Dissemination of the *Klebsiella pneumoniae* Carbapenemase in the Health Care Settings: Tracking the Trails of an Elusive Offender

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ABSTRACT Transmission of antibiotic resistance genes may be mediated by a variety of molecular mechanisms, from mobility of small genetic elements to clonal spread. Since 1997, the carbapenem-hydrolyzing enzyme *Klebsiella pneumoniae* carbapenemase (KPC) has spread in the United States and across the world, mainly via a single *K. pneumoniae* clone, sequence type 258. By tracking the trail of dissemination of the *bla*KPC gene inside their institution, Mathers et al. (mBio 2:e00204–11, 2011) have shown evidence of the ability of this gene to spread by several modes, including plasmid transfer and clonal spread. The ever-evolving modes of transmission of resistance genes challenge our ability to detect, track, and eventually control the spread of what has become a major threat to hospitalized patients worldwide.

Carbapenemase-producing enterobacteriaceae (CPE) were first detected at the beginning of the 1980s, with the discovery of SME-1-producing *Serratia marcescens* in the United Kingdom and the United States (1–3). In the three decades since, new cases of infections caused by SME-2- and SME-3-producing *Serratia marcescens* strains have been described (2, 4), but overall, these infections have remained extremely rare. In contrast, the first cases of infections with *Klebsiella pneumoniae* strains producing *Klebsiella pneumoniae* carbapenemase 2/3 (KPC-2/3) were reported in the mid-Atlantic coastal region of the United States between 1997 and 2000 (5–7), but these strains have spread considerably during the past decade. Today, KPC producers are found across the world and have become endemic in several countries in Europe, the Middle East, South America, and Asia (8, 9). More than one-third of all *K. pneumoniae* isolates in Brooklyn, New York medical centers are KPC producers (10), and close to 11% of all *K. pneumoniae* strains reported to the National Health Care Safety Network (NHSN) as being involved in nosocomial infections in the United States are resistant to carbapenems (11). Why do these two families of carbapenemases have such different degrees of epidemiological success?

First, the presence of the *bla*KPC gene in *K. pneumoniae*, a far more common human pathogen than *S. marcescens*, creates a better biological opportunity for dissemination. Second, the presence of the *bla*KPC gene in a successful clone, sequence type 258 (ST-258), which gained global predominance, suggests a highly transmissible and fit strain that contributes to the dissemination and persistence of KPC in the health care environment (12–14). Third, as shown in the November/December issue of *mBio* by Mathers et al. (15), the carriage of the *bla*KPC gene on a plasmid, rather than on the chromosome as with the SME carbapenemases, allows better mobility between strains and species.

Mathers et al. (15) retrospectively tracked the dissemination of KPC in their institution during an 8-month period. They detected 16 *bla*KPC-PCR-positive isolates from 14 patients, belonging to 4 genera and 6 species. As surveillance cultures were not done, all isolates were from clinical cultures. The authors analyzed the transmission opportunities by overlapping the patients’ locations throughout their hospitalization and their staff assignment. After analyzing the clonal structure and the *bla*KPC-carrying plasmids and transposons, they came up with a plausible explanation for the dissemination of KPC in their institution. In addition to the typical dissemination mode of KPC, i.e., transmission of identical strains between patients (16), the authors suggest that the primary route of dissemination was horizontal transfer of *bla*KPC-carrying plasmids (see Fig. 4 and Fig. S3 in reference 15). In addition, the authors speculated that in two cases, the *bla*KPC gene was transmitted via the transfer of a transposon, Tn4401 (see Fig. S3 in reference 15). Although horizontal transfer of mobile genetic elements was previously described for KPC-encoding genes (17, 18), these modes are typical of other carbapenemases, such as OXA-48 (19, 20) and NDM-1 (21, 22) (Table 1). Unlike clonal spread, dissemination of resistance genes via mobile genetic elements leads to a much more complex epidemiology, characterized by a variety of strains and species possessing different virulence traits. This makes tracking dissemination during an outbreak a difficult task, due to the complexity in the detection and identification of a variety of CPE strains, exhibiting a wide range of MICs for carbapenem, some with only low levels of carbapenem resistance (23), as was also shown in the report by Mathers et al. (15; see Table 1 in this reference). Also, such tracking requires molecular studies of plasmids and transposon structures, which are rarely available in real time, even in tertiary academic centers. In this regard, the authors’ validation of the nested arbitrary PCR method for studying the flanking region of the transposon insertion site may be of great assistance to the real-time studying of a plasmid-borne outbreak.

Are there missing links in their investigation? CPE, as any *Enterobacteriaceae*, are commonly present in the gastrointestinal tract (GIT) in patients without active infection (24). These patients may serve as an important reservoir for ongoing transmission of CPE, and therefore, the prospective identification and isolation of these patients play an important role in the control of an outbreak (24, 25). As the investigation by Mathers et al. was conducted in retrospect, surveillance cultures were not taken, and...
TABLE 1 Microbiological features and dissemination potential of four carbapenemases

| Carbapenemase | Class a | Predominant species | Imipenem MIC | Location of gene b | Dissemination potential/mode | References |
|---------------|---------|---------------------|--------------|--------------------|----------------------------|------------|
| SME-1/2/3     | A       | S. marcescens       | High         | Ch                 | Limited                    | 1, 3, 15   |
| KPC-2/3       | A       | K. pneumoniae       | High         | Pl                 | High/clonal (ST-258)       | 8–11       |
| OXA-48        | D       | Variable            | Low          | Pl                 | High/plasmid               | 16, 17     |
| NDM-1         | B       | Variable            | Variable     | Pl, Ch             | High/combined              | 9, 20      |

* a According to Ambler’s structural classification.

b Ch, chromosome; Pl, plasmid.

hence asymptomatic GIT carriers of CPE were likely missed. Identifying these patients might have allowed a better explanation of the transmission source in patients 6, 8, and 10 (see Fig. 4 and Fig. S3 in reference 15) and facilitated control measures. Also, it might have revealed the true extent of the epidemics (the “ iceberg effect”) and allowed assessment of the dissemination and virulence potentials of the different CPE clones.

This study demonstrates the evolution of one of the most clinically important resistance mechanisms, the KPC carbapenemases, from a monoclonal mode of dissemination (16, 26) to a complex mode also involving the transfer of mobile genetic elements. In contrast, the carbapenemase OXA-48, initially characterized by the spread of a single plasmid (20), may also be involved in local outbreaks of a single strain (27, 28). Hence, thorough epidemiological investigation combined with comprehensive knowledge of the possible transmission modes will be invaluable for the understanding and successful control of future epidemics (29, 30).

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