A random-effects model yielded the pooled cure rate of piperacillin-tazobactam (88%, 95%CI=77-90%), ceftazidime-avibactam (88%, 95% CI=82-93%), and ceftolozane-tazobactam (94%, 95%CI:=71-99%) (Figs. 5, 6, and 7). Studies investigating piperacillin-tazobactam included only patients with UTIs due to ESBL whereas studies investigating other antibiotics included patients with both cUTI and cIAI caused by ESBL/AmpC. Sensitivity analyses were performed to estimate the pooled clinical outcome of antibiotics for treatment of infections only due

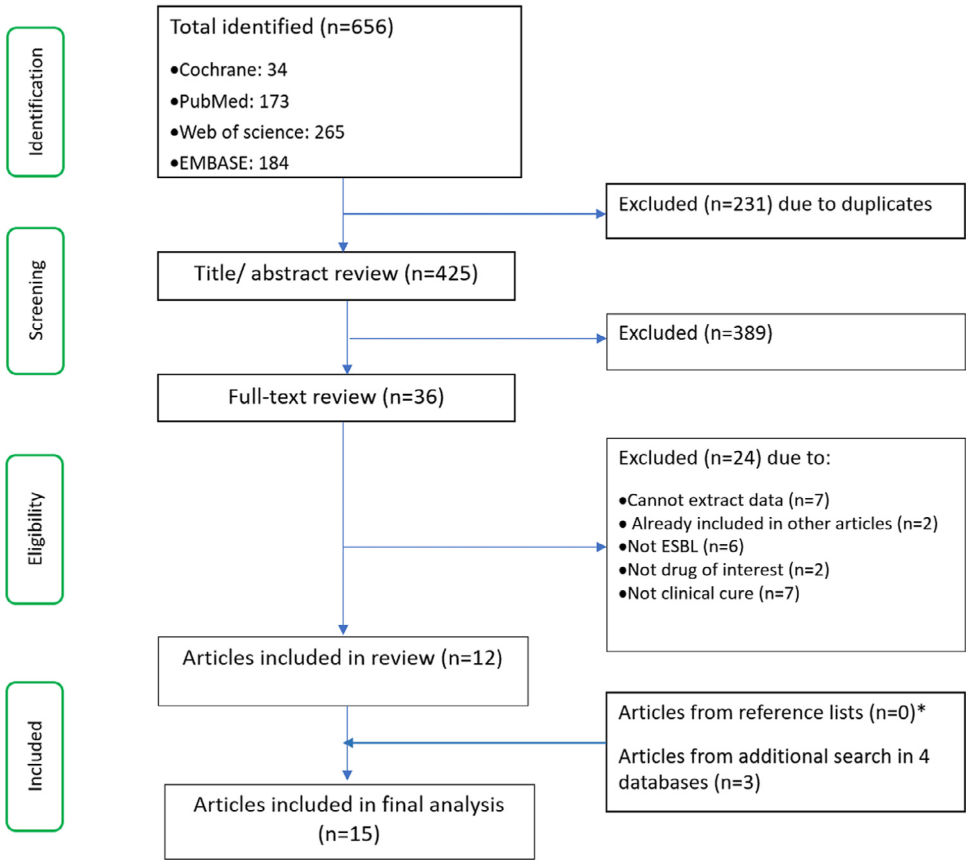

Fig. 3. PRISMA flow chart of the selection process. *Two articles from reference lists were used in sensitivity analysis.

