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Nosocomial Outbreak of *Klebsiella pneumoniae* Carbapenemase-Producing *Klebsiella oxytoca* in Austria

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To date, no outbreak of carbapenemase-producing bacteria has been reported for Austria. While outbreaks of *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* have been increasingly reported, no outbreak caused by KPC-producing *Klebsiella oxytoca* has been described yet, to the best of our knowledge. We report an outbreak of KPC-producing *K. oxytoca*. In 5 months, 31 KPC-producing *Klebsiella oxytoca* strains were isolated from five patients. All patients were admitted to the same medical intensive care unit in Austria.

Carbapenems are considered the agents of choice for treatment of serious infections caused by resistant Gram-negative bacteria. Resistance to carbapenems is therefore the major threat for treatment of these infections, and production of carbapenemases is the most important molecular mechanism, both epidemiologically and clinically.

Carbapenemases in *Enterobacteriaceae* are represented by three molecular classes of beta-lactamase: A, B, and D (3). *Klebsiella pneumoniae* carbapenemase (KPC) is a class A beta-lactamase that poses a serious clinical challenge, as KPC-producing *Klebsiella pneumoniae* isolates are rapidly disseminating worldwide (1, 4).

KPC-type enzymes in carbapenem-resistant *Klebsiella pneumonia* were first detected in 2001 in North Carolina and since then have spread all over the United States (14, 18, 24). Sizeable outbreaks of KPC-producing *K. pneumoniae* have also occurred in Israel, Greece, South America, and China (6, 12, 15, 22, 27, 28). The emergence of KPC-producing *K. pneumoniae*, often associated with smaller outbreaks, has recently been reported also from several European countries, including Germany, Italy, Poland, Switzerland, and France (9, 10, 13, 17, 23). In contrast, reports of KPC-producing *Klebsiella oxytoca* are rare (5, 11, 19, 25). Most of these reports cover one or two isolates and, to the best of our knowledge, no outbreak caused by KPC-producing *K. oxytoca* has been described yet. Even non-carbapenemase-producing *K. oxytoca* has rarely been reported as the cause of nosocomial outbreaks (7, 20).

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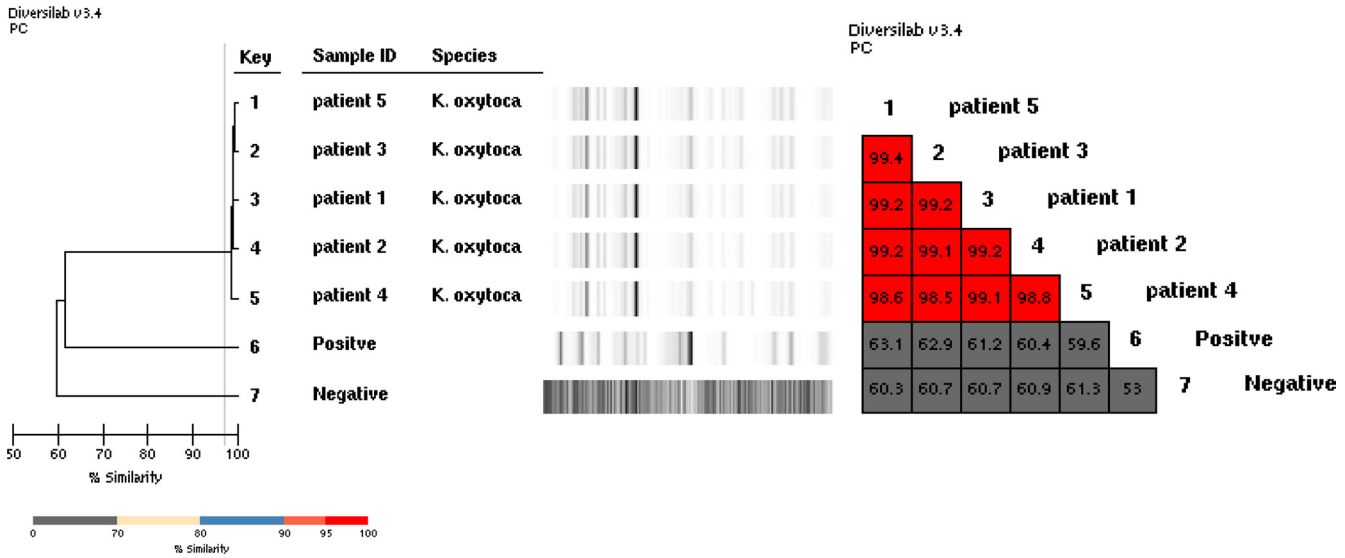

FIG 1 Dendrogram and similarity matrix for *K. oxytoca* for five patients. The *K. oxytoca* isolates of this outbreak were indistinguishable, with a similarity of between 98.6% and 99.4% (and no band difference) in the DiversiLab system.

