Carbapenem-Sparing Antibiotic Regimens for Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae* in Intensive Care Unit

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A carbapenem-sparing regimen of tigecycline plus gentamicin or colistin was effective for treating 24 of 26 (92%) *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* infectious episodes in 22 polytrauma intensive care unit patients without comorbidities. The 30-day crude mortality rate was 14%. Regimens were considered appropriate in 12% of episodes according to the Vitek 2 System and in 100% based on E-test.

Keywords. KPC-producing *Klebsiella pneumoniae*; intensive care unit; outcome.

Klebsiella pneumoniae carbapenemase–producing *K. pneumoniae* (KPC-Kp) is an emerging pathogen representing an alarming clinical threat especially in intensive care units (ICUs) [1]. KPC-Kp isolates are usually resistant to several classes of antibiotics including carbapenems [2]. Therapeutic options for KPC-Kp are limited to colistin, tigecycline, gentamicin, less frequently amikacin, and fosfomycin used in various combinations with a carbapenem. However, evidence supporting which antibiotics to use and the optimal combination regimen for the treatment of KPC-Kp infections is still limited [2, 3]. Qureshi et al [4] and Tumbarello et al [5] recently suggested that carbapenem-containing combination regimens might be superior compared with noncarbapenem-containing combinations. However, these reports focused on bacteremia and included a patient population not exclusively cared for in ICU.

The necessity of including a carbapenem in the treatment regimen for KPC-Kp infections is questionable for several reasons. First, carbapenem minimum inhibitory concentrations (MICs) for many KPC-Kp isolates are sufficiently high (usually >32 mg/L) such that even high-dose, pharmacodynamically optimized regimens are still unlikely to be effective. Second, there are limited data to suggest that carbapenems are consistently synergistic with other antibiotics (colistin, gentamicin, etc) against KPC-Kp isolates. Finally, antibiotic selective pressure associated with carbapenem use may contribute to the persistence of KPC-Kp in the colonized patients, having a detrimental effect on the individual patient as well as the hospital epidemiology [1, 6].

In this study, we examined the effectiveness of carbapenem-sparing combination regimens for treating KPC-Kp infections in ICU patients who are in otherwise good health, that is, mainly polytrauma subjects without other substantial comorbidities or immunosuppression.

METHODS

This retrospective study was conducted in a 10-bed ICU at a regional referral center for trauma patients. During the period April 2011–March 2012, consecutive, unselected patients with KPC-Kp infection were evaluated. All patients were followed until 30 days after hospital discharge. Validated Centers for Disease Control and Prevention/National Healthcare Safety Network diagnostic criteria were used for infection [7] and sepsis definitions [8].

Tigecycline was used in 25 of 26 KPC-Kp infections as backbone drug (intravenous 100 mg every 12 hours) [9]. Antibiotics administered in combination included (1) gentamicin in 19 of 26 KPC-Kp episodes (intravenous 5–7 mg/kg daily) or (2) colistin methanesulfonate in 12 of 26 KPC-Kp episodes (intravenous 4.5 million IU every 12 hours). Fosfomycin was used as a third drug in 13 of 26 infectious episodes (intravenous 3 g every 8 hours). Antibiotic regimens were selected primarily on the basis of specific patient clinical risk factors, site of infection, and MIC results assessed by the attending physicians.

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Antibiotic therapy was considered appropriate if the isolate was susceptible in vitro (Vitek 2 or E-test) to at least 1 of the drugs started within 24 hours of clinical diagnosis of infection.

A favorable response to therapy was considered for any patient receiving the initial antibiotic regimen for at least 5 days who demonstrated (1) resolution of sepsis/severe sepsis or septic shock; (2) improvement of PaO_2/FiO_2 ratio (≥240) in the setting of ventilator-associated pneumonia (VAP); (3) 2 consecutive negative blood cultures in the setting of bloodstream infection (BSI); and (4) a negative urine culture in the setting of urinary tract infection (UTI). Survival 30 days after hospital discharge was also analyzed.

Suspected isolates were confirmed as KPC-Kp using a direct phenotypic screening method with phenylboronic acid. MICs were determined using an automated broth microdilution system (Vitek *2* System, running expert rules version 5.04) and reported as preliminary results to clinicians. E-test (AB-Biodisk) strips were used to confirm MICs for colistin, imipenem, meropenem, gentamicin, fosfomycin, and tigecycline. Results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints, version 2.0 [10]. Additionally, multilocus sequence typing was performed on 13 of 26 isolates. Microbiology laboratories underwent to accreditation procedures and receive frequent quality control checks for MIC testing and KPC-Kp detection by the Tuscany Regional Health System.

RESULTS

Overall, 26 infectious episodes due to KPC-Kp were documented in 22 patients (20 male, 2 female; mean age 51 ± 16 years) during the study period. Multilocus sequence typing identified 12 of 13 isolates as sequence type 512. Most patients (18 of 22) were admitted to the ICU for polytrauma. All patients required mechanical ventilation at admission, and no patient suffered from major underlying comorbidities. The mean Sequential Organ Failure Assessment score was 9 (SD, 3) and the mean Simplified Acute Physiology Score II was 50 (SD, 15).

Among the 26 infectious episodes, VAP was documented in 16 patients (5 with BSI); BSI was documented in 7 patients (5 catheter-related); UTI was documented in 2 patients; and peritonitis was documented in 1 patient. Sepsis was documented in 1 episode, severe sepsis in 22 episodes, and septic shock in 3 episodes of KPC-Kp infection.