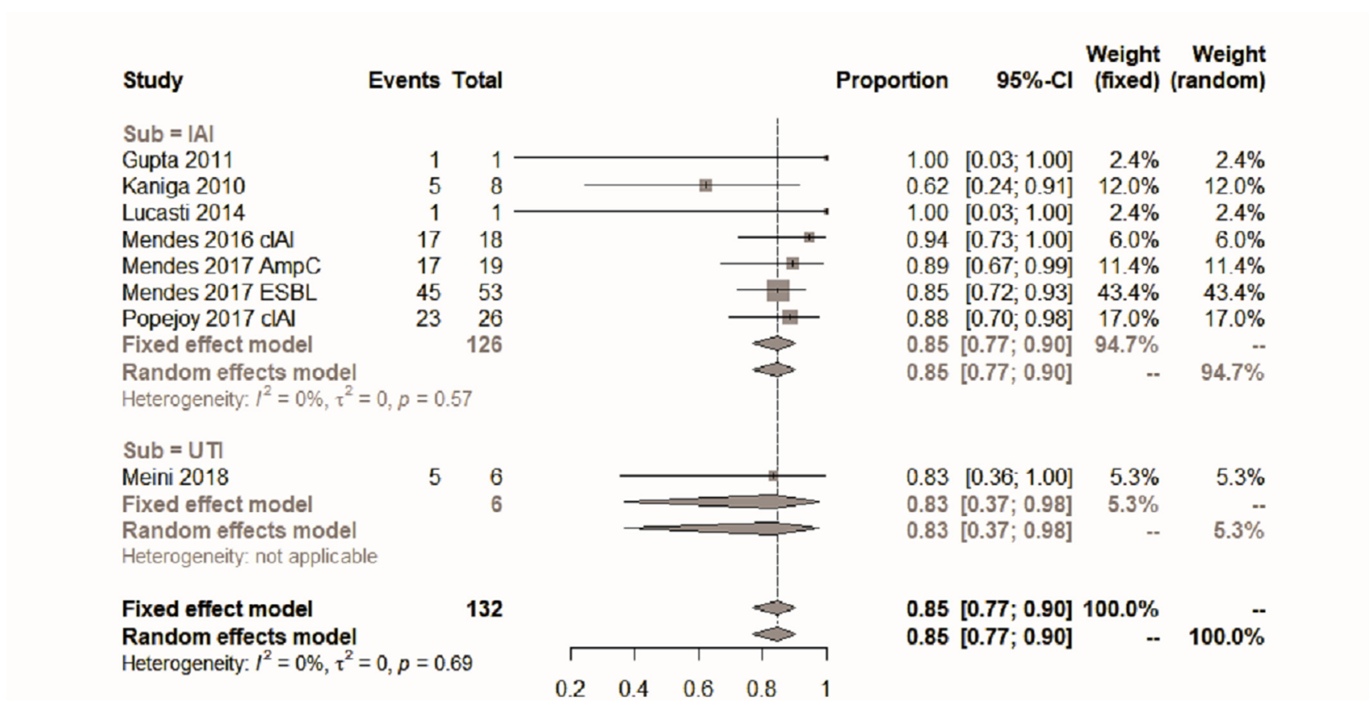

Fig. 4. Forest plot of clinical cure of meropenem in patients with cIAIs and cUTIs due to ESBL/AmpC. Grey squares represent clinical cure rate, horizontal lines represent 95%CI, and grey diamonds represent pooled rate.

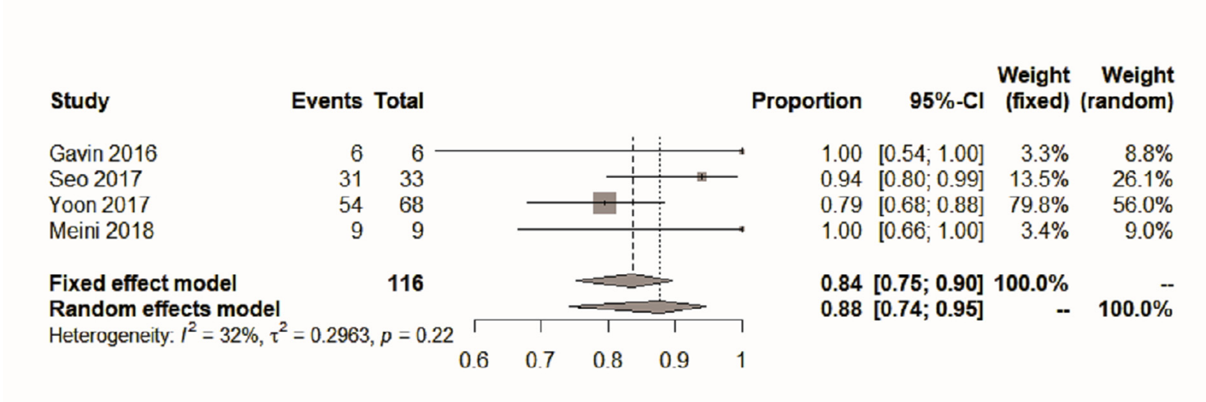

Fig. 5. Forest plot of clinical cure of piperacillin/tazobactam in patients with UTIs due to ESBL.

