

Executive Summary

Comparative effectiveness of carbapenems and alternative antibiotics for the treatment of bacteraemia and/or urinary tract infectious disease by Enterobacteriaceae producing extended-spectrum β -lactamase

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□ Background

ESBL (Extended-Spectrum Beta-Lactamase)-producing enterobacteriaceae is highly associated with healthcare associated infection (HAI). The prevalence of gram-negative bacteria resistant to broad spectrum β -lactam antibiotics is rapidly increasing over the last 10 years. Although carbapenem therapy is considered as a selective alternative to treat ESBL-producing enterobacteriaceae, the use of carbapenems has been associated with the emergence of Carbapenem-resistant enterobacteriaceae (CRE). Since the wide use of carbapenems increases the incidence of CRE and there is a lack of

alternative treatment options when carbapenem treatment is failed, appropriate use of carbapenems is necessary. Recent studies suggest that other antibiotics (BL/BLIs, aminoglycoside, the fourth generation of cephalosporines, quinolones etc.) can be used as an alternative to carbapenems. Thus, the needs of studies on the efficacy of alternative antibiotics are continuously emerged.

□ Objective

This study systematically reviewed the recently published evidence to evaluate the clinical effectiveness of carbapenems and other alternative antibiotics in treating bacteremia and urinary tract infection caused by ESBL-producing *Enterobacteriaceae* and analyzed the comparative clinical outcomes of those therapies using multi-center data in Korea.

□ Methods

Systematic review

Systematic review was performed to evaluate the clinical safety and efficacy of carbapenems and other alternative antibiotics in treating bacteremia and urinary tract infection caused by ESBL-producing *Enterobacteriaceae*. Literature was searched through three international databases (Ovid-Medline, Ovid-EMBASE and Cochrane library) and seven domestic databases (KoreaMed, KMBASE, KISS, RISS, KisTi, National Central Library and National Assembly Library) after search strategies are established in conjunction of clinical specialists. Since the selected papers were all non-randomized comparative studies and observation studies, risk of bias was assessed using RoBANS version 2. After the quality evaluation, treatment efficacy of the finally selected study was extracted and a meta-analysis was performed for medical outcomes of interest.

Retrospective cohort analysis

Patient data was retrospectively collected from four hospitals located in

Seoul and Kyunggi province to evaluate the current use of antibiotics and isolation of microorganisms and to compare the clinical safety and efficacy of carbapenems and other alternative antibiotics (non-carbapenems, BL/BLIs) in treating bacteremia and upper urinary tract infection caused by ESBL-producing *Enterobacteriaceae*. The primary outcome in bacteremia was the mortality within 30 days and that in urinary tract infection was the early clinical remission of the treatment. Since the clinical characteristics of patients can affect the selection of antibiotics, basic analysis including all subjects who met inclusion and exclusion criteria as well as an analysis using “stabilized Inverse Probability of Treatment Weighting (stabilized IPTW)” that adjusted patient clinical characteristics were conducted.

□ Results

- In bacteremia, there was no statistically significant difference in the mortality for carbapenem compared to non-carbapenem, but sub-group analysis according to type of antibiotics show that there was statistically significant difference in the mortality for carbapenem compared to non-BL/BLIs. Multivariate analysis of thirty day survival rate conducted also revealed that there was no significant difference.
- In urinary tract infection, there was no statistically significant difference in the microbiological failure for carbapenem compared to non-carbapenem, also multivariate analysis of early clinical remission revealed that there was no significant difference.

I. Bacteremia

1. Systematic review

According to the inclusion criteria, a total of 31 studies were finally selected to compare the efficacy of carbapenems and other alternative antibiotics in treating bacteremia caused by ESBL-producing

Enterobacteriaceae. Most of the studies were conducted to identify risk factors rather than to compare effectiveness of carbapenems and other alternative antibiotics. The results of the risk of bias of included study were high in terms of comparability of participants, selection of participants, and confounding variables.

(1) Empirical treatment

A meta-analysis of mortality of the carbapenem group and the non-carbapenem group showed that there was no statistically significant difference (OR=0.84, 95% CI 0.54-1.32) and statistical heterogeneity between the literature was found to be significant ($\text{Chi}^2=42.89$, $\text{df}=17$, $P=0.0005$, $I^2=60\%$). Sub-group analyses such as comparative study designs between the drugs and appropriate use of antibiotics also showed that there was no statistically significant difference (Although comparative design studies showed a significant difference but statistical heterogeneity was found to be high).

The result of meta analysis according to type of non-carbapenem antibiotics (BL/BLIs, non-BL/BLIs, cephalosporins, quinolones, aminoglycoside) also showed that there was no statistically significant difference.

(2) Definitive treatment

A meta-analysis of mortality of the carbapenem group and the non-carbapenem group showed that there was no statistically significant difference (OR=0.70, 95% CI 0.48- 1.04), and statistical heterogeneity between the literature was found to be insignificant ($\text{Chi}^2=29.69$, $\text{df}=19$, $P=0.06$, $I^2=36\%$). Sub-group analyses such as comparative study designs between the drugs and appropriate use of antibiotics also showed that there was no statistically significant difference.

