Antibiotic treatment of infections due to carbapenem-resistant Enterobacteriaceae: systematic evaluation of the available evidence

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Short title: Antibiotic treatment for infections by CRE

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ABSTRACT

Objectives: We sought to evaluate the effectiveness of the antibiotic treatment administered for infections caused by carbapenemase-producing Enterobacteriaceae.

Methods: PubMed and Scopus databases were systematically searched. Articles reporting the clinical outcomes of patients infected with carbapenemase-producing Enterobacteriaceae according to the antibiotic treatment administered were eligible.

Results: Twenty non-randomized studies comprising 692 patients who received definitive treatment were included. Almost all studies reported on Klebsiella spp. In 8 studies, the majority of infections were bacteremia, while pneumonia and urinary tract infections were the most common infections in 12 studies. In 10 studies, the majority of patients were critically ill. There are methodological issues, including clinical heterogeneity, that preclude the synthesis of the available evidence using statistical analyses including meta-analysis. From the descriptive point of view, among patients who received combination treatment, mortality was up to 50% for tigecycline-gentamicin combination, up to 64% for tigecycline-colistin, and up to 67% for carbapenem-colistin. Among the monotherapy-treated patients, mortality was up to 57% for colistin and up to 80% for tigecycline. Certain regimens were administered to a small number of patients in certain studies. Three studies reporting on 194 critically ill patients with bacteremia showed individually significantly lower mortality in the combination arm compared to the monotherapy arm. In the other studies, no significant difference in mortality was recorded between the compared groups.

Conclusion: Combination antibiotic treatment may be considered the optimal option for severely ill patients with severe infections. However, well-designed randomized studies in specific patient populations are needed to further clarify this issue.

Keywords: KPC, VIM, NDM, OXA, IMP, CRE, Escherichia coli, Enterobacter, bloodstream infection, UTI
INTRODUCTION

Carbapenemase-producing Enterobacteriaceae have been steadily spreading worldwide during the last decade. Production of *Klebsiella pneumoniae* carbapenemase (KPC) enzymes is the most common mechanism of resistance among carbapenemase-producing Enterobacteriaceae, while these enzymes are most commonly encountered among *K. pneumoniae* isolates. Outbreaks due to KPC-producing *K. pneumoniae* have been recorded in many countries around the world; (1) however, these infections have become endemic in the United States, Greece, Israel and China. (1) Carbapenems have been successfully, until recently, used for the treatment of infections caused by Enterobacteriaceae including those producing extended-spectrum beta-lactamases. (2) However, carbapenemases confer resistance to broad-spectrum antibiotics usually including carbapenems and, therefore, the majority of carbapenemase-producing Enterobacteriaceae are carbapenem-resistant (CRE).

According to recent data from Centers for Disease Control and Prevention, in the United States, the percentage of CRE increased from 1.2% in 2001 to 4.2% to 2011. (3) The highest increase in proportion, from 1.6% to 10.4%, was observed for *Klebsiella* spp during the same period. (3)

Antibiotic treatment options for these multidrug-resistant infections are limited. Tigecycline which was approved by the Food and Drug Administration in 2005, the "old" antibiotics colistin and fosfomycin which have been revived, (4, 5) and aminoglycosides are among the remaining treatment options for the clinicians to battle against these difficult-to-treat infections. An important question which still remains unanswered among clinicians regarding antibiotic treatment is whether combination or monotherapy antibiotic regimens are more effective. With regard to published literature, the major problem is that most studies reporting on treatment include retrospective data and a rather small number of patients. Besides, it has been shown that patients with infections due to carbapenemase-producing Enterobacteriaceae or CRE experience high mortality. (6-8) Therefore, collection and analysis of the current published literature on the effectiveness of the antibiotic treatment used against these infections is a necessity.
In this context, we aimed to systematically review the available evidence in order to evaluate the effectiveness of the antibiotic treatment commonly administered to patients with infections caused by carbapenemase-producing Enterobacteriaceae and CRE.

METHODS

Literature search
A systematic search was performed in the PubMed and Scopus databases during February-March 2013. The following search term was applied to the PubMed database: “(CRE or carbapenem-resistant or KPC or carbapenemase-producing or VIM or NDM or OXA or IMP) and (escherichia or klebsiella or enterobacter or proteus or serratia or citrobacter or salmonella or shigella) and (treatment)”. A shorter search term was applied to Scopus: “(CRE or carbapenem-resistant or KPC or carbapenemase-producing or VIM or NDM or OXA or IMP) and (escherichia or klebsiella or enterobacter or enterobacteriaceae) and (treatment). The bibliographies of all eligible studies were hand-searched in an effort to identify additional potentially eligible studies. Only articles published in English, German, French, Spanish, Italian, or Greek were evaluated.

Study selection
Any article providing the clinical outcomes of patients treated for infections caused by carbapenemase-producing Enterobacteriaceae or CRE were considered eligible for inclusion in the review. Studies reporting on the treatment and clinical outcomes of colonized patients with carbapenemase-producing Enterobacteriaceae or CRE were excluded. When the clinical outcomes of the infected patients were presented separately from the outcomes of the colonized patients, only the outcomes of the infected patients were extracted. Case reports and case series including less than 10 infected patients were excluded from the review.

