

Carbapenemase-producing *Klebsiella pneumoniae* and Hematologic Malignancies

To the Editor: Until a few years ago, the most frequent microbiologically documented cause of severe bloodstream infections among patients with hematologic malignancies was gram-positive bacteria (1). However, over the years, gram-negative bacteria have become the main infectious cause of death among patients with hematologic malignancies, and rates of different phenotypes associated with antimicrobial drug resistance are increasing (2). This trend could be the result of increasing empirical use of antimicrobial drug therapy and prophylaxis and use of new, more effective antimicrobial drugs. In particular, over the past few years at our hospital (Agostino Gemelli Teaching Hospital, Rome, Italy), we have observed a progressive increase in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-Kp), which are responsible for a dramatic new scenario.

We reviewed records of all patients affected by hematologic malignancies who were admitted to the hospital hematology department from January 2009 through December 2012 and in whom a bloodstream infection caused by gram-negative bacteria developed. A KPC-Kp bloodstream infection was defined as a bloodstream infection documented on the basis of blood culture positivity (at

least 1 specimen) for a KPC-Kp strain and clinical signs of systemic inflammatory response syndrome. The Vitek 2 system (bioMérieux, Firenze, Italy) was used for isolate identification and antimicrobial drug susceptibility testing; PCR and sequencing, as previously described, was used to identify *bla*_{KPC} genes (3). Antibigrams were reported 72–120 hours (median 76 hours) after onset of bloodstream infection. Death was considered attributable to infection for patients who died within 2 weeks after the first positive blood culture and for whom other potential causes of death could be excluded.

During the study period, we detected 147 bloodstream infections caused by gram-negative bacteria, 38 (25%) of which were caused by *K. pneumoniae*; of these, 26 (18%) were caused by KPC-Kp. We did not identify any episodes of recurrent KPC-Kp bloodstream infection. We did document a progressive, exponential increase in infections caused by KPC-Kp. No KPC-Kp cases were documented until 2009, and cases increased from only 1 case in 2010 to 12 cases in 2012 (Table). The incidence of KPC-Kp among all gram-negative causes of bloodstream infections increased significantly from 2009–2010 (1/69, 1.4%) to 2011–2012 (25/78, 32.1%) ($p < 0.0001$). Most patients with KPC-Kp bloodstream infection had acute myeloid leukemia (14, 53.8%); others had non-Hodgkin lymphoma (4, 15.4%), acute lymphoid leukemia (3, 11.6%), Hodgkin lymphoma (2, 7.8%), myeloproliferative disease (1, 3.8%), myelodysplastic syndrome (1, 3.8%), or aplastic anemia (1, 3.8%). At time of bloodstream infection onset, 19 (73.1%) of 26 patients were markedly

neutropenic ($< 500 \times 10^9$ neutrophils/mL for > 10 days); almost half (12/26, 46.1%) of these patients experienced complete remission during the course of consolidation therapy or were receiving initial chemotherapy. Among KPC-Kp isolates, 80.8% were susceptible to colistin, 69.2% to tigecycline, and 65.4% to gentamicin. The overall KPC-Kp bloodstream infection-attributable mortality rate was 57.6% (15/26), which was significantly higher than that for bloodstream infections caused by gram-negative bacteria other than KPC Kp (17/121, 14%; $p < 0.0002$) and for bloodstream infections caused by non-KPC-Kp (2/12, 16.7%; $p = 0.02$) (Table).

Despite tailoring of antimicrobial drug therapy to antibiogram results, the KPC-Kp bloodstream infection-attributable mortality rate was high. For $\approx 50\%$ of patients, therapy consisted of combinations of ≥ 2 antimicrobial drugs with in vitro activity against the KPC-Kp isolate. Outcomes are reportedly better after this therapy than after monotherapy (3,4).

In our opinion, the high mortality rate related to KPC-Kp bloodstream infections in patients with hematologic malignancies could be related to various factors. First, patients with hematologic malignancies usually receive antimicrobial drugs recommended for the management of fever in immunocompromised patients with cancer but rarely receive empirically administered drugs active against KPC-Kp bloodstream infections. The delay in appropriate antimicrobial treatment reportedly has a strong negative effect on patient outcomes (5). Second, KPC-Kp isolates may not be susceptible to the antimicrobial drugs generally considered

Table. Prevalence and attributable mortality rate of BSI, Rome, Italy, 2009–2012*

Year	Any gram-negative bacteria		Non-KPC-producing <i>K. pneumoniae</i>		KPC-producing <i>K. pneumoniae</i>	
	BSI, no.	Deaths, no. (%)	BSI, no.	Deaths, no. (%)	BSI, no.	Deaths, no. (%)
2009	30	5 (16.6)	1	0	0	0
2010	39	7 (17.9)	2	0	1	1 (100)
2011	41	9 (24.3)	5	1 (20)	13	7 (53.8)
2012	37	11 (29.7)	4	1 (25)	12	7 (58.3)
Total	147	32 (21.7)	12	2 (16.6)	26	15 (57.6)

*BSI, bloodstream infections; KPC, *Klebsiella pneumoniae* carbapenemase.

as the therapy of choice for such infections. In our study, the rates of nonsusceptibility to colistin, tigecycline, and gentamicin were 19%, 31%, and 35%, respectively. Third, many patients have severe clinical conditions caused by hematologic malignancy and other concurrent conditions (e.g., renal failure, heart disease).

