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Major article

Long-term carriage of *Klebsiella pneumoniae* carbapenemase–2-producing *K pneumoniae* after a large single-center outbreak in Germany

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Background: The natural progress of intestinal colonization with *Klebsiella pneumoniae* carbapenemase–2-producing *K pneumoniae* (KPC-2-KP) is almost unknown.

Methods: After a large, single-center outbreak of KPC-2-KP, we analyzed carrier prevalence through retrospective and prospective investigation of intestinal KPC-2-KP carriage 1 month, 3 months, 6 months, 1 year, and 2 years after acquisition, defined as the earliest date of KPC-2-KP detection. Rectal swabs or stool samples were collected at baseline and at each visit and submitted for both culture and KPC-specific polymerase chain reaction. Resolution of intestinal KPC-2-KP carriage was defined as a minimum of 3 consecutive negative polymerase chain reaction test results separated by at least 48 hours.

Results: In patients available for long-term evaluation 26 out of 84 patients (31%) tested negative for KPC-2-KP after 1 month, 14 out of 34 (41%) after 3 months, 17 out of 26 (65%) after 6 months, 14 out of 19 (74%) after 1 year, and 5 out of 6 (83%) after 2 years. Decolonization of KPC-2-KP was hampered in patients with prolonged or repeated hospitalization ($P = .044$-$.140$, depending on the time interval). Two patients retested positive for KPC-2-KP after they had previously shown 3 consecutive negative tests. The longest positive KPC-2-KP carrier status so far was observed after nearly 40 months (1,191 days).

Conclusions: The majority of patients experienced spontaneous decolonization within 6 months after acquisition, mainly after discharge from the hospital. However, long-term carriage of >3 years is possible. Appropriate infection control measures must be taken when these patients are readmitted to health care facilities. A series of at least 4 consecutive negative rectal swabs or stool samples separated by sufficient time intervals appears necessary before the declaration of successful KPC-2-KP decolonization is made.

Klebsiella pneumoniae (KP) is a major cause of nosocomial infections, primarily among debilitated patients.[1,2] The emergence of strains resistant to carbapenems has left only limited treatment options; that is, tigecycline, colistin, and aminoglycosides. KP carbapenemases (KPCs) have rapidly spread since 1996.[1,2] Outbreaks in Europe are mainly associated with the bla_{KPC-2} gene and sequence type ST258.[2]

From July 2010-April 2013, the Leipzig University Hospital, a 1,300-bed referral center, experienced the largest outbreak due to a KPC-2-producing KP (KPC-2-KP) strain, ST258, observed in Germany to date.[2-4] The outbreak occurred subsequent to the transfer of a single patient from a hospital in Rhodes, Greece, where KPC-producing pathogens are endemic.[2,5] A total of 103 patients (57 males, 46 females; median age 62 years; range, 21-85 years) became either colonized (60 out of 103; 58%) or infected (43 out of

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Conflicts of interest: None to report.

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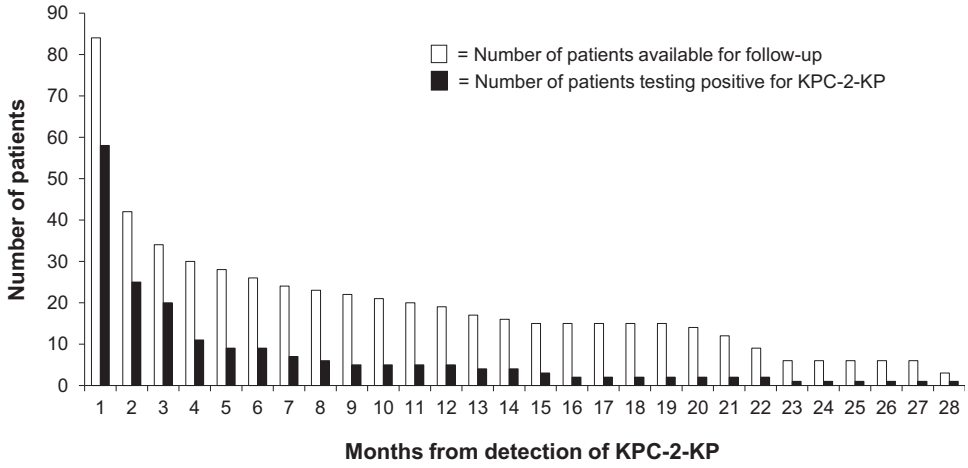

Fig 1. Timeline of intestinal *Klebsiella pneumoniae* carbapenemase-2-producing *K pneumoniae* (KPC-2-KP) carriage in patients available for long-term follow-up.

