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# Septic Shock Caused by *Klebsiella pneumoniae* Carbapenemase-Producing *Enterobacter gergoviae* in a Neutropenic Patient with Leukemia

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**We present the first reported infection caused by *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacter gergoviae*. The patient had leukemia and neutropenia and died of septic shock from KPC-producing *E. gergoviae* bacteremia. The emergence of KPCs in additional species of *Enterobacteriaceae* is alarming and may disproportionately affect patients with hematologic malignancies.**

## CASE REPORT

A 70-year-old man with refractory acute myeloid leukemia was hospitalized for a trial of an investigational chemotherapeutic agent, elacytarabine. Nine days after starting therapy, he developed fever, abdominal pain, and hypotension, in the setting of neutropenia, requiring admission to the intensive care unit (ICU). Abdominal computed tomography revealed findings consistent with typhlitis, and blood cultures grew *Enterobacter cloacae* that was susceptible to all tested agents, methicillin-susceptible *Staphylococcus aureus*, and *Clostridium septicum*. He was treated with intravenous vancomycin and piperacillin-tazobactam and showed clinical improvement and clearance of bacteremia.

Ten days after the initial bacteremia, he developed a second episode of fever and abdominal pain in the setting of continued neutropenia and was found to have a partial small bowel obstruction. He received 3 days of empirical meropenem, but this was changed to trimethoprim-sulfamethoxazole (TMP-SMX) after blood cultures grew *Stenotrophomonas maltophilia*. Fever and bacteremia resolved, but a bone marrow biopsy revealed refractory leukemia. Meropenem was restarted 1 week later because of new fever, but cultures from that day were negative.

On hospital day 30, 2 days after restarting meropenem, he developed acute dyspnea and abdominal pain without fever. On examination, he was in respiratory distress and was lethargic, tachycardic, hypotensive, and hypoxic. Breath sounds were diminished over the right lower lung field, and his abdomen was distended and tender. Laboratory testing revealed a white blood cell count of 100 cells/μl, platelet count of 8,000 cells/μl, and total bilirubin of 4.4 mg/dl. Chest and abdominal radiographs demonstrated a right-sided pleural effusion and a paucity of bowel gas.

He rapidly developed respiratory failure and required endotracheal intubation and mechanical ventilation. Vasopressors were initiated for persistent hypotension despite fluid resuscitation. His central venous catheter (CVC) was removed and a new CVC was inserted. Three sets of blood cultures were obtained, and linezolid, amikacin, and micafungin were added empirically to meropenem and TMP-SMX. All three sets of blood cultures flagged positive within 16 h for Gram-negative rods. He continued on meropenem, amikacin, and TMP-SMX but developed acute renal failure and worsening liver injury and remained ventilator dependent. Given his poor prognosis from refractory leukemia and multiorgan system failure, supportive measures were withdrawn. He died 4 days after his acute decompensation, on hospital day 34.

The Gram-negative rods were identified as meropenem-resistant *Enterobacter gergoviae*. The isolate was a mucoid lactose fermenter that was oxidase and indole negative. *Enterobacter gergoviae* was identified by a Vitek2 GN card (product no. 21341; bioMérieux, Durham, NC) at a 100% match and by API-20E (bioMérieux) at a 99.9% match. The isolate identity was confirmed in duplicate by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker Biotyper; Bruker Daltonics Inc., Billerica, MA) with a high log score of 2.315 on direct smear and by full-length 16S ribosomal DNA sequencing (1).

In addition to being meropenem resistant, the *E. gergoviae* bloodstream isolate was also resistant to piperacillin-tazobactam, aztreonam, cefepime, and trimethoprim-sulfamethoxazole. It was susceptible to levofloxacin, gentamicin, amikacin, and tigecycline. Although there are no Clinical and Laboratory Standards Institute breakpoints for polymyxin B and *Enterobacteriaceae*, the susceptible breakpoint of $<2$ μg/ml which is approved for *Pseudomonas aeruginosa* and *Acinetobacter* spp. was applied, and the isolate was reported to be susceptible to polymyxin B. Complete antimicrobial susceptibility testing results are shown in Table 1. The initial NucliSENS EasyQ *Klebsiella pneumoniae* carbapenemase (KPC) real-time nucleic acid sequence-based amplification (NASBA) assay indicated that this strain was positive for the KPC gene (NucliSENS EasyQ; bioMérieux). Further PCR and sequencing

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**TABLE 1** Antimicrobial susceptibility testing results for KPC-producing *Enterobacter gergoviae*

| Antimicrobial agent | MIC (μg/ml) | Interpretation[c] | Testing method[a] |
|---|---|---|---|
| Amikacin | ≤2 | S | Vitek2 |
| Aztreonam | ≥64 | R | Vitek2 |
| Cefepime | 48 | R | Etest |
| Cefotetan | ≥64 | R | Vitek2 |
| Ceftazidime | ≥64 | R | Vitek2 |
| Ceftriaxone | 32 | R | Vitek2 |
| Ertapenem | ≥8 | R | Vitek2 |
| Gentamicin | 4 | S | Vitek2 |
| Levofloxacin | 0.25 | S | Vitek2 |
| Meropenem | 16 | R | Sensititre |
| Piperacillin-tazobactam | ≥256 | R | Etest |
| Polymyxin B | <0.25 | S[b] | Sensititre |
| Tigecycline | 2 | S | Vitek2 |
| Tobramycin | 8 | I | Vitek2 |
| Trimethoprim-sulfamethoxazole | ≥320 | R | Vitek2 |

[a] Testing methodologies included a Vitek2 AST GN59 card (bioMérieux, Durham, NC), Etest (bioMérieux), and Sensititre broth microdilution panel GNX2F (Thermo Scientific TREK Diagnostic Systems, Inc., Cleveland, OH).
[b] Clinical and Laboratory Standards Institute interpretive criteria do not exist for the *Enterobacteriaceae* when testing polymyxin B. Therefore, the susceptible breakpoint of 2 μg/ml approved for *Pseudomonas aeruginosa* and *Acinetobacter* spp. was applied.
[c] S, susceptible; R, resistant. I, intermediate.

revealed that the isolate harbored genes encoding KPC-3 and TEM-1 but was negative for genes encoding other β-lactamases, including NDM, VIM, IMP, OXA-48, CTX-M, SHV, and AmpCs (2–4).