Data extraction
The extracted data was consisted of the main characteristics of a study (first author name, year of publication, country, study period and design), main characteristics and underlying diseases of the study population, number of patients with infections due to...
carbapenemase-producing Enterobacteriaceae or CRE, causative pathogen(s), sites of infections, and antibiotic treatment (combination/monotherapy). Clinical outcomes (mortality, treatment failure) of patients in each treatment group were recorded, as well.

Definitions and outcomes

The interpretation of the antimicrobial susceptibility patterns was performed according to the breakpoints used by the investigators of the individual studies.

The primary outcome of the review was 30-day mortality, while the secondary outcome was treatment failure. When 30-day mortality was unavailable, other types of mortality were extracted. Treatment failure was defined according to the definitions used by the investigators of the included studies.

RESULTS

A total of 925 articles were retrieved during the search process in both databases (542 on PubMed, 379 on Scopus, 4 during hand-searching). Twenty studies met the inclusion criteria. The detailed search process and study selection are depicted in Figure 1. Thirty-one studies were excluded because they did not present the clinical outcomes according to the antibiotic treatment administered. Among the included studies, eighteen provided data on mortality including 651 patients who received definitive antibiotic treatment, while two other studies provided data on treatment failure including 41 patients who received definitive antibiotic treatment. The characteristics and outcomes of the included studies according to the studied outcome are presented in Tables 1 and 2.

Seven out of twenty-one studies were prospective cohort, twelve were retrospective cohort and one was retrospective case-control study. Fifteen studies reported on carbapenemase-producing Enterobacteriaceae and five other on carbapenem-resistant Enterobacteriaceae. One study included infections due to carbapenem-resistant K. pneumoniae, mainly KPC-producing. The sole causative pathogen in 14 studies,
while it was the predominant causative in 5 other studies. In one study, the major causative pathogen was *Enterobacter cloacae*. In 8 out of 20 studies, the total or the majority (> 50% of the included infections) of the included infections were bacteremia. Pneumonia and urinary tract infections were the most common infections among the remaining 12 studies. In 10 out of 20 studies, the majority of patients were critically ill.

**Mortality**

In seven studies, the 28- or 30-day mortality was provided, in one the 14-day mortality, in four studies the in-hospital mortality, in two the overall mortality, in one the infection-related mortality, and in three the type of mortality provided was not determined.

**Carbapenemase-producing *Klebsiella* spp.: KPC, MBL, or OXA**

Eight studies (316 patients) reported data on KPC-producing *Klebsiella* spp., while five other studies (201 patients) reported data regarding MBL- or OXA-producing *Klebsiella* spp. The mortality of the most commonly administered antibiotic treatment regimens among the included studies was recorded. Due to the fact that some treatment regimens were administered to very few patients in certain studies, only regimens reporting on more than 3 patients from each study were taken into account.

With regard to patients who received combination treatment, mortality varied from 0% to 30% among 51 patients (4 studies) who received the tigecycline-colistin combination, from 0% to 50% among 15 patients (2 studies) who received the tigecycline-gentamicin combination, from 0% to 67% for 25 patients (4 studies) treated with carbapenem-colistin combination, and from 40% to 61% for 30 patients (3 studies) treated with colistin-gentamicin combination. In a study including only intensive care unit (ICU)-patients, the 11 patients with infections due to VIM-1-producing isolates who were treated with the tigecycline-colistin combination had 64% mortality. Among the 28 patients who were treated with the carbapenem-colistin combination, sixteen were infected with carbapenem-susceptible strains, while the remaining 12 patients had...
infections due to carbapenem-resistant strains. In addition, 67% mortality for patients receiving the carbapenem-colistin combination was recorded in two studies including solid-organ transplant recipients and ICU-patients in the majority, respectively.

Regarding patients who received monotherapy, mortality varied from 9% to 50% for 29 patients (3 studies) who received carbapenem, from 0% to 53% for 102 patients (8 studies) who received tigecycline, from 6.3% to 80% among 102 patients (8 studies) who received colistin, and from 33% to 57% for 102 patients (8 studies) who received tigecycline in a study including ICU-patients in the majority, patients who received monotherapy with tigecycline had 80% mortality. Among the 26 patients who were treated with gentamicin monotherapy, at least nineteen patients had urinary tract infection, uncomplicated in most cases. Twenty-five out of 29 patients who received carbapenem monotherapy were infected with carbapenem-susceptible strains, while 3 patients were infected with strains with intermediate susceptibility to carbapenems. Finally, in a study including 34 elderly patients who received definitive antibiotic treatment for bloodstream infection due to OXA-48-producing Enterobacteriaceae, all the antibiotics included in the combination treatment regimens were not precisely determined. Specifically, 30-day mortality was 52.4% among patients who were treated with ≥ 2 active drugs not including a carbapenem, while 30-day mortality was 33.3% among patients who were treated with ≥ 2 active drugs including carbapenems. Patients who received monotherapy with amikacin had 33.3% mortality.

Carbapenem-resistant *Klebsiella* spp.