TABLE 1 Clinical data, strains, and detected carbapenemases in KPC *Klebsiella oxytoca* outbreak, Austria, 2010-2011[a]

Patient	Age (yr)/ sex	Date of first detection	Comorbidities	LOS before detection (days)	Total LOS (days)	Site of first detection	Other sites detected	No. of KPC *K. oxytoca* isolates detected	Duration of colonization (days)	Date of infection caused by KPC *K. oxytoca*	Site of infection caused by KPC *K. oxytoca*	Treatment outcome (final outcome)	Antimicrobial therapy before isolation of KPC *K. oxytoca* infection	Antimicrobial therapy for KPC *K. oxytoca* infection	Susceptibility phenotype of KPC *K. oxytoca* (MIC, mg/liter)[b]
1	43/f	12 Oct 2010	Ischemic stroke, DIC, ARF, AH	31	82	Urine	Tracheostoma, tracheal aspirate, nasal, axilla	19	49	12 Oct 2010	UTI, VAP	Successful (death)	Meropenem, gentamicin, linezolid, moxifloxacin	COL, FOS	AMK (2.0), COL (1.0), FOS (2.0), TIG (0.5)
2	76/f	19 Oct 2010	SSSS, ARF, AH, DM	11	12	Surveillance swab (throat)	None	1	1	NA	NA	NA (death)	Ceftriaxone	NA	AMK (2.0), COL (0.125), FOS (2.0), TIG (0.5)
3	43/m	27 Oct 2010	CAP (*Legionella pneumphila*)	9	30	BAL	Throat, nasal, sputum, groin	9	15	27 Oct 2010	VAP	Successful (discharge)	Ceftriaxone, moxifloxacin	FOS, TIG	AMK (4.0), COL (1.0), FOS (4.0), TIG (0.5)
4	70/m	14 Dec 2010	Secondary AML, COPD	106	115	Pressure ulcer from urinary catheter	None	1	1	NA	NA	NA (discharge)	Meropenem, levofloxacin	NA	AMK (2.0), COL (0.125), FOS (4.0), TIG (0.5)
5	89/f	16 Feb 2011	UTI, CAD, heart failure, CMP, ARF	26	29	BAL	None	1	1	16 Feb 2011	VAP	NA (death)	Ciprofloxacin, Amox/Clav	NA	AMK (2.0), COL (1.5), FOS (4.0), TIG (0.25)

[a] AH, arterial hypertension; AMK, amikacin; AML, acute myeloid leukemia; Amox/Clav, amoxicillin-clavulanic acid; ARF, acute renal failure; BAL, broncoalvelar lavage fluid; CAD, coronary artery disease; CAP, community-acquired pneumonia; CMP, cardiomyopathy; COL, colistin; Dec, December; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; f, female; Feb, February; FOS, fosfomycin; GM, gentamicin; LOS, length of stay; m, male; NA, not applicable; Oct, October; SSSS, staphylococcal scalded skin syndrome; TIG, tigecycline; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

[b] MICs were determined by the Etest method (AB bioMérieux, Solna, Sweden).

We recently reported the emergence of New Dehli metallo-beta-lactamase 1 (NDM-1) strains in Austria (26). To date, no outbreak of carbapenemase-producing bacteria has been reported for Austria. In this study, we describe an outbreak of a KPC-producing *K. oxytoca*, which affected five patients. All of them had stayed in the same room of a medical intensive care unit (ICU).

The study. A retrospective observational study of patients infected or colonized with KPC-producing *K. oxytoca* was conducted. Thirty-one strains (from five patients) were isolated within 5 months at the Medical University Hospital Graz, Austria, a hospital with a total of 1,600 beds. All strains had been stored at −70°C. For microbiology studies, one isolate per patient (either the first colonizing or the first pathogenic isolate identified) was thawed and retested. Three of these strains had been isolated in the medical ICU (15 beds) and one each at the Division of Hematology (28 beds) and the respiratory care unit (RCU; 4 beds) that is spatially divided from the medical ICU. Identification and antimicrobial susceptibility profiles were determined using a Vitek II Instrument (bioMérieux Vitek, Inc., Hazelwood, MO) and the Etest method (AB bioMérieux, Solna, Sweden) and interpreted according to the CLSI guidelines (3a). For detection of KPC, primers and PCR protocols were used as previously described (8). Automated repetitive PCR (rep-PCR) was performed with a DiversiLab Instrument to determine clonal relationships (7).