In conclusion, in areas where KPC-Kp is endemic, progress in treating hematologic malignancies could be slowed by the emergence of severe KPC-Kp infections. In these settings, the early identification of patients likely to be colonized and/or infected by KPC-Kp strains represents a major step toward preventing and containing the spread of these strains among hospitalized patients. Policies on empirical treatment might need to be revised, depending on the possibility of serious infections caused by carbapenem-resistant *Enterobacteriaceae*.

This work was financially supported by a grant from the Ministry of University and Scientific and Technological Research (MURST) of Italy.

**Livio Pagano, Morena Caira,
Enrico Maria Trecarichi,
Teresa Spanu,
Roberta Di Blasi, Simona Sica,
Maurizio Sanguinetti,
and Mario Tumbarello**

Author affiliation: Catholic University of the Sacred Heart, Rome, Italy

DOI: <http://dx.doi.org/10.3201/eid2007.130094>

References

1. Tumbarello M, Spanu T, Caira M, Trecarichi EM, Laurenti L, Montuori E, et al. Factors associated with mortality in bacteremic patients with hematologic malignancies. *Diagn Microbiol Infect Dis*. 2009;64:320–6. <http://dx.doi.org/10.1016/j.diagmicrobio.2009.02.008>
2. Trecarichi EM, Tumbarello M, Spanu T, Caira M, Fianchi L, Chiusolo P, et al. Incidence and clinical impact of extended-spectrum- β -lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by *Escherichia coli* in patients with hematological malignancies. *J Infect*. 2009;58:299–307. <http://dx.doi.org/10.1016/j.jinf.2009.02.002>
3. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. *Clin Infect Dis*. 2012;55:943–50. <http://dx.doi.org/10.1093/cid/cis588>
4. Qureshi ZA, Paterson DL, Potoski BA, Kilayko MC, Sandovsky G, Sordillo E, et al. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. *Antimicrob Agents Chemother*. 2012;56:2108–13. <http://dx.doi.org/10.1128/AAC.06268-11>
5. Satlin MJ, Calfee DP, Chen L, Fauntleroy KA, Wilson SJ, Jenkins SG, et al. Emergence of carbapenem-resistant *Enterobacteriaceae* as causes of bloodstream infections in patients with hematologic malignancies. *Leuk Lymphoma*. 2013;54:799–806. <http://dx.doi.org/10.3109/10428194.2012.723210>

Address for correspondence: Livio Pagano, Istituto di Ematologia, Università Cattolica S. Cuore, Largo Francesco Vito, 1, I-00168 Roma, Italia; email: lpagano@rm.unicatt.it

***Neisseria meningitidis* Serogroup W135 Sequence Type 11, Anhui Province, China, 2011–2013**

To the Editor: *Neisseria meningitidis* colonizes the nasopharynx of humans and can cross the epithelial barrier of the nasopharynx, causing septicemia, meningitis, or both (1,2). In Anhui Province, China, there has been a previously high risk for epidemic cerebrospinal meningitis. Before 2012, all meningococcal diseases were caused by *N. meningitidis* serogroups A, B, and C, and the unique sequence type (ST) 4821 clone of

serogroup C was first identified in this region during 2003–2004 (3).

No widespread epidemics of cerebrospinal meningitis and no *N. meningitidis*-associated deaths have occurred in Anhui since bivalent meningococcal vaccines against serogroups A and C were first used in 2003 (4). During 2011–2013, however, 15 infections caused by *N. meningitidis* serogroup W135 ST11, which belongs to a hyperinvasive lineage (5), were reported in Hefei, Anhui Province. Two of the cases (1 each in 2012 and 2013) were fatal and occurred in patients who denied having recently traveled, which suggests that the clone may have spread in an endemic fashion. The 2 patients also had no history of vaccination with tetravalent polysaccharide vaccine (serogroups A/C/Y/W). The other 13 cases occurred in close contacts of the patients who died.

The fatal cases of serogroup W135 infection were in 14- and 17-year-old boys. One of the boys had dropped out of school and worked in a hotel. He sought medical care for a headache with sudden onset, vomiting, and high fever (temperature 40°C). The other boy was a junior college student. At hospital admission, he had vomiting, diarrhea, and high fever (temperature 39°C).

According to the Chinese surveillance system, meningococcal disease is reported by local hospitals to the local Center for Disease Control and Prevention and then to the provincial Center for Disease Control and Prevention, where specific measures are taken to control and prevent the disease. Serogroup W135 infection in the 2 boys in Hefei was identified and reported by different hospitals. Both boys reported that they had not traveled outside Hefei in the 2 months before illness onset or had any contact with persons with meningococcal disease. A total of 61 close contacts were identified for the boys.

Despite treatment, the 2 boys died of disseminated intravascular coagulation and multiple organ failure. Cerebrospinal fluid and blood specimens