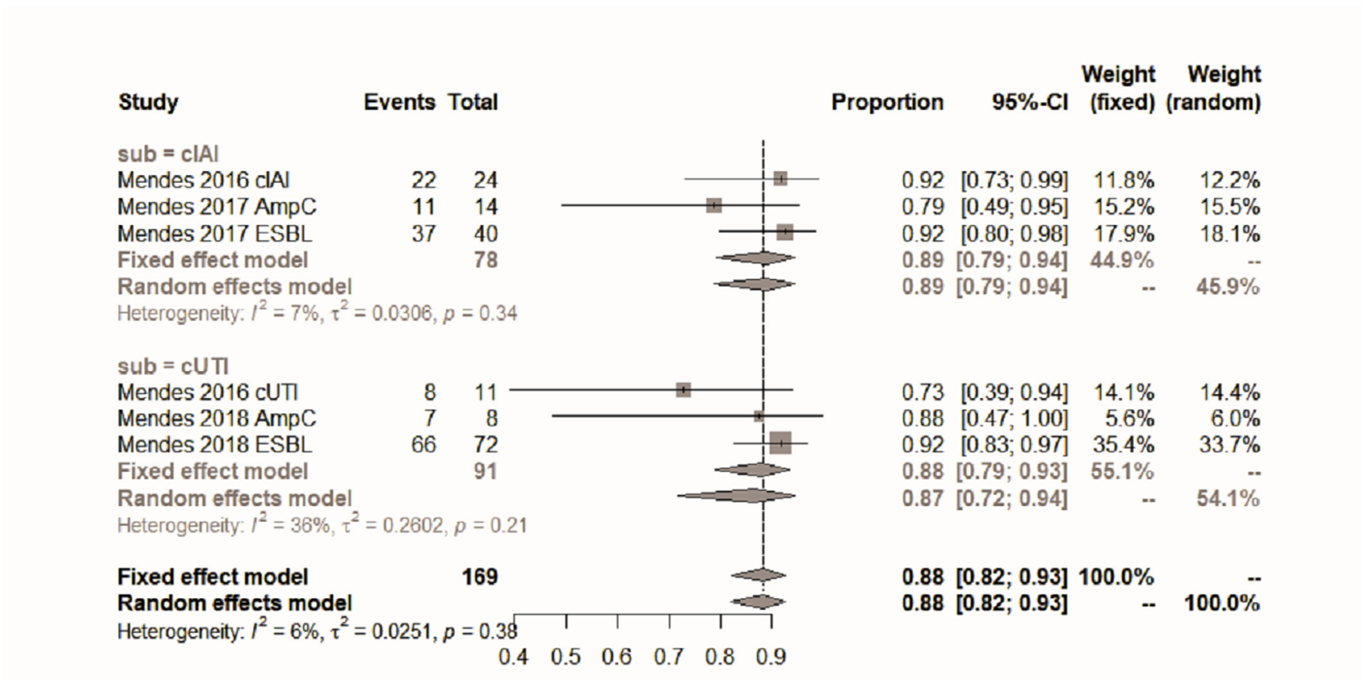

Fig. 6. Forest plot of clinical cure of ceftazidime/avibactam in patients with cIAIs/cUTIs due to ESBL/AmpC.

