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Clinical outcomes of patients with KPC-producing *Klebsiella pneumoniae* following treatment with imipenem or meropenem

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Abstract

KPC-producing *Klebsiella pneumoniae* may appear susceptible to imipenem or meropenem by routine susceptibility testing. We report a series of patients with infectious caused by *K. pneumoniae* isolates that yielded imipenem-susceptible results but were subsequently KPC-positive by PCR. When these infections were treated with imipenem or meropenem, frequent clinical and microbiological failures were observed.

Klebsiella pneumoniae carbapenemases (KPCs) were first described in a *K. pneumoniae* strain from North Carolina in 2001 (Yigit et al., 2001). Since then, KPCs have been described in *K. pneumoniae* from New York, Virginia, Arkansas, and elsewhere (Deshpande et al., 2006). Several related KPC enzymes have been described (Wolter et al., 2008). KPC-producing *K. pneumoniae*—herein referred to as KPC *K. pneumoniae*—is epidemic in New York City, where 38% of the *K. pneumoniae* isolated from Brooklyn hospitals in 2006 contained a gene encoding KPC-2 (Landman et al., 2007). Of particular concern, standard methods for determining antibiotic resistance may report *K. pneumoniae* containing KPC as susceptible to imipenem or meropenem (Espinal-Witter et al., 2007), although the clinical efficacy of these carbapenems in treatment of KPC *K. pneumoniae*-infected patients is unknown.

To study the clinical and microbiological outcomes of infections caused by KPC *K. pneumoniae* and compare outcomes of infections with isolates initially reported as susceptible to imipenem or meropenem, we performed a historical cohort of KPC K. pneumoniae isolated in our hospital over a one year period. For purposes of this study, “initial test susceptible” KPC isolates are those that appeared susceptible on initial automated VITEK 2 testing against imipenem, and “initial test nonsusceptible” KPC isolates are those reported as intermediate or resistant on initial automated testing (susceptibility to meropenem was not routinely tested).

A convenience sample of *K. pneumoniae* isolates obtained during 2006 at Weill Cornell Center, NewYork-Presbyterian Hospital were identified as containing KPC by a combination of ertapenem resistant results from our routine laboratory test system (Vitek 2; bioMerieux, Durham, NC) and confirmation of KPC using polymerase chain reaction (Espinal-Witter et al.

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2007). After Institutional Review Board approval, medical records of patients infected with KPC *K. pneumoniae* were reviewed. Success or failure of treatment was determined by clinical response and/or subsequent culture results. Two physicians independently reviewed charts on all patients.

Thirty-three KPC-2 *K. pneumoniae* isolates were identified. Of the 33 patients with KPC *K. pneumoniae*, 18 were male and 15 female. Age ranged from infancy to 92 years old (median 64). Five of the 33 were outpatients for which complete records were not available, and these patients were excluded from further analysis. Of the remaining 28 inpatients with a positive KPC *K. pneumoniae* culture, 14 (50%) had been hospitalized for at least three weeks at the time of culture. Most had received multiple antibiotic courses in the weeks before isolation of the KPC *K. pneumoniae*: 18 (64.3%) had recently been treated with a beta-lactam antibiotic, 15 (53.6%) had received a glycopeptide antibiotic and 10 (35.7%) had received a fluoroquinolone antibiotic. Only 6 (21.4%) had received a carbapenem antibiotic.