Five studies (160 patients) reported data on carbapenem-resistant *Klebsiella* spp. In two studies, mortality was 25% and 31% among 16 and 13 patients, respectively, who received the tigecycline-colistin combination. In one study, patients had infections caused by CRE, *K. pneumoniae* in the majority. Mortality at day 30 was 50%, 50%, and 73% among patients who received monotherapy with a
carbapenem, colistin, and tigecycline, respectively. There was no significant difference in the 30-day mortality rate between the 15 patients treated with tigecycline and the other 18 patients treated with colistin, imipenem, or meropenem (p=0.31). In another study including 10 patients, mortality was 50% (2/4) for patients who were treated with amikacin combined with a carbapenem. Finally, in the last study, eleven ICU-patients with hospital-acquired infections received intravenous fosfomycin either combined with other antibiotics or alone. Two of the patients who received fosfomycin in combination with colistin died while in hospital.

Other carbapenemase-producing Enterobacteriaceae

One study reported on the definitive antibiotic treatment that was administered to 32 patients with bloodstream infections due to IMP-8-producing Enterobacteriaceae, mainly *Enterobacter cloacae*. Patients who received treatment with carbapenems had 10% 28-day mortality (2/20), whereas those who received non-carbapenem treatment had 16.7% 28-day mortality (2/12). Approximately half the patients were infected with carbapenem-resistant strains.

Treatment failure

Two studies (41 patients) reported relevant data on infections caused by carbapenemase-producing *K. pneumoniae*. In the one study, including mainly ICU-patients, showed that treatment failure was 16.7% (2/12) among patients who received combination treatment, while treatment failure was 40% (4/10) among those who received monotherapy (p=0.35). In the other study, also mainly reporting on ICU-patients, showed that patients who received the tigecycline-colistin combination as well as those receiving the colistin-tigecycline-gentamicin combination had 42.9% (3/7) and 0% (0/2) treatment failure, respectively.

In total, in the majority of the studies, statistically significant differences in mortality and treatment failure were not detected between patients who received combination antibiotic treatment and those receiving monotherapy. However, three studies, reporting on totally 194 patients, showed significantly lower mortality in the combination treatment arms compared to the monotherapy arms. These studies reported on bloodstream infections in critically ill patients. In addition, another
study showed numerically but not statistically significant higher clinical cure and microbiological eradication among patients treated with a combination of antibiotics than those treated with monotherapy. (20) This study reported on critically ill patients, as well.

DISCUSSION
Methodological issues, including clinical heterogeneity, that have been detected among the included studies precluded the synthesis of the evidence using statistical analyses including meta-analysis. However, among critically ill patients with bacteremia due to carbapenemase-producing *Klebsiella* spp., combination antibiotic treatment may result in lower mortality than monotherapy.

Tigecycline in combination with colistin, carbapenem in combination with colistin, and tigecycline in combination with gentamicin were commonly administered antibiotic treatment regimens among the included studies and might result in lower mortality compared to other combinations of antibiotics. Similar effectiveness with the aforementioned combinations was observed among patients treated with monotherapy with colistin, tigecycline, and carbapenems. However, the available data for the majority of the studied treatment regimens, both the combinations and the monotherapy regimens, reported on less than 50 patients and great variation existed with respect to site and severity of infection. Among patients treated with the same antibiotic treatment, either combination or monotherapy, mortality exceeded 60% for patients in the critical care setting, while it was below 50% for non-ICU patients.

Carbapenems were overall administered to patients infected with strains with low MICs. Interestingly, three of the included studies mention important increase in survival when a carbapenem was administered in combination with another drug. (12, 19, 25) In one of them, it is mentioned that the survival of patients treated with the colistin-tigecycline combination significantly increased when meropenem was added to the scheme. (25) The authors commented that the survival benefit is possibly associated with meropenem because that was the most commonly added antibiotic to the colistin-tigecycline combination. It is also interesting that increase in survival was observed both among patients infected with isolates of a meropenem MIC ≤ 4 and...
among those with isolates of elevated MIC. Likewise, another study suggested that colistin-tigecycline along with a carbapenem was the most successful combination, even among patients with isolates resistant to carbapenems, possibly due to potential synergy between colistin and carbapenems, but results may be affected by the small number of cases studied and by the fact that carbapenems were very commonly included in the combination treatment regimens. Last, in the remaining study it is reported that the lowest mortality was noted among patients who received two active drugs one of which was a carbapenem. However, all the combination regimens in this study included a carbapenem, precluding comparisons with other combination treatment regimens.

Gentamicin monotherapy was preferred in patients with urinary tract infections and this may account for the high clinical success observed. There were few cases of successful treatment of bacteremia with gentamicin monotherapy as well as few cases of pneumonia, but monotherapy with aminoglycoside is against the guidelines in these serious infections. Also, catheter removal from patients with catheter-related bacteremia was probably the main factor leading to cure in those cases. With regard to tigecycline, it was administered either in combination with colistin or gentamicin or even as monotherapy among the included studies. In the majority of these studies, tigecycline treatment regimens were not administered for approved indications (i.e. complicated intra-abdominal infections, complicated skin and soft tissue infections) but instead for bloodstream infection, pneumonia, and urinary tract infection. The use of tigecycline in an off-label manner is widespread due to the scarcity of approved effective alternative antibiotics for multidrug-resistant infections. Attention should be paid by clinicians because tigecycline was associated with higher mortality than comparator antibiotics. However, a recent meta-analysis showed that the drug was not associated with significantly higher mortality than comparator antibiotics and was as effective as comparators, when the analysis was restricted to patients who received tigecycline for approved indications.