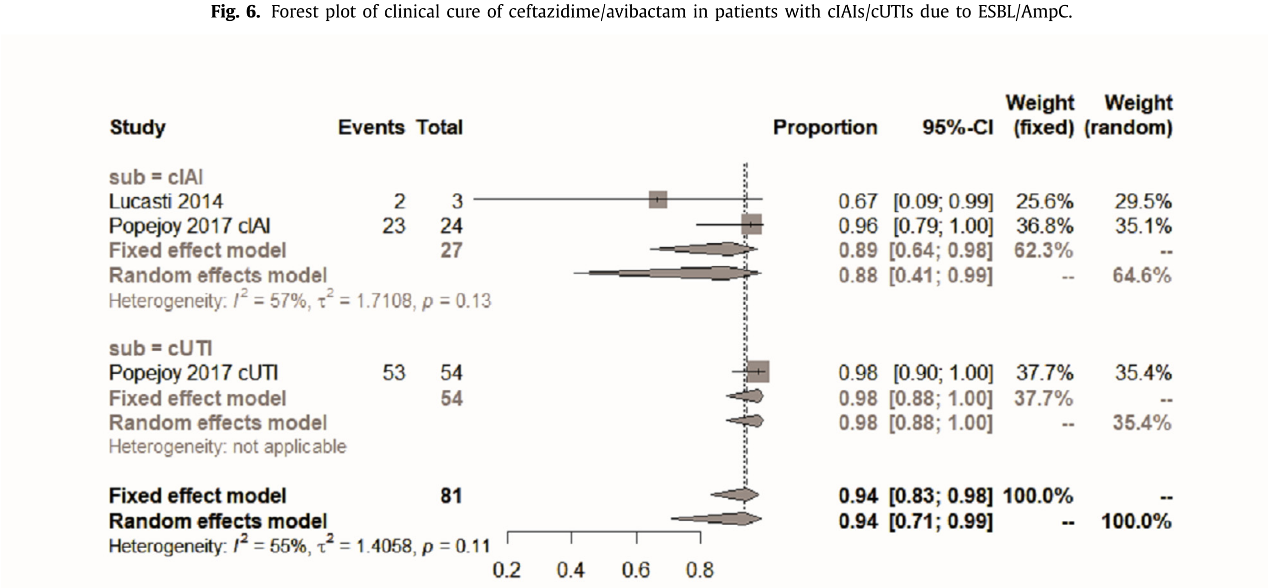

Fig. 7. Forest plot of clinical cure of ceftolozane/tazobactam in patients with cIAIs/cUTIs due to ESBL.

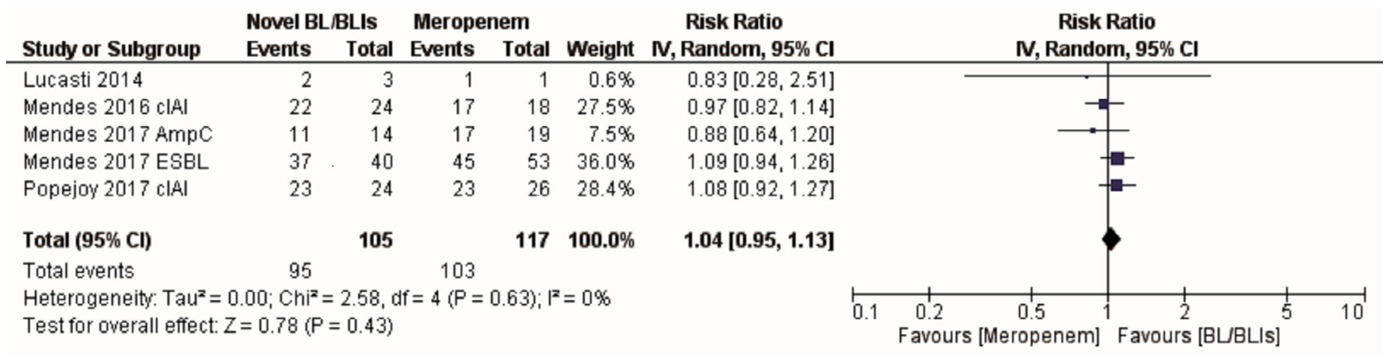

Fig. 8. Clinical cure of two novel BL/BLIs vs. meropenem for cIAIs due to ESBL/AmpC. Squares represent RR, horizontal lines represent 95%CI, the vertical line represents no difference between the two options, and the black diamond represents pooled RR. The right side is favorable to BL/BLIs and the left side is favorable to meropenem.

Table 1
Total cost and LYG of meropenem and CSBs in 1000 patients due to ESBL-producing Gram-negative pathogens.

Strategy	Cost (€)	Increment cost (€)	LYG	Increment LYG	ICER
Patients with cIAIs					
Meropenem	3 372 748.02	-	4513.81	-	-
Ceftolozane-tazobactam	4 869 475.89	1 496 727.87	4 567.68	53.87	27 785.74
Ceftazidime-avibactam	5 196 037.46	1 823 289.44	4 621.59	107.78	16 916.77
Patients with cUTIs					
Meropenem	3 184 950.02	-	4 529.24	-	-
Temocillin	3 186 669.88	1 719.86	4 540.16	10.91	157.58
Ceftolozane-tazobactam	4 740 363.65	1 555 413.63	4 645.33	116.09	13 398.34
Ceftazidime-avibactam	4 954 404.11	1 769 454.09	4 320.75	-208.49	Dominated

cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; CSB, carbapenem-sparing beta-lactam; ESBL, extended-spectrum beta-lactamase; ICER, incremental cost-effectiveness ratio; LYG, life year gained.

to ESBL or combination with ceftazidime-resistant Gram-negative pathogens and revealed the same results (Appendix F).