Medical records of the five patients colonized or infected with KPC-producing *K. oxytoca* were retrospectively reviewed. For the clinical and microbiological diagnosis of infections, previously published criteria were used (2). Treatment outcome was evaluated on day 7. Successful outcome was defined as cure or improvement (partial resolution of signs and symptoms and improvement of laboratory parameters) while on anti-infective therapy.

From October 2010 through February 2011, five patients were found to have been colonized ($n = 2$) or infected ($n = 3$) by KPC-producing *K. oxytoca*. The first isolate was introduced to the medical ICU by a patient who was already hospitalized in various regional ICUs for 31 days due to an ischemic stroke and consecutively developed a urinary tract infection and ventilator-associated pneumonia (VAP) due to KPC-producing *K. oxytoca*. The strain was horizontally transmitted to at least two additional patients in the same four-bed room of the medical ICU (patient 2 and patient 3). While patient 2 died due to staphylococcal scalded skin syndrome before identification of the carbapenemase-producing pathogen, KPC-producing *K. oxytoca* was repeatedly isolated from the other two patients for 49 and 15 days, respectively. The same KPC-producing *K. oxytoca* strain was isolated from the fourth patient in mid-December 2010 at the division of hematology. This patient had stayed in the medical ICU simultaneously with the three other patients in mid-October, making cross-transmission likely. Thereafter, the strain disappeared for 2 months. A strain belonging to the same clonal group was detected at the RCU in February 2011 in bronchoalveolar lavage fluid from patient 5. This patient had been transferred from the medical ICU 10 days before isolation of the multiresistant strain and had stayed in the same room as all other patients with KPC-producing *K. oxytoca*. The strain may have continuously circulated at the medical ICU while remaining undetected for more than 2 months. The source, however, remained unidentified. Endoscope-related transmission

was ruled out, as environmental cultures of bronchoscopes and equipment used with them remained negative in repeated tests.

Rep-PCR with the DiversiLab instrument showed that all strains were indistinguishable from one another, with a similarity index of >98.5% (Fig. 1).

KPC-producing *K. oxytoca* was causative for infection in three patients (VAP in all three patients and also a urinary tract infection in one patient). Systemic anti-infective treatment for KPC-producing *K. oxytoca* infection was started for two of the patients and was successful for both. The third patient with VAP died before adequate anti-infective treatment could be started.

Travel history was unremarkable for all of the patients. Patients 1 and 2 had not even been outside Austria for the last 10 years. This is of particular interest, as carbapenem-resistant *K. pneumoniae* isolates have rarely been reported for Austria in the European Antimicrobial Resistance Surveillance Network (http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/table_reports.aspx). All detected KPC-producing *K. oxytoca* strains were multiresistant, and they exhibited susceptibility to colistin, fosfomycin, tigecyclin, and amikacin only. Details of the outbreak are given in Table 1.

The emergence and worldwide spread of carbapenem-resistant *Enterobacteriaceae* is a challenge for both clinicians and clinical microbiologists. We report a clonal outbreak of KPC-producing *K. oxytoca* in Austria involving five patients and lasting for 5 months. While outbreaks of KPC-producing *K. pneumoniae* have been described frequently, no outbreak of KPC-producing *K. oxytoca* has yet been described, to the best of our knowledge.

Previous studies have identified poor functional status, ICU stay, transplantation, mechanical ventilation, prolonged hospitalization, and receipt of antibiotics as risk factors for acquisition of KPC-producing organisms (16, 21). The observational design of our study did not allow us to make any conclusions regarding risk factors for KPC-producing *K. oxytoca* acquisition at our institution. All of these risk factors except transplantation, however, were present in three or more of the patients described here.

The susceptibility profile of the isolates recovered during the present outbreak underscores the extremely limited therapeutic options available for the treatment of infected patients. Similar results have also been reported in previous studies (22). Surprisingly, fosfomycin was active *in vitro* in all of the isolated strains.. *In vivo* efficacy of this bactericidal agent has not yet been evaluated. In our study, however, fosfomycin combination therapy with either tigecycline or colistin was associated with a successful outcome.

In conclusion, we describe a nosocomial outbreak of KPC-producing *K. oxytoca*. These observations provide some insight into the epidemiology and clinical importance of KPC carbapenemases that also pose a serious clinical threat when produced by *K. oxytoca*.

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