The option between combination of antibiotics and monotherapy can vary among different sites of infection, causative pathogens, antimicrobial susceptibility patterns,
or patient co-morbidity. In clinical practice, combinations of antibiotics are commonly administered to patients with severe infections either empirically to broaden the coverage or definitively for polymicrobial infections. Evidence derived from clinical and in vitro studies reveals that combination of antibiotics might prevent the emergence of resistant strains during therapy. However, clinical data do not clearly support that antibiotic combinations reduce the emergence of resistance. Synergy is another potential benefit arising from the use of antibiotic combinations but in vitro synergy of specific antibiotics may not always translate into clinical effectiveness. Similarly, inactive in vitro antibiotics could potentially be useful when administered as adjuncts with an active antibiotic in cases when alternative antibiotics are not available.

Tigecycline with colistin, colistin with a carbapenem, fosfomycin with a carbapenem, fosfomycin with an aminoglycoside, and a carbapenem with an aminoglycoside have been reported as antibiotic combinations effectively administered to series of patients infected with carbapenemase-producing Enterobacteriaceae. In addition, there is clinical evidence suggesting that the tigecycline-colistin combination may be superior to colistin monotherapy in terms of emergence of colistin resistance during therapy for infection due to carbapenem-resistant K. pneumoniae. On the contrary, a meta-analysis focusing on beta-lactams showed that beta-lactam combined with an aminoglycoside was not superior to beta-lactam monotherapy regarding emergence of resistance. Administration of colistin in combination with an aminoglycoside has also been reported; however, attention should be paid during therapy since both agents can cause nephrotoxicity. In general, combinations of antibiotics should always be administered cautiously bearing in mind the potential additive toxicity of the drugs. Among aminoglycosides, gentamicin has been suggested as the one with the highest in vitro activity against KPC- and VIM-producing Enterobacteriaceae. Combination treatment including a carbapenem could be considered in infections due to carbapenemase-producing Enterobacteriaceae with low MIC and using extended or continuous but not short-term infusions.

Similarly, the once-daily (extended-interval) dosing should be considered when aminoglycosides are administered, since this regimen provides optimal pharmacokinetics/pharmacodynamics for those drugs. Last, preliminary assays in
in vitro and animal models support that double-carbapenem treatment might be considered in the treatment of infections caused by KPC-producing *K. pneumoniae* (49, 50).

On the other hand, treatment with a single antimicrobial agent, mainly colistin and tigecycline has also been a choice (11, 13, 16, 18, 25). However, a recent review showed that treatment failure was more common among patients who were treated with monotherapy compared to those who were treated with a combination of antibiotics for infections due to KPC-producing *K. pneumoniae* (51). The effectiveness of colistin monotherapy has been challenged due to low plasma concentrations owed to suboptimal dosing of the drug, especially in critically ill patients with impaired renal function (52). However, an increase in the daily dose of the antibiotic is risky due to colistin-induced nephrotoxicity. Also, low serum levels are achieved with the usual dosing of tigecycline. Furthermore, colistin heteroresistance has emerged among *Klebsiella* spp. isolates (53) while outbreaks due to colistin-resistant carbapenemase-producing Enterobacteriaceae (54-57) and resistance to tigecycline have also been recorded (58) in some countries. Resistance to both antibiotics has been associated with prior exposure to the drugs (59, 60). Therefore, combination with another antibiotic might be the optimal option when patients are treated with colistin or tigecycline. Last, until further studies clarify the issue of the emergence of resistance during therapy with fosfomycin, fosfomycin should not be administered as monotherapy.

Our study should be interpreted in view of certain limitations. The major one is that the scarcity of evidence on how to treat these potentially severe infections forced us to present together different patient populations, different sites of infections, different genotypes of a pathogen (i.e. KPC, VIM, OXA), and different assessments of mortality. In addition, the interpretation of the findings should be done in view of the fact that lower antimicrobial susceptibility breakpoints have been proposed for carbapenems by Clinical and Laboratory Standards Institute (CLSI) in June 2010, while older breakpoints were used in some of the included studies. Another important limitation is that all included studies were non-randomized and the majority of them had a retrospective design. Furthermore, specific conclusions were drawn from...
studies with a small number of patients. Another important issue is that the administration of the antibiotics differed among the studies regarding the duration of infusion or the total daily dose. Accordingly, these differences might influence the clinical outcomes. With regard to safety of the administered treatment regimens, the included studies did not provide relevant data. Last, the matter of the emergence of resistance during therapy was not raised by any of the included studies.

In conclusion, the available evidence entirely consisted of non-randomized studies suggests that combination antibiotic treatment may offer comparative advantage over monotherapy regarding mortality in critically ill patients with severe infections due to carbapenemase-producing *Klebsiella* spp. Well-designed randomized controlled trials in specific patient populations are required to address this crucial question of every day clinical practice.