Four RCTs reported the clinical outcome of two novel BL/BLIs (ceftolozane-tazobactam and ceftazidime-avibactam) vs. meropenem and revealed no significant differences between two cIAI groups due to ESBL/AmpC-producing Gram-negative organisms (RR=1·04, 95%CI=0·95-1·13) (Fig. 8). In the subgroup analysis including cIAIs caused by either ESBL or AmpC, clinical outcome was similar between two treatment options (Appendix F). Other outcomes of interest are summarized in Appendix G.

Clinical cure of two novel BL/BLIs vs. meropenem for cIAIs due to ESBL/AmpC. Squares represent RR, horizontal lines represent 95%CI, the vertical line represents no difference between the two options, and the black diamond represents pooled RR. The right side is favorable to BL/BLIs and the left side is favorable to meropenem" are corrected.

3.2. Cost-effectiveness of carbapenem-sparing agents vs. meropenem

Average total costs and LYG for different strategies are presented in Table 1. For cIAIs due to ESBL, only ceftazidime-avibactam was cost-effective at a WTP threshold of €20 000 (€16 916·77 per LYG). In patients with cUTI due to ESBL receiving non-carbapenem therapies, both temocillin (€157·58 per LYG) and ceftolozane-tazobactam (€13 398·34 per LYG) were cost-effective compared with meropenem. When a 3-year Markov model was applied, only temocillin was still considered cost-effective in patients with cUTIs due to ESBL (€288·95 per LYG). Our findings indicated that CSBs were not cost-effective in other scenarios (Appendix H).

One-way sensitivity analyses indicated that the clinical cure rate of study drugs, daily drug costs, duration of therapy, and mortality rate after changing salvage therapy had a high impact on the ICERs of CSBs vs. meropenem. Results of PSA showed the probability that ceftazidime-avibactam is cost-effective at a threshold of €20 000 per LYG was 61·9% in patients with cIAIs.

With the cUTI model, the cost-effectiveness of treatment with ceftolozane-tazobactam and temocillin compared with meropenem was 56·6% and 68·1%, respectively, at a threshold of €20 000 per LYG (Appendix I).

4. Discussion

This systematic review showed the clinical cure rate of two new BL/BLIs was high, 88% for ceftazidime-avibactam and 94% for ceftolozane-tazobactam, in subsets with cUTI and cIAI caused by ESBL/AmpC-producing Enterobacteriaceae. Ceftazidime-avibactam has a broad-spectrum activity and is considered a treatment of carbapenem-resistant Enterobacteriaceae infections [31]. The study findings revealed there was no statistically significant difference in clinical cure rate between two novel BL/BLIs plus metronidazole and meropenem for cIAIs due to ESBL/AmpC (RR=1·04, 95%CI=0·95-1·13). Notably, the results of two novel BL/BLIs were derived from RCTs whereas the clinical cure rates of temocillin (93%) and piperacillin-tazobactam (88%) were from observational studies. Clinical cure rate of piperacillin-tazobactam was only 74% in patients with IAIs caused by AmpC-producing pathogens according to Chang et al. (this study was excluded from our systematic review as it was a conference abstract) [32]. The inclusion of a significant proportion of patients with a non-urinary source of bacteremia could be one explanation for inferior results of piperacillin-tazobactam in studies [33]. A recent RCT showed treatment of BSI caused by ESBL (34% of urinary source) with piperacillin-tazobactam was associated with a higher risk of all-cause mortality at 30 days (RR=3·4, 95%CI=1·5-7·6) compared with meropenem [34].

Limitations in the present systematic review and meta-analysis should be noted. Publication bias could not be performed through a funnel plot because only 17 studies were included in this systematic review. Nevertheless, a search on trial registries was conducted to seek relevant information from unpublished studies and publication bias is unlikely (Appendix J). The clinical cure rate of study drugs was derived from different infectious cohorts (i.e., bacteremia with a urinary source, cUTIs, cIAIs, and only acute pyelonephritis). The design of studies included in this systematic review varied (RCT, cohort study and case series). Furthermore, definitions for cIAI and cUTI were not consistent among the studies included.

