Infection with Panresistant *Klebsiella pneumoniae*: A Report of 2 Cases and a Brief Review of the Literature

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Infections caused by carbapenemase-producing *Klebsiella pneumoniae* have been reported with increasing frequency, thereby limiting the choice of effective antimicrobial agents available to clinicians. This has prompted the increased use of polymyxins and tigecycline, but resistance to these agents is already emerging. We report 2 cases of infection with pan-resistant *K. pneumoniae*.

Nosocomial infections with resistant gram-negative organisms, particularly strains of *Klebsiella pneumoniae*, have become a significant problem at a time when there is a lack of promising new antimicrobial agents on the horizon [1, 2]. In response to the prevalence of extended-spectrum β-lactamases, carbapenem use increased, and carbapenem resistance soon followed. In 2001, Yigit et al. [3] reported a novel β-lactamase termed “K. pneumoniae carbapenemase” (KPC-1) in North Carolina. Soon after, strains of KPC-producing *Klebsiella* species were reported in New York City and then upstate New York [4–6]. We report 2 cases of infection with highly resistant, KPC-producing *K. pneumoniae* at a tertiary care hospital in New York City. The isolates were resistant to all antibiotic agents tested, including the carbapenems, polymyxin B, and tigecycline. To our knowledge, there have been no previously reported cases of infection due to panresistant *K. pneumoniae* in the United States.

**Case report 1.** In July 2007, a 70-year-old woman was admitted to the hospital with a urinary tract infection. She was residing in a nursing home after a recent hospitalization for pneumonia due to KPC-producing *K. pneumoniae* treated with tigecycline and polymyxin B. An indwelling bladder catheter had been placed at the nursing facility. During admission to the hospital, she reporting having dysuria and suprapubic pain for 2 days. A urinalysis revealed nitrites and a white blood cell count >100 cells per high-power field. Her examination was notable for a temperature of 37.4°C and suprapubic tenderness. A urine culture showed >100,000 colony-forming units (cfu) per mL of a highly resistant, KPC-producing *K. pneumoniae* strain. The minimum inhibitory concentration (MIC) was 4 μg/mL for tigecycline and 96 μg/mL for polymyxin B. The patient’s catheter was removed, and she began treatment with tigecycline and rifampin. She developed a rash, and the rifampin was discontinued. Her urinalysis results remained unchanged, and her urine culture again showed the presence of >100,000 cfu/mL of *K. pneumoniae*, which now had an MIC >8 μg/mL for tigecycline. Tigecycline was discontinued after 10 days of treatment, and the patient was discharged to home with persistent dysuria. She subsequently had spontaneous resolution of symptoms, although the last available urine culture specimen, obtained >1 year later, continued to show >100,000 cfu/mL of the panresistant *K. pneumoniae*.

**Case report 2.** In March 2008, a 67-year-old man underwent a Whipple procedure at another hospital. Postoperatively, he developed a hepatic abscess. *Enterobacter cloacae* and *K. pneumoniae* grew from cultures of samples from the liver abscess. Both organisms were resistant to carbapenem but susceptible to polymyxin B and tigecycline. He was given treatment with tigecycline and empirical treatment with daptomycin and caspofungin. The patient’s postoperative course was prolonged and complicated by multiple organ system dysfunction.

In May 2008, the patient was transferred to our institution. On the day of admission, the patient was febrile, with a temperature of 38.7°C. He arrived sedated and with mechanical ventilation via tracheostomy and an abdominal drain in place. The peripheral white blood cell count was 5.6 × 10^9 cells/mm^3 (neutrophil percentage, 77.1%), and the serum creatinine level was 4.2 mg/dL. Blood cultures of specimens obtained at admission showed no growth. Computed tomography of the abdomen and pelvis showed a large perihepatic abscess and a drain suboptimally positioned. On the basis of the prior culture results, daptomycin and caspofungin were discontinued from the treatment regimen, and polymyxin B was added to tigecycline. The abdominal drain was replaced, and culture specimens were sent to the laboratory.

On hospital day 5, the patient remained febrile and developed hypotension requiring vasopressor support. Cultures of samples from the hepatic abscess showed *E. cloacae*, *K. pneumoniae*, and *Enterococcus faecium*. Both the *K. pneumoniae* and the *E. cloacae* isolates were identified as producers of KPC by polymerase

Received 6 October 2008; accepted 5 March 2009; electronically published 15 June 2009.

Clinical Infectious Diseases 2009;49:271–4
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1058-4838/2009/4902-0017$15.00
DOI: 10.1086/600042
Table 1. Antimicrobial susceptibility patterns for *Klebsiella pneumoniae* isolates.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC value, µg/mL</th>
<th>Patient 1: urine specimen</th>
<th>Patient 2: blood specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≥64</td>
<td>≥64</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>≥32</td>
<td>≥32</td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td>≥64</td>
<td>≥64</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>≥64</td>
<td>≥64</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>32</td>
<td></td>
<td>≥16</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&gt;64</td>
<td>≥64</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≥4</td>
<td>≥4</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≥16</td>
<td>≥16</td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≥16</td>
<td>≥16</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-sulfa</td>
<td>&gt;320</td>
<td>≥320</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>256</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≥8</td>
<td>≥8</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>≥16</td>
<td>&gt;R&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>NA</td>
<td>≥8, R&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>≥8</td>
<td>≥8</td>
<td></td>
</tr>
<tr>
<td>Polymyxin B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4</td>
<td>≥16</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** All susceptibility testing, except for polymyxin B, was done using the Vitek 2 automated system (bioMérieux). MIC, minimum inhibitory concentration; NA, not available.