**Figure 1.** Flow diagram of the detailed search process and study selection
REFERENCES


Table 1. Mortality of infections caused by carbapenemase-producing Enterobacteriaceae or CRE among different antibiotic treatment regimens

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study design; period, country</th>
<th>Population characteristics; most common underlying diseases</th>
<th>Site of infection of the total population</th>
<th>Infected patients who received definitive antibiotic treatment</th>
<th>Causative pathogen(s)</th>
<th>Susceptibility breakpoingts used,$^\text{¶}$ year</th>
<th>Antibiotic treatment administered (n); mortality (%)</th>
<th>Mortality assessed at</th>
<th>Combination therapy</th>
<th>Monootherapy</th>
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</thead>
</table>
| Capone             | 2013(11) | MC prospective cohort; 2010-2011, Italy | Inpatients, 48.4% ICU-patients, DM, COPD, chronic kidney or liver disease, malignancy | BSI (37.4%), UTI (31.9%), septic shock (16.5%), LRTI (13.4%), SSTI (12.1%)* | 67 appropriate antibiotic treatment (known abx at 51) | KPC-producing *Klebsiella* pneumonia | EUCAST, NR | In-hospital | Coli-Tige: 16; 25%  
Tige-Fos: 6; 33%  
Coli-Fos: 5; 0%  
Coli-Gen: 5; 40% | Carba-PoB: 3; 0%  
Tige-PoB: 3; 0%  
Carba-Tige: 1; 0%  
Carba: 2; 100%  
Poli: 1; 0%  
Azt-FQ: 1; 0%  
Tzp: 1; 100% | 28-day |
| Alexander          | 2012(9)  | SC retrospective cohort; 2006-2008, USA | Inpatients | UTI (2 patients developed bacteremia) | 14 | KPC-producing *K. pneumoniae* and *Citrobacter freundii* | CLSI, 2005 FDA (tige)$^\text{¶}$ | 30-day | Carba-PoB: 3; 67%  
Tige-PoB: 3; 0%  
Carba-Tige: 1; 0% | Carba: 2; 100%  
Poli: 1; 33% |
| Bergamasco         | 2012(10) | SC retrospective cohort; 2009-2010, Brazil | Solid-organ transplant recipients; DM, cardiovascular disease, liver disease, renal disease | BSI (33.3%), UTI (33.3%), SSI (16.7%), pneumonia (16.7%) | 12 | KPC-producing *K. pneumoniae* | CLSI, 2009 FDA (tige)$^\text{¶}$ | In-hospital | NR$^\text{¶}$ | Gen: 5; 40%  
Cipro: 6; 0%  
Dov: 1; 0%  
Nef: 1; 0% |
| Qureshi            | 2012(9)  | SC retrospective cohort; 2005-2008, USA | Enrollmen: DM, cardiovascular disease, CRF, renal dialysis, COPD, malignancy; 51.2% *Acute II ≥ 20*  
Bacteremia; source:  
24.4% pneumonia,  
31.7% line-related,  
17.1% LRTI, 14.6% primary | 34 | KPC-producing *K. pneumoniae* | CLSI, 2011 | 28-day | Coli-Carba: 5; 20%  
Coli-Tige: 3; 0%  
Coli-FQ: 3; 0%  
Tige-Carba: 3; 0%  
Carba-Tige: 3; 0%  
Carba-FQ: 1; 100%  
Ant-FQ: 1; 0% | Cola: 7; 57%  
Tige: 5; 50%  
Carba: 4; 50%  
Gen: 1; 0%  
A/S: 1; 0%  
Tzp: 1; 100% |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Source of Infection</th>
<th>Infections</th>
<th>Pathogen</th>
<th>Susceptibility</th>
<th>UTI (30-day)</th>
<th>Institution-related</th>
<th>Other 2-drug combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumbarello 2012(25)</td>
<td>Retrospective cohort; 2010-2011, Italy</td>
<td>LRTI, CVC, UTI, other, unknown</td>
<td>13.6% shock, DM, heart failure, CRF, malignancy</td>
<td>BSL</td>
<td>KPC-producing K. pneumoniae</td>
<td>CLSI, 2011</td>
<td>Tige: 30%</td>
<td>Tige-Coli: 23%</td>
</tr>
<tr>
<td>Zarkotou 2011(28)</td>
<td>Prospective cohort; 2008-2010, Greece</td>
<td>ICU admission</td>
<td>71.7% ICU admission</td>
<td>BSL</td>
<td>KPC-producing K. pneumoniae</td>
<td>CLSI, 2010 EUCAST, 2010</td>
<td>Coli: 35%</td>
<td>Tige-Coli-Carba: 1%</td>
</tr>
<tr>
<td>Souli 2010(22)</td>
<td>Retrospective cohort; 2007-2008, Greece</td>
<td>ICU admission</td>
<td>61.5% ICU-patients, DM, cardiovascular disease, COPD, renal failure, malignancy</td>
<td>BSL</td>
<td>KPC-producing K. pneumoniae</td>
<td>CLSI, 2009 EUCAST, 2009</td>
<td>Carba-Coli: 1%</td>
<td>Carba-Coli-Tige: 1%</td>
</tr>
</tbody>
</table>