103; 42%),[4,6] employing the Centers for Disease Control and Prevention definitions of nosocomial infections.[7,8] Successful containment of the outbreak, defined by the absence of new KPC-positive cases for at least 2 months in the presence of systematic screening measures, was related to the implementation of an efficient infection control program. This included strict barrier measures and improved hand hygiene, refined use of broad-spectrum antibiotics, especially carbapenems (from January 2011 onward), systematic polymerase chain reaction (PCR)-based screening for carbapenem-resistant Enterobacteriaceae (CRE) on admission (established in May 2012), repeated CRE screening during hospitalization (established in June 2012), as well as strict cohorting of KPC-positive patients and separation of contacts (established in July 2012).[4,9] The last case of the outbreak was detected in April 2013 resulting in a total of 103 KPC-2-KP positive patients.

Prolonged person-to-person transmission was identified as the most likely way of spread, possibly with the contribution of undetected KPC-2-KP cases before systematic screening was established (previously described as silent dissemination[10]). There was no evidence that the outbreak was caused by a single point source or that staff members colonized by KPC-2-KP served as an unrecognized reservoir.

In this article we aim to describe the duration of intestinal KPC-2-KP carriage following discharge from our hospital in patients affected by the outbreak, with particular respect to prolonged or repeated hospitalization, immunosuppressive treatment, and re-exposure to antibiotics.

METHODS

In this carrier prevalence study we included 103 patients with confirmed evidence of KPC-2-KP in rectal swabs and/or stool cultures, blood cultures, urine cultures, bile cultures, tracheal cultures, peritoneal swabs, or wound swabs. Intestinal presence of KPC-2-KP was confirmed by a KPC-specific PCR and/or culture of the organism. Ninety-two cases were confirmed by culture and 11 cases by at least 2 positive KPC-specific PCR results. Pulsed-field gel electrophoresis patterns of all but 2 KPC-2-KP strains isolated during the outbreak were considered to be identical to the initial isolate recovered from the index patient transferred from Greece to our hospital for treatment of nosocomial pneumonia.

For long-term evaluation of KPC-2-KP carriage (Fig 1 and Table 1), we assessed the carrier prevalence rate 1 month, 3 months, 6 months, 1 year, and 2 years after KPC-2-KP acquisition, defined as the earliest date of detection. Hereby, patients were followed-up by several methods. Following the initial hospitalization, many patients were subsequently readmitted, and a surveillance test (culture and/or KPC-specific PCR) was taken per screening protocol, or KPC-2-KP was isolated from clinical cultures. Such test results were counted as follow-up. Other patients had surveillance or clinical cultures taken as part of follow-up in hospital outpatient clinics or were contacted by the investigators. Thus, rectal swabs or stool samples were collected at baseline and at each visit and submitted for both culture and KPC-specific PCR. Overall, the data of 241 samples were analyzed retrospectively and 307 samples were obtained prospectively. Decolonization of KPC-2-KP from the digestive tract was defined as a minimum of 3 consecutive negative PCR test results separated by at least 48 hours.

Fourteen patients were excluded from the analysis because they had received a short course (7 days) of selective digestive tract decontamination treatment employing colistin and gentamicin.[4,11] Another 3 patients could not be analyzed because access to clinical records partially failed. During the individual 2-year observation period 42 patients died in the hospital. Twenty-five patients were lost to follow-up during the first year, and 19 more were lost to follow-up during the second year. The remaining patients were screened on at least a monthly basis to assess their carrier status.

Clinical and microbiologic data were retrieved using the hospital's patient data management system. Exposure to antibiotics was defined as antibiotic treatment on the day of data collection or within the past 30 days. Patients were counted as outpatients if they were not hospitalized on the day of data collection or within the past 30 days.

Statistical analysis was performed using SPSS version 20.0 for Windows (IBM SPSS Corp, Armonk, NY). Numerical variables are summarized as median and categorical variables are given as frequencies or proportions. For comparison, the categorical data were assessed using Pearson's χ^2 test or Fisher's exact test. P values $< .05$ were considered statistically significant.

Approval from the University of Leipzig Ethics Committee was obtained before the beginning of the data evaluation.

RESULTS

From the 103 KPC-2-KP positive patients, 17 were excluded based on the stated criteria. Of the remaining 86 patients, including dropouts because of death or loss to follow-up, the participation rate was 98% (84 out of 86) after 1 month, 40% (34 out of 86) after 3 months, 30% (26 out of 86) after 6 months, 22% (19 out of 86) after 1 year, and 7% (6 out of 86) after 2 years.