Of the 28 KPC *K. pneumoniae* cultured from inpatients, 13 (46.4%) were originally reported as imipenem susceptible and only later found to contain KPC. All isolates were found to be ertapenem-resistant by Vitek 2. Two of these 13 cultures were judged to represent colonization. Nine (81.8%) of the remaining 11 patients with in vitro initial test susceptible KPC *K. pneumoniae* infection were treated with imipenem or meropenem. Of these nine carbapenem-treated patients, 4 (44.4%) had successful outcomes and 5 (55.6%) experienced clinical or microbiological failure (see Table I for antibiotic course and infection type). Of the successful cases, imipenem was used for pneumonia, urosepsis/urinary tract infection, and device related bacteremia (with device removal). Imipenem is controlled in our institution and standard intermittent dosing was done based on creatinine clearance and reviewed by a pharmacist. Failures in imipenem or meropenem-treated patients included microbiological failure in three cases of tracheobronchitis, as well as cases of pneumonia with bacteremia, and urinary tract infection. One of the patients with tracheobronchitis also had the *K. pneumoniae* isolated from a blood culture while on treatment. All cases of tracheobronchitis were felt to be clinically significant by the treating physicians and upon review. Two of the patients with carbapenem-initial test-susceptible isolates were treated with tigecycline with one success and one failure.

Fifteen (53.6%) of the 28 hospitalized patients had cultures with KPC-2 *K. pneumoniae* initially reported as imipenem nonsusceptible (intermediate or resistant on automated testing). Four of these 15 patients were colonized, and one was not treated as he was on comfort measures only. The remaining 10 patients were treated with a variety of antibiotic regimens (see Table 1). Eight (80%) were successfully treated and 2 (20.0%) failed therapy (80% success rate). The rate of treatment success was not significantly different between groups (80.0% vs. 44.4%, $p = 0.17$, two tailed Fisher's Exact Test). APACHE II scores were calculated for patients older than age 15, with the limitation that some were non-ICU patients, and the score was from the day of culture. Apache II scores were not significantly different between groups (21.1 vs. 21.1, $p = 0.99$, 2-sided Students t-test).

These results add to the limited literature on the clinical consequences of KPC *K. pneumoniae* infections. Mortality rates in patients infected with KPC *K. pneumoniae* have been reported between 47-57% (Bratu et al., 2005; Woodford et al., 2004). In one series, death occurred in 6 of 9 patients who only received inactive antibiotics (Bratu et al., 2005). There are few reports on the outcomes of patients with KPC *K. pneumoniae* infections treated with carbapenems. A patient with a meropenem susceptible KPC-2 *K. pneumoniae* experienced recurrent bacteremia after two days of meropenem and seven subsequent days of ertapenem. The isolate was later confirmed to be ertapenem resistant by Etest (Lomaestro et al. 2006). Successful treatment of KPC *K. pneumoniae* infections in 3 patients using a carbapenem

combined with piperacillin-tazobactam, polymyxin, or amikacin has been reported (Bradford et al., 2004).

We found that our patients infected with a KPC *K. pneumoniae* initially determined to be imipenem-nonsusceptible had a higher rate of successful treatment when compared with patients infected with a KPC *K. pneumoniae* with initial test-susceptible test results, although due to the small sample size the difference did not reach statistical significance. Most of the patients with imipenem initial test -susceptible isolates were treated with imipenem or meropenem and over half experienced clinical or microbiological failure after treatment with a carbapenem alone. Several of the carbapenem failures were in cases of tracheobronchitis. Although these appeared clinically significant upon retrospective review by the treating physicians, residual colonization was difficult to exclude. Conversely, clinical and microbiological successes with carbapenems were noted in several patients, but the degree to which the carbapenem treatment contributed to these outcomes is difficult to ascertain. Tigecycline was used successfully in 5 of 7 KPC-positive patients.

The optimal treatment of KPC-producing *K. pneumoniae* remains uncertain, but proper *in vitro* susceptibility testing appears to best predict clinical outcome (Bratu et al., 2005). Caution should be exercised prior to using carbapenems against susceptible appearing KPC-containing *K. pneumoniae*. Continuous administration of carbapenems has the potential to be more effective than standard dosing in the treatment of KPC *K. pneumoniae* (Sakka et al., 2007). In our laboratory we have found ertapenem resistance by Vitek 2 to be an effective screening tool for the presence of a KPC (Espinal-Witter et al., 2007). Clinicians need to be aware of the importance of laboratory screening for KPC *K. pneumoniae* using ertapenem susceptibility or other methods to avoid potentially inappropriate antibiotic selection.