*Carba: 1% Tzp, then Tige: 1%
<p>| Study | Source | Design | Year(s) | Setting | Patients | Isolates | Minimum Size | Species | Minimum | 30-day Mortality | Minimum 2 Active Drugs | Minimum 2 Active Drugs + Carbapenem | Carbapenem Resistance | Carbapenem Non-Resistance | Carbapenem Non-Resistance + Carbapenem | Carbapenem Non-Resistance + Carbapenem + Carbapenem | Carbapenem Non-Resistance + Carbapenem + Carbapenem + Carbapenem | Carbapenem Non-Resistance + Carbapenem + Carbapenem + Carbapenem + Carbapenem |
|-------|--------|--------|---------|---------|----------|----------|-------------|---------|---------|-----------------|-------------------------------|------------------------|------------------|------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Weisenberg 2009(26) | SC retrospective cohort; 2006, USA | Inpatients | 2006, USA | Inpatients | Bacteremia (19%), pneumonia (23.4%), UTI (9.5%), sepsis (12.5%), other (19%), urinary tract infection (44%), wound infection (17%), line-related infection (40%) | 21 | KPC-producing K. pneumoniae | NR | Undetermined | Tige-Gen: 1; 0% | Tige-Carba: 1; 100% | Carba: 11; 9% | Tige: 3; 0% | Gen: 2; 0% | Amk: 1; 0% |
| Navarro-San Francisco 2013(17) | SC prospective cohort; 2010-2012, Spain | Elderly patients, 60% septic shock or severe sepsis, 37.5% malignancy | 2010-2012, Spain | Elderly patients | BSIL, source: UTI (59%), deep LAI SSI (29%), primary (15.7%), catheter-related (10%), other (17.5%) | 34 | OXA-48-producing Enterobacteriaceae (K. pneumoniae, Escherichia coli) | CLSI, 2012 FDA (tig) | 30-day | ≥ 2 active drugs (carba not included): 21; 32.4% | ≥ 2 active drugs (carba included): 6; 17% | Amk: 3; 33% | Tige: 2; 0% | Coli: 1; 0% | Carba: 1; 100% |
| Sanchez-Romo 2012(21) | SC retrospective cohort; 2009, Spain | ICU-patients | 2009, Spain | ICU-patients | Pneumonia (29.2%), other LAI (20.8%), UTI (12.5%), meningitis (6.3%), CAF (6.3%), EMB (3.2%), UTI (8.3%), soft-tissue (4.2%) | 24 | VIM-1-producing K. pneumoniae | CLSI, 2011 EUCAST, 2011 (tig) | Undetermined | Tige-Coli: 11; 44% | Tige-Coli: 1; 0% | Amk: 6; 25% | Erta: 1; 0% |
| Mouleidi 2010(16) | SC retrospective case-control | ICU-patients, diabetic, obese, respiratory | 2010, Spain | ICU-patients | BSIL | 59 | KPC- or MBL-producing K. pneumoniae | CLSI, 2011 EUCAST, 2010 (tig) | In-hospital | Coli-Gen: 18; 63% | Coli: 35; 51% | | | | |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Country</th>
<th>Year(s)</th>
<th>Setting</th>
<th>Disease(s)</th>
<th>Pathogen(s)</th>
<th>Treatment(s)</th>
<th>Duration</th>
<th>Outcomes</th>
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<tr>
<td>Daikos 2009(12)</td>
<td>MC prospective cohort; 2004-2006, Greece</td>
<td>Greece</td>
<td>2007-2008</td>
<td>Disease, liver disease, trauma, transplant recipient</td>
<td>FDA (tige) ¥</td>
<td>Inpatients</td>
<td>BSI, VIM-1-producing <em>K. pneumoniae</em></td>
<td>CLSI, 2004</td>
<td>14-day  Carba-Coli: 8, 9%  Carba-AM: 4, 25%  Carba: 10, 21%  Coli: 15, 27%  AG: 8, 38%  No active drug: 18, 28%</td>
</tr>
<tr>
<td>Souli 2008(23)</td>