To our knowledge, this is the first study to assess the cost-effectiveness of meropenem and CSBs for the treatment of cUTIs and cIAIs caused by ESBL. According to the Dutch antibiotic treatment guidelines, patients with cUTIs and cIAIs requiring hospitalization should be treated empirically with aminoglycoside (or a second- or third-generation cephalosporin) and ceftriaxone plus metronidazole, respectively [35]. When microbiological culture results show ESBL-producing Gram-negative bacteria, physicians often tend to switch antibiotic treatment to carbapenems. Accordingly, the costs and effectiveness of definitive therapies for the treatment of cUTIs and cIAIs caused by ESBL were estimated only when the initial regimen was unsuccessful. The study findings revealed that only an ICER of ceftazidime-avibactam was lower than a threshold of €20 000 per LYG for treatment of cIAI due to ESBL. The Dutch WTP threshold varies from €20 000 to €80 000 and depends on the type of intervention or disease. If €50 000 per LYG is applied, both ceftazidime-avibactam and ceftolozane-tazobactam are cost-effective in patients with cIAIs due to ESBL. As for cUTIs caused by ESBL, temocillin and ceftolozane-tazobactam were considered cost-effective compared with meropenem. Piperacillin-tazobactam was not considered in our cost-effectiveness model because of increasing risk of mortality in BSI caused by ESBL [34]. Several studies have reported that ceftolozane-tazobactam was more cost-effective than piperacillin/tazobactam for the empirical treatment of cUTIs and cIAIs [14,36].

Carbapenems have been reported in previous studies to be more effective and have lower total treatment costs than piperacillin/tazobactam when not accounting for the spread of carbapenem resistance over time [37–39]. Considering the consequences of resistance to carbapenems, the present study showed that CSBs were cost-effective from a Dutch healthcare viewpoint. However, only BSI was considered in the study models to estimate consequences of carbapenem-resistant Gram-negative pathogens whereas carbapenem resistance also restricts treatment options of other infections. In addition, nosocomial transmission of carbapenem resistance between patients was not considered, which may underestimate the cost-effectiveness of CSBs. Only carbapenem usage was assumed to lead to a higher rate of carbapenem resistance in this study, although BL/BLI consumption may also impact on resistance to carbapenems [40]. The present study did not account for the potential consequences of other resistance, e.g., temocillin resistance and avibactam resistance, which might develop under therapy in the study models. Some RCTs showed two novel BL/BLIs were non-inferior compared to meropenem in terms of safety [8–10]. Consequently, different outcomes in sequelae and adverse events during hospitalization were not considered in the present study models.

Results of sensitivity analyses indicated that the clinical cure rate of antibiotics, daily drug costs, and therapy duration had a substantial impact on the ICERs of CSBs in both cUTI and cIAI models. The clinical cure of antibiotics was drawn from the systematic review to enhance the precision of these key input parameters. Regarding daily drug costs, the meropenem price can be discounted from the manufacturer in practice and should be recalculated to estimate the cost-effectiveness of strategies in this scenario. Temocillin was not cost-effective when using the recommended retail price from the manufacturer in scenario analysis.

In conclusion, these study findings provide additional evidence in terms of the cost-effectiveness of CSBs for Dutch policy makers to suppress carbapenem overuse for ESBL infections. The findings indicate that ceftazidime-avibactam is cost-effective compared with meropenem for the definitive treatment of cIAIs, and temocillin and ceftolozane-tazobactam are potential alternatives to meropenem as definitive therapy of cUTIs regarding cost-effectiveness. This modeling with input parameters from the systematic review and published data could be transferred to other similar settings with different WTP thresholds to assess the cost-effectiveness of CSBs.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.07.003.

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Declarations

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Competing interests: We declare no competing interests.

Ethical Approval: Due to using input parameters from previously published literature, this study did not require approval from the Ethics Committee.

Contributors

Conception and design of the work: HW, RB, CPN, EA, JO, and EK. Data collection: CPN, TNDD, HW. Analysis and interpretation of the data: CPN, TNDD, HW, and EA. Statistical analysis: CPN. Supervision: HW. Writing-original draft: CPN. Critical revision and approval of the final manuscript: all authors.

Data sharing statement

All relevant data are within the manuscript (in 'Methods' section) and its supplementary data.

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