Postantibiogram antibiotic regimens were tigecycline and gentamicin (13 episodes, with fosfomycin in 8 cases), tigecycline and colistin (11 episodes, with gentamicin in 5 cases and with fosfomycin in 5 cases). Other treatment regimens consisted of colistin plus gentamicin (1 case) and tigecycline alone (1 case). The length of postantibiogram antibiotic therapy ranged 12–16 days.

Response to Therapy

Overall, a favorable response to therapy was documented for 24 of 26 (92%) infectious episodes (Table 1). Two deaths due to KPC-Kp infection were observed during the study period—1 patient died with bacteremic VAP, the other patient died with urosepsis and septic shock. A third death unrelated to previous KPC-Kp bacteremic VAP occurred in a patient with severe head trauma. Treatment responses to the carbapenem-sparing combinations were similar for patients with bacteremic vs nonbacteremic VAP, as well as for patients with central venous catheter (CVC)–related vs non-CVC-related bacteremia.

MIC test results reported by the Vitek 2 system showed that 24 of 26 strains (92%) were resistant to colistin (MIC >2 mg/L), tigecycline (MIC >1 mg/L), and gentamicin (MIC >2 mg/L). Meropenem MICs were >16 mg/L in 25 of 26 isolates (96%). Susceptibility testing by E-test showed resistance to colistin in 67% of cases, tigecycline in 27% of cases, gentamicin

Table 1. Site of Infection and Response to Therapy

Site of Infection	No. of Infections			
	Appropriate Therapy by Vitek 2 System[a]	Appropriate Therapy by E-test[a]	Response to Therapy	Survival at 30 Days After Discharge
VAP	1/11	11/11	11/11	11/11
VAP with bacteremia	0/5	5/5	4/5	3/5[c]
Bloodstream infection	1/7	7/7	7/7	7/7
Others[b]	1/3	3/3	2/3	2/3[d]

Abbreviations: KPC-Kp, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*; VAP, ventilator-associated pneumonia.

[a] Strain susceptible to at least 1 antibiotic in use.

[b] Two cases of urinary tract infection and 1 case of peritonitis.

[c] One patient died due to KPC-Kp infection and the other died due to severe head injury report in the polytrauma unit after being successfully treated for bacteremic VAP.

[d] Died due to KPC-Kp urinary tract infection and septic shock.

in 20% of cases, and fosfomycin in 13% of cases. Antibiotic therapy was considered appropriate in only 3 of 26 (12%) infectious episodes according to the Vitek 2 system but in 100% of cases by E-test.

Reversible renal toxicity was observed in only 1 patient with urinary tract infection and severe sepsis who received gentamicin plus colistin.

DISCUSSION

In our ICU patient population with severe KPC-Kp infections, we observed a favorable outcome with antibiotic regimens including tigecycline combined with gentamicin or colistin and sometimes fosfomycin. Carbapenems were never employed as part of a combination regimen.

We observed much higher clinical response rates to combination therapy for KPC-Kp infections and lower 30-day crude mortality rates compared with previous reports. Specifically, the survival rate in our study (23/26 [88%]) was approximately 20% higher than previously reported response rates of 60%–70% [3–5]. A possible explanation may be in the differences between the case mix of patient populations studied, namely, younger patients without major comorbidities.

Notably, both Qureshi et al and Tumbarello et al [4, 5] reported that septic shock at KPC-Kp bloodstream infection onset was an important predictor of patient death. In our case series, septic shock was documented in only a few episodes (3/26).

Inadequate initial antimicrobial therapy, although not confirmed by all authors [3, 6], was also associated with increased mortality in their studies [4, 5]. In our study cohort, the high clinical response rates, irrespective of the high percentage of isolates with resistance to prescribed agents based on Vitek 2 System MICs, would not appear to be a major factor driving mortality.

Our experience is consistent with that of Zarkoutou et al and Patel et al [3, 6], in that the Vitek 2 System test results of the KPC-Kp isolates revealed that postantibiogram therapy was inadequate in the vast majority of infections (23 of 26). The more favorable E-test results suggest that resistance may be overestimated by automated methods. Therefore, automated MIC results should, at minimum, be confirmed by secondary methods such as E-test before the antibiogram is considered finalized.

Several authors have suggested that carbapenem-containing combination regimens are associated with the highest clinical response rates for KPC-Kp bacteremia [4, 5]. The efficacy of carbapenems for KPC-Kp is somewhat unexpected because these agents are hydrolyzed by KPCs. Meropenem MICs for a majority of KPC-Kp strains exceed >32 mg/L, which is well above pharmacokinetic/pharmacodynamic (PK/PD) drug exposure that can be reliably achieved even with high-dose, extended infusion therapy. Another possibility is that meropenem activity is "restored" in the presence of other antibiotics through synergistic interactions; however, this has not been consistently documented in vitro [11].

A carbapenem-sparing regimen may have some advantage in terms of decreasing selective pressure on the gut microflora of ICU patients (KPC-Kp gut persistent colonization). However, effective use of carbapenem-sparing combination regimens for KPC-Kp infection likely requires the use of high antibiotic doses to overcome some of the pharmacokinetic limitations of these agents. For example, we used tigecycline in a higher dose than recommended in package labeling (100 mg twice daily) [9] and colistin was administered at 9 million IU/day based on recent dosing recommendations for improving the PK/PD profile [12].

In conclusion, our observational study, with the limitation of small number of patients, suggests that tigecycline combined with colistin or gentamicin with the possible addition of a third drug (ie, fosfomycin), administered as high-dose regimens, may be adequate for the treatment of KPC-Kp infections in selected patients. Results of antibiotic susceptibility testing may vary according to the methods used, and this might influence the choice of appropriate therapy.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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