<td>SC retrospective cohort; 2005-2006, Greece</td>
<td>Greece</td>
<td>2004-2006</td>
<td>Inpatients, 58.8%, ICU-patients, congestive heart failure, renal failure, malignancy, DM</td>
<td>BSI (82.5%), VAP (11.8%)</td>
<td>VIM-1 MBL-producing <em>Enterobacteriaceae</em> (Klebsiella spp., <em>Enterobacter</em> spp.)</td>
<td>CLSI, 2006  BSAC (coli)*  FDA (tige)¥</td>
<td>Overall</td>
<td>Carba-Coli: 6, 30%  Cola-Tig: 1, 100%  Carba-Coli-Lad: 1, 0%  Cola-Tig-Lad: 1, 100%  Carba-Cola-Amn-Gen- Van: 1, 100%  Carola-Cola-Tig-Gen-Dex: 1, 100%  Cola-Cipro-Van-Dex: 1, 100%  Cola-Amk-Van-Car: 1, 100%</td>
</tr>
<tr>
<td>Capone 2013(11)</td>
<td>MC prospective cohort; 2010-2011, Italy</td>
<td>Italy</td>
<td>2010-2011</td>
<td>Inpatients, 44.8%, ICU-patients, DM, COPD, chronic kidney or liver disease, malignancy</td>
<td>BSI (37.4%), UTI (31.9%), septic shock (16.5%), LRTI (13.4%), SSTI (5.2%), SA (3.3%)</td>
<td>67 appropriate antibiotic treatment (known abx in 58)</td>
<td>Carbenem-resistant <em>K. pneumoniae</em>  EUCAST, NR</td>
<td>In-hospital</td>
<td>Cola-Tig: 16, 23%  Tig-Fos: 6, 33%  Cola-Fos: 5, 0%  Cola-Gem: 3, 40%  Gem: 16, 6.3%  Cola: 10, 40%</td>
</tr>
<tr>
<td>Huang 2012(13)</td>
<td>SC prospective cohort; 2010-2011, Taiwan</td>
<td>Taiwan</td>
<td>Undetermined</td>
<td>NR</td>
<td>Undetermined</td>
<td>33</td>
<td>Carbenem-resistant <em>K. pneumoniae</em>  CLSI, 2009</td>
<td>30-day</td>
<td>NR  Tig: 15, 73%  Carba: 14, 50%  Cola: 4, 50%</td>
</tr>
<tr>
<td>Trevino 2011(24)</td>
<td>SC prospective</td>
<td>Taiwan</td>
<td>2010-2011</td>
<td>Pts submitted to surgery and/or Miscellaneous infections</td>
<td>10</td>
<td>Carbenem-resistant Klebsiella</td>
<td>CLSI, 2010</td>
<td>Undetermined</td>
<td>Amk-Carba: 4, 50%  Tig-Ampk: 2%  Cipro: 1, 0%  Ampk: 1, 0%</td>
</tr>
<tr>
<td>Country</td>
<td>Type of Study</td>
<td>Year</td>
<td>Patient Characteristics</td>
<td>Outcomes</td>
<td>Antimicrobial Susceptibility</td>
<td>Abbreviations</td>
<td></td>
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<tr>
<td>Spain</td>
<td>Prospective</td>
<td>2010</td>
<td>2009-2010, ICU-patients, DM, COPD</td>
<td>Bacteremia</td>
<td>Carbapenem-resistant K. pneumoniae, CLSI, NR</td>
<td>30-day PoB: 9; 44%, Tige: 10; 70%</td>
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<tr>
<td>Greece</td>
<td>Prospective</td>
<td>2010</td>
<td>ICU-patients, DM, COPD</td>
<td>Hospital-acquired infections</td>
<td>NR (≤ 8 mm) or zone inhibition ≥ 16 mm</td>
<td>30-day PoB: 9; 44%, Tige: 10; 70%</td>
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<tr>
<td>USA</td>
<td>Retrospective</td>
<td>2010</td>
<td>2004-2008, ICU-patients, DM, COPD</td>
<td>Bacteremia</td>
<td>Carbapenem-resistant K. pneumoniae, CLSI, NR</td>
<td>30-day PoB: 9; 44%, Tige: 10; 70%</td>
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</tr>
<tr>
<td>Taiwan</td>
<td>Retrospective</td>
<td>2013</td>
<td>2013, ICU-patients, DM, COPD</td>
<td>Bacteremia</td>
<td>Carbapenem-resistant K. pneumoniae, CLSI, NR</td>
<td>30-day PoB: 9; 44%, Tige: 10; 70%</td>
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</tbody>
</table>