<sup>a</sup> Antimicrobial agents indicated with “R” instead of an MIC value were read as susceptible by the automated system, but findings were modified on the basis of polymerase chain reaction testing results indicating the presence of *K. pneumoniae* carbapenemase genes.

<sup>b</sup> Tested using Etest.

chain reaction (PCR) testing. The *K. pneumoniae* strain was resistant to all antibiotics tested, including tigecycline, and had an elevated MIC for polymyxin B. The *E. cloacae* strain was similarly resistant, with the exception of an intermediate result for tigecycline (MIC, 4 µg/mL). The patient was taken to the operating room for irrigation and debridement of infected material.

Postoperatively, the patient’s condition continued to deteriorate. Blood cultures of specimens collected on hospital day 8 grew a KPC-producing *K. pneumoniae* strain resistant to all tested antibiotics except polymyxin B (MIC, 0.75 µg/mL). Daily blood cultures continued to grow *K. pneumoniae*. On hospital day 12, blood cultures showed a *K. pneumoniae* strain with a MIC for polymyxin B of 12 µg/mL. Over the next few days, the patient’s condition worsened despite supportive care and continuation of treatment with tigecycline and polymyxin B. He developed worsening sepsis and shock. On hospital day 14, the patient died.

**Discussion.** Infection with KPC-producing *K. pneumoniae* has become prevalent in New York City. However, there have been no reports of KPC-producing *K. pneumoniae* isolates that are also resistant to polymyxin and tigecycline in the United States. There are published reports of highly resistant *K. pneumoniae* isolates in Greece with decreased susceptibility to the polymyxins, but these isolates were not tested for resistance to tigecycline [7–9]. We present our experience with these 2 patients to afford a glimpse of a future of potentially untreatable infections and to highlight some unique challenges in dealing with KPC-producing organisms.

We have termed these isolates “panresistant,” but because there is no generally accepted definition for this term, we present the antimicrobial susceptibility data for both isolates in table 1. The isolates were tested using a custom gram-negative card for the automated system Vitek 2 (bioMérieux) that included tigecycline. They were also tested for bla<sub>KPC</sub> genes by real-time PCR. Susceptibility to polymyxin B was determined using a commercially available Etest.

Clinicians need accurate susceptibility data to provide effective therapy. However, automated susceptibility systems may be unreliable for detection of carbapenem resistance [10, 11]. A review of several automated systems showed that they incorrectly labeled up to 87% of carbapenemase-producing *K. pneumoniae* isolates as susceptible to imipenem, as well as reporting varying susceptibilities for the same isolate from day to day [10]. Ertapenem resistance seems to be a marker for carbapenemase production when automated testing methods
are used [10, 11]. In our second patient, automated testing reported the MIC for imipenem as \( \leq 1 \mu g/mL \), but the MIC for ertapenem was elevated. PCR testing was used to confirm the presence of KPC genes. PCR testing for bla\(_{KPC} \) genes can be a useful method of confirming resistance to carbapenem in the United States, where metallo-\( \beta \)-lactamases are not a common mechanism of resistance. If resources are limited, an elevated MIC for ertapenem could be used as a screening method to determine which isolates need further testing [10, 11]. A phenotypic testing method, such as a carbapenem inactivation assay (Hodge test), can also be a reliable method of detecting carbapenemase-producing organisms for laboratories not equipped for PCR [10]. Clinicians must be aware of the testing methods at their institution and their possible limitations.

Currently, the therapeutic options for highly resistant, carbapenemase-producing organisms are limited. Polymyxin B and tigecycline both seem to have reliable efficacy, although this report suggests that resistance to them is emerging.

Susceptibility testing for tigecycline can be readily done using automated systems, and gram-negative cards containing tigecycline are commercially available. Testing can also be done using Etest, which has been shown to have relatively good agreement with broth microdilution methods and few major errors in results for \( K\). pneumoniae, although some questions have been raised regarding the reliability of the tigecycline Etest for other organisms [12].

Currently, the Vitek 2 system offers automated testing for polymyxin E (colistin) but not for polymyxin B. However, an Etest is available for polymyxin B. The Clinical and Laboratory Standards Institute (CLSI) provides limited guidance with regard to polymyxin B, leaving individual laboratories to determine appropriate methods and cutoffs. The CLSI document M100-S18 update does note that susceptibility testing for polymyxin B for Enterobacteriaceae and Acinetobacter species should be done by MIC methodologies [13]. These include broth microdilution or Etest. There is published evidence to suggest that disk-diffusion methods are unreliable and should be avoided [14]. CLSI, however, does not provide MIC cutoff values for Enterobacteriaceae. Some authors recommend using \( \geq 4 \mu g/mL \), which is the CLSI cutoff for Acinetobacter species [13, 14].

Perhaps the most important challenge in dealing with resistant gram-negative pathogens is the lack of new antibiotic agents. Prudent antimicrobial use becomes increasingly important as we are faced with a shrinking armamentarium of effective drugs. A recent review of polymyxin-resistant pathogens found that the only significant risk factor for polymyxin resistance was previous polymyxin use [15]. Both of our patients developed progressive increases in the MIC for polymyxin B while they were receiving therapy. This is worrisome, because polymyxin use has been steadily increasing in our institution because of the prevalence of carbapenem-resistant gram-negative organisms. In the face of resistance to the polymyxins and tigecycline, we are unaware of any effective alternative therapies for infection caused by carbapenemase-producing Enterobacteriaceae.

It is a rarity for a physician in the developed world to have a patient die of an overwhelming infection for which there are no therapeutic options. These cases were the first instance in our clinical experience in which we had no effective treatment to offer. Trends in urban hospitals are often the harbinger of the future. We share these cases to highlight some troubling issues that soon may be relevant to increasing numbers of physicians and patients across the United States.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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