A meta-analysis according to the types of antibiotics showed that the mortality of the carbapenem group was 62% lower compared to that of the non-carbapenem antibiotics (OR=0.38, 95% CI 0.22-0.65) and it was also

lower when compared to that of non-BL/BLIs (OR=0.65, 95% CI 0.43-0.99). However, there was no statistically significant difference between carbapenems and other non-carbapenem anti-biotics (BL/BLIs, quinolones, aminoglycoside).

2. Retrospective cohort study

We identified 554 patients who met the eligibility criteria. The sensitivity to carbapenems was greater than 95% and that to BL/BLIs (Piperacillin-tazobactam) was also high with the percentage of 83.6%. There was no statistically significant difference in thirty day survival rate between the groups both prior and post to propensity score weighting. Multivariate analysis of thirty day survival rate conducted after the adjustment of confounding variables affecting mortality rate such as age, infection route, transfer to ICU within 48 hours, infection sites, APACHE II, liver diseases, lung diseases, renal disease and diabetes also revealed that there was no significant difference (HR=1.01, 95%CI 0.27-3.76). After propensity score weighting, the statistical difference remained insignificant (weighted HR=0.76, 95%CI 0.23-2.58). There was no statistically significant difference in thirty day survival rate between the groups when carbapenems and BL/BLIs were used as empirical treatment (weighted HR=0.99, 95%CI 0.29-3.30).

II. Urinary tract infection

1. Systematic review

According to the inclusion criteria, a total of six papers were finally selected to compare the efficacy of carbapenems and other alternative antibiotics in urinary tract infection caused by ESBL-producing *Enterobacteriaceae*. The diseases included urinary tract infection, complicated lower urinary tract infection and nephropylitis. A variety of drugs were used in the carbapenem group and more than two carbapenems were used in four studies (66.7%). Three studies had a comparative study design for carbapenems and non-carbapenems and the overall quality of

studies was judged to be poor.

Analysis of four studies reporting successful treatment eradicating microorganisms showed that there was no statistically significant difference between the carbapenem group and the non-carbapenem group (OR=1.56, 95% CI 0.44-5.56). There was also no statistically significant difference in the clinically success rate in treatment (OR=1.86, 95% CI 0.51-6.84).

2. Retrospective cohort study

Finally selected subjects who met the inclusion criteria were 319 cases. The sensitivity to carbapenems (ertapenem, imipenem and meropenem) was higher than 90% and that to non-carbapenem antibiotics (tigecycline, amikacin, and piperacillin/tazobactam) was also relatively high. Multivariate regression analysis of early clinical remission of treatment after the adjustment of confounding factors affecting outcomes of treatment such as sex, age, sites of infection, history of UTI and connective tissue disease revealed that there was no significant difference (OR=1.70, 95% CI 0.50-5.80). After propensity score weighting, the statistical difference remained insignificant (OR=1.99, 95% CI 0.66-5.94).

□ Conclusions

Although there was no clear evidence that superiority of carbapenem in empirical therapy, this study results suggest that carbapenem therapy is associated with a reduction of overall mortality when it is used as a definitive treatment in bacteremia caused by ESBL-producing *Enterobacteriaceae*. However, considering an increasing carbapenem resistance and non inferiority of BL/BLIs use over carbapenems according to the study results, BL/BLIs can be used as alternatives for the treatment of patients with ESBL-positive *Enterobacteriaceae* bacteraemia. In patients with ESBL-positive *Enterobacteriaceae* urinary tract infection, the role of carbapenem and other antibiotics should be further evaluated for empirical and definitive treatment.

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Key words

extended-spectrum β -lactamase, ESBL, *Enterobacteriaceae*, carbapenems, bacteraemia, urinary tract infection

ESBL	Extended-Spectrum Beta-Lactamase
Amox/Clav	Amoxicillin-Clavulanic
Amp/sul	Ampicillin-sulbactam
BL/BLIs	Beta-lactam/Beta-lactamase inhibitors
BSI	Blood stream infection
CCI	Charlson Comorbidity Index
CDAD	Clostridium difficile-associated diarrhea
CNS	central nervous system
CRE	Carbapenem-Resistant <i>Enterobacteriaceae</i>
CIP/LEV	Ciprofloxacin-Levofloxacin
DNR	Do no resuscitate
<i>E. coli</i>	<i>Escherichia coli</i>
IPTW	Inverse Probability of Treatment Weighting
<i>K. pneumoniae</i>	<i>Klebsiella pneumoniae</i>
MIC	Minimal Inhibitory Concentration
Pip/tazo	Piperacillin-tazobactam
PS	Propensity Score
Ticar/Clav	Ticarcillin-clavulanate
TMP/SMX	Trimethoprim-sulfamethoxazole
UTI	Urinary tract infection