**Abbreviations:**
- CRE: carbapenem-resistant Enterobacteriaceae
- KPC: Klebsiella pneumoniae carbapenemase
- SC: single-center
- MC: multi-center
- CLSI: Clinical and Laboratory Standards Institute
- EUCAST: European Committee on Antimicrobial Susceptibility Testing
- FDA: Food and Drug Administration
- BSAC: British Society for Antimicrobial Chemotherapy
- DM: diabetes mellitus
- COPD: chronic obstructive pulmonary disease
- BSI: bloodstream infection
In this study, certain patients had > 1 site of infection.

The susceptibility breakpoint for tigecycline according to FDA was \( \leq 2 \) \( \mu \)g/ml.

In this study, 3 patients were excluded because it was unclear whether the antibiotic treatment was combination or monotherapy.

Two patients received the combination tigecycline-amikacin; the one was cured but the final outcome of the other was unknown at the time of the follow-up. One patient received the combination fosfomycin-amikacin but the final outcome was also unknown at the time of the follow-up.

In these studies, it was unclear whether those treatment regimens were combination or monotherapy.

The susceptibility breakpoints for CLSI and EUCAST used in the included studies are the following:

**CLSI 2004**: Carba \( \leq 4 \\
Gen \( \leq 4 \\
Cipro \leq 1 \\
Dox \leq 4 \\
Lvf \leq 4 \\
A/S \leq 8/4 \\
Azt \leq 4 \\
Cfpm \leq 8 \\
Tbz \leq 4 \\
Tzp \leq 1/2 \\
Lzd \leq 4 \\
Amx \leq 8 \\
Rifa \leq 4 \\
Llvf \leq 2 \\
Ntf \leq 16 \\
Erta \leq 0.25 \\
Amk \leq 16 \\
Cipm \leq 16 \\
Tig \leq 4 \\
Dox \leq 4 \\
Amp \leq 16 \\
Ampc \leq 4 \\
Ampc/4 \leq 2 \\
Ampc/8 \leq 1 \\
Ampc/16 \leq 1 \\
Ampc/32 \leq 0.25 \\
Ampc/128 \leq 0.5 \\
Ampc/256 \leq 1 \\
Ampc/512 \leq 1 \\
Ampc/1024 \leq 1 \\
Ampc/2048 \leq 1
Table 2. Treatment failure of infections caused by carbapenemase-producing Enterobacteriaceae among different antibiotic treatment regimens

<table>
<thead>
<tr>
<th>First author</th>
<th>Study design; period, country</th>
<th>Population characteristics; most common underlying diseases</th>
<th>Site of infection of the total population</th>
<th>Infected patients who received definitive treatment</th>
<th>Causative pathogen(s)</th>
<th>Susceptibility breakpoints used, year</th>
<th>Antimicrobial treatment administered (n); treatment failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rihani 2012(20)</td>
<td>SC retrospective cohort, 2008-2009, USA</td>
<td>77% ICU at enrollment</td>
<td>Blood, RTI, tissue/ward/drainage, UTI</td>
<td>22</td>
<td>Carbapenemase-producing Enterobacteriaceae (K. pneumoniae, E. coli, Enterobacter spp.)</td>
<td>CLSI, 2010</td>
<td>Gm: Coli: 4, Carba: 4, Carba-Tige: 2, Coli-Rifa: 2, Tige-Amk-Cfpm: 2, Coli-Carba-Tige-Amk: 2, Total: 17%</td>
</tr>
<tr>
<td>Maltezou 2009(14)</td>
<td>SC retrospective cohort, 2007-2008, Greece</td>
<td>76.2% ICU-patients; DM, COPD, cardiovascular disease</td>
<td>Pneumonia (64.9%), SSI (34%), bacteremia (4.8%), UTI (4.8%), peritonitis (4.8%)</td>
<td>19</td>
<td>KPC-producing K. pneumoniae</td>
<td>CLSI, 2007</td>
<td>Gm: Tige-Tig: 3; Coli-Tige-Tig: Gen: 0; Coli-Tige-Gen: 3; Coli-Gen: 3; Gen: 0; Unknown treatment: 6; 33%</td>
</tr>
</tbody>
</table>

Abbreviations:

* In this study, certain patients had > 1 site of infection.

† The susceptibility breakpoint for tigecycline according to FDA was ≤ 2 µg/ml.

‡ In this study, 3 patients were excluded because it was unclear whether the antibiotic treatment was combination or monotherapy.
Two patients had both pneumonia and catheter-associated bacteremia.

The antibiotic treatment was unclear for six patients in this study; however, they did not receive either colistin in combination with gentamicin nor colistin monotherapy.

The susceptibility breakpoint for colistin according to BSAC was ≤ 4 µg/mL.

Two patients received the combination tigecycline-amikacin; the one was cured but the final outcome of the other was unknown at the time of the follow-up. One patient received the combination fosfomycin-amikacin but the final outcome was also unknown at the time of the follow-up.

In these studies, it was unclear whether those treatment regimens were combination or monotherapy.

The susceptibility breakpoints for CLSI and EUCAST used in the included studies are the following:

CLSI 2004: Carba≤ 4

CLSI 2006: Gen≤ 4, Cipro≤ 1, Doc≤ 4, Net≤ 32, Amx≤ 8, Taz≤ 16/4

CLSI 2007: Gen≤ 4

CLSI 2009: Carba≤ 4, Gen≤ 4, Cipro≤ 1, Amx≤ 16, Taz≤ 16/4

CLSI 2010: Carba≤ 4, Gen≤ 4, Cipro≤ 1, Lev≤ 2, Aza≤ 4, Gen≤ 8, Taz≤ 8, Tob≤ 4

CLSI 2011: Carba≤ 4, Erta≤ 0.25, Gen≤ 4, Amx≤ 16, A/Sc≤ 8/4, Aza≤ 4, Taz≤ 16/4

CLSI 2012: Carba≤ 1, Amk≤ 16

EUCAST 2009: Coli≤ 2, Erec≤ 12

EUCAST 2010: Coli≤ 2

EUCAST 2011: Taz≤ 1

EUCAST 2012: Aza≤ 4

EUCAST 2013: Aza≤ 4, Tob≤ 4, Taz≤ 4, A/Sc≤ 8/4, Erta≤ 0.25, Amk≤ 16, Aza≤ 4, Tob≤ 4, Taz≤ 16/4

EUCAST 2014: Coli≤ 2, Erec≤ 12

EUCAST 2015: Coli≤ 2, Erec≤ 12

EUCAST 2016: Coli≤ 2, Erec≤ 12

EUCAST 2017: Coli≤ 2, Erec≤ 12

EUCAST 2018: Coli≤ 2

EUCAST 2019: Coli≤ 2

EUCAST 2020: Coli≤ 2