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Table 1

Characteristics of inpatients with treated KPC *K. pneumoniae* infections. The first 11 isolates yielded imipenem-susceptible results by Vitek 2 testing (MIC ≤ 4); the remainder of isolates yielded imipenem-resistant results on routine testing.

Age/sex	Underlying Condition	Acute illness (tested isolate site)	Apache II	MIC (Vitek/Etest)	Treatment (days)	Response
46/F	Skin graft	Bacterermia (blood)	6	4 / 8	imipenem (7); port removal	Microbiologic and Clinical Success
61/F	CHF	Pyelonephritis (urine)	21	2 / ≥ 32	imipenem (7)	Microbiologic and Clinical Success
82/M	None	Urosepsis (blood)	25	4 / 2	imipenem (14)	Microbiologic and Clinical Success
92/M	Dementia	Pneumonia (resp)	12	4 / 2	imipenem (3)	Clinical Success
64/F	Esophageal Cancer	Tracheobronchitis (resp)	15	4 / 2	imipenem (12)	Microbiologic Failure
76/M	Cerebral hemorrhage	Tracheobronchitis (resp)	21	2 / 0.25	meropenem (7)	Clinical and Microbiologic Failure
69/F	Metastatic Cancer	Pneumonia (resp)	36	4 / 8	imipenem (6)	Clinical Failure/Death
77/M	MRSA l abscess	Tracheobronchitis (resp)	23	4 / ≥ 32	imipenem (7)	Microbiologic Failure
52/M	Melanoma	UTI (urine)	37	4 / 12	imipenem (14)	Microbiologic Failure
67/M	Polyneuropathy	Urosepsis (blood)	21	4 / ≥ 32	tigecycline (7)	Clinical and Microbiologic Failure
65/M	Lung Mass	Tracheobronchitis (resp)	15	4 / 1	tigecycline (7)	Clinical and Microbiologic Success
83/F	Laryngeal Cancer	Pneumonia (blood)	14	≥ 16 / ≥ 32	tigecycline (7)	Clinical Success
39/F	Stem cell transplant	Urosepsis (urine)	12	8 / 8	Tigecycline (14)	Clinical Success
79/M	None	Pneumonia (resp)	27	8 / 32	Tigecycline (14)	Clinical Success
19/M	Trauma, craniotomy	Shunt associated Meningitis (CSF)	28	N/A	tigecycline/gentamicin*	Clinical and microbiological success
79/F	s/p CABG	Bacteremia (blood)	29	8 / 2	tigecycline/imipenem	Clinical Failure/Death
0/M	Seizures	Pneumonia (resp)	n/a	≥ 16 / ≥ 32	gentamicin (7)	Clinical Success
60/F	Metastatic Cancer	Wound (wound)	25	8 / ≥ 32	Amikacin (7)	Clinical Success
59/F	ESRD	Line infection (blood)	22	≥ 16 / ≥ 32	Gentamicin (10)	Clinical and Microbiologic Success
60/F	Pelvic Infection	Bacteremia (blood)	24	≥ 16 / 8	Meropenem (10)	Clinical and Microbiologic Failure
50/M	Liver Transplant	Bacteremia	9	≥ 16 / 8	Meropenem (7)	Clinical and Microbiologic Success

All imipenem treatments given as standard intermittent dosing based on CrCl; All tigecycline treatments given as 100 mg loading dose, followed by 50 mg IV every 12 hours.

* gentamicin administered intrathecally and intravenous

Apache II=Apache II Score (at time of infection)

MICs (minimum inhibitory concentrations) are represented as Vitek 2 and Etest results for imipenem—both are in mcg/ml;

Resp = respiratory, CSF = cerebrospinal fluid, M=Male, F=Female