KPC is a plasmid-mediated Ambler class A carbapenemase that hydrolyzes carbapenems and all other β-lactam antimicrobial agents. KPC-producing *Enterobacteriaceae* (KPC-E) also typically possess genes that confer resistance to other antimicrobial classes used for Gram-negative infections. Thus, many KPC-E isolates test susceptible only to polymyxin and tigecycline (5). KPC was first reported in 2001 from an isolate from North Carolina (6). Over the past decade, KPC producers have spread throughout the United States and globally and have become the dominant mechanism of carbapenem resistance among *Enterobacteriaceae* (7). Although KPCs have most commonly been identified from *K. pneumoniae* isolates, they have also been reported in other *Enterobacteriaceae*, including *Escherichia coli* (8), *Klebsiella oxytoca* (9), *Serratia marcescens* (10), *Proteus mirabilis* (11), *Citrobacter freundii* (10), and *Salmonella enterica* subsp. *enterica* serovar Cubana (12). KPCs have also become increasingly common among isolates of *Enterobacter cloacae* and *Enterobacter aerogenes* (13). However, reports of KPC in other species of *Enterobacter* are sparse.

Although *Enterobacter* species are among the most common causes of Gram-negative health care-associated infections (14), *E. gergoviae* is an uncommon human pathogen. *E. gergoviae* was initially described in 1976 and is found in various environmental locations, including sewage, soil, and food (15). It has also been identified in spoiled cosmetic products (16). In a survey of 399 *Enterobacter* isolates causing bacteremia at 48 medical centers in the United States, Canada, and Latin America, only 2 (0.5%) were *E. gergoviae* (17). Published reports of infections caused by *E. gergoviae* include bacteremias in neonates and in a human immunodeficiency virus (HIV)-infected intravenous drug user (18, 19), lower respiratory tract infections in an infant and in a patient with metastatic lung cancer (20, 21), nosocomial urinary tract infections (15), osteomyelitis (22), and traumatic endophthalmitis (23). The majority of infected patients in these reports had compromised immune systems due to extremes of age, HIV infection, or malignancy.

*Enterobacter gergoviae* isolates are typically resistant to penicillin and oxacillin and are often resistant to cefoxitin. However, they produce lower levels of β-lactamase than many other *Enterobacter* species and frequently are susceptible to ampicillin and first-generation cephalosporins (24, 25). This report is the first to describe a clinically significant infection caused by KPC-producing *E. gergoviae*. To the best of our knowledge, only one KPC-producing *E. gergoviae* isolate has been reported, and this was part of a surveillance program that did not include any clinical information (10). The continued transfer of $bla_{KPC}$ between bacterial genera and species presents a serious challenge to clinicians and infection prevention personnel.

The patient in this report had multiple factors that are associated with an increased risk of infection with a KPC-producing organism, including a recent ICU stay, recent carbapenem use, and a prolonged hospitalization (26, 27). KPC-producing organisms are endemic in New York City hospitals (28) and are particularly common in ICUs at our hospital, where 18% of *K. pneumoniae* and 16% of *Enterobacter cloacae* isolates are meropenem resistant. Thus, this patient likely acquired his KPC-producing *E. gergoviae* infection during his ICU stay.

Neutropenic patients with hematologic malignancies are profoundly immunocompromised and thus are at risk for invasive infections due to uncommon pathogens of limited virulence, such as *E. gergoviae*. The emergence of KPC in these opportunistic pathogens poses an additional threat to these immunocompromised hosts. In the absence of immediate treatment with activity against the infecting isolate, neutropenic patients with Gram-negative bacteremia have high mortality rates (29). Broad-spectrum β-lactams, agents that are inactivated by KPC, are recommended for empirical management of fever in neutropenic patients (30). Thus, neutropenic patients with bacteremia due to KPC-producing organisms typically have long delays until receipt of active therapy and a mortality rate of nearly 70% (31). The patient in this report received empirical amikacin, which had *in vitro* activity against his infecting isolate. However, he still died of septic shock within 4 days of the onset of bacteremia. Aminoglycosides demonstrate poor efficacy as monotherapy in neutropenic patients with Gram-negative bacteremia and are not consistently active against KPC-E (5, 32).

New strategies are needed to combat the emerging threat posed by KPC-E to neutropenic patients. A strategy to consider in institutions where KPC-E are endemic is to identify neutropenic patients who are at high risk of KPC-E infection, such as the patient in this report, and add a polymyxin to their empirical antimicrobial regimen while awaiting blood culture results when they present with sepsis. However, more data are needed on risk factors for KPC-E infection in this population before this strategy can be successfully implemented. The emergence of KPC-E in neutropenic patients also highlights the need for improved molecular diagnostics, to rapidly identify these and other multidrug-resistant pathogens, and new antimicrobial agents with activity against KPC-E.

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