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Journal Title: Antimicrobial Agents and Chemotherapy
Volume: Volume 57, Number 9
Publisher: American Society for Microbiology | 2013-09-01, Pages 4602-4603
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1128/AAC.00725-13
Permanent URL: https://pid.emory.edu/ark:/25593/s750s

Final published version: http://dx.doi.org/10.1128/AAC.00725-13

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Accessed December 5, 2022 1:54 AM EST
OqxAB, a Quinolone and Olaquindox Efflux Pump, Is Widely Distributed among Multidrug-Resistant *Klebsiella pneumoniae* Isolates of Human Origin

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Use of antibiotics among livestock contributes to the selection and dissemination of multidrug resistant (MDR) bacteria (1). Olaquindox and carbadox are quinoline derivatives with antibacterial properties that prevent dysentery and enhance weight gain in suckling pigs (2). Resistance to quinoxalines is mediated by the efflux pump OqxAB, which also extrudes antibiotics such as chloramphenicol and fluoroquinolones (3). The gene encoding this efflux pump, *oqxAB*, was initially detected within plasmid pOLA52, which was found in *Escherichia coli* isolated from swine manure (4). Dissemination of *oqxAB* has been noted in *Salmonella* species, and the original genetic reservoir of *oqxAB* was traced to the chromosome of *Salmonella* (5,6). Surprisingly, OqxAB has been reported only in clinical isolates of *Klebsiella pneumoniae* since China, South Korea, and Spain (7–9).

Like other *Enterobacteriaceae*, *K. pneumoniae* is able to colonize and cause infection in animals and humans. As isolates harboring extended-spectrum β-lactamas (ESBLs) and *Klebsiella pneumoniae* carbapenemases (KPCs) have become so prevalent, we hypothesized that OqxAB may be widely present among these clinically relevant types of *K. pneumoniae*.

Isolates were screened by PCR for the *oqxA* gene (forward primer, 5'-GGTCTCGGATACATTGAT-3'; reverse primer, 5'-GGCGAGGTTTTGATAGTGGA-3') and, if positive, were also screened for *oqxB* (forward primer, 5'-CTGGGCTTCTCGCTGA-3') and, if positive, were also screened for *oqxA* (forward primer, 5'-GGCAGGTITTGTAGTGGAG-3') and, if positive, were also screened for *oqxB* (forward primer, 5'-GCAGGTITTGTAGTGGAG-3'). Known positive strains were used as controls. Resistance to ciprofloxacin (as a representative fluoroquinolone) was recorded (10). Sequence type was established using the multilocus sequence typing (MLST) scheme developed at the Institut Pasteur (http://www.pasteur.fr/recherche/genopole/PG/MLST/Kpneumoniae.html).

The following sets of isolates were studied (Table 1): (i) *K. pneumoniae* isolates harboring *bla*KPC (n = 12) collected in a pediatric long-term-care facility in northeast Ohio in 2004 (11), (ii) *K. pneumoniae* isolates harboring *bla*KPC (n = 36) obtained from acute-care hospitals in northeast Ohio in 2012, (iii) *K. pneumoniae* isolates harboring *bla*KPC (n = 43) obtained between 2004 and 2011 from the mid-Atlantic states of the United States (New Jersey, New York, Pennsylvania), and (iv) ESBL-producing *K. pneumoniae* isolates (n = 16) with a variety of *bla*SHV, *bla*TEM, and *bla*CTX-M genes, collected in the 1990s from Taiwan, Australia, Argentina, Belgium, Turkey, South Africa, and the United States (12).

The prevalence of *oqxAB* varied widely in the different sets of strains (Table 1). Among KPC-producing *K. pneumoniae* isolates from northeast Ohio, *oqxAB* was present in 100%. This included contemporary isolates from acute-care facilities that were also quinolone resistant and belonged to sequence type (ST) 258, as well as isolates from a pediatric long-term-care facility that were quinolone susceptible and belonged to ST 36. Among KPC-producing *K. pneumoniae* isolates from the mid-Atlantic, the genes

### TABLE 1 Presence of oqxAB in diverse clinical isolates of Klebsiella pneumoniae

<table>
<thead>
<tr>
<th>Location, yr of isolation</th>
<th>No. of isolates</th>
<th>Source(s)</th>
<th>Sequence type(s)</th>
<th>Acquired β-lactamase (bla) gene type(s)</th>
<th>Prevalence of oqxAB (%)</th>
<th>% with ciprofloxacin resistance (MIC ≥ 4 μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric long-term-care facility, northeast Ohio, 2004</td>
<td>12</td>
<td>Stool</td>
<td>ST 36</td>
<td>KPC-3</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Acute-care hospitals, northeast Ohio, 2012</td>
<td>36</td>
<td>Blood, urine, sputum</td>
<td>ST 258</td>
<td>KPC-2, KPC-3</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Acute-care hospitals, New York, New Jersey, Pennsylvania, 2006–2009</td>
<td>6</td>
<td>Urine, sputum</td>
<td>ST 134, ST 254, ST 379, ST 429</td>
<td>KPC-2, KPC-3</td>
<td>83.3</td>
<td>83.3</td>
</tr>
<tr>
<td>Hospitals in Taiwan, Australia, Argentina, Belgium, Turkey, South Africa, and the United States, 1996–1997</td>
<td>16</td>
<td>Blood</td>
<td>Not determined</td>
<td>TEM-10, SHV-2, SHV-5, CTX-M-2, CTX-M-3</td>
<td>87.5</td>
<td>Not determined</td>
</tr>
</tbody>
</table>
were present in 71% (22/31) of ST 258 isolates and 91.7% (11/12) of other non-ST 258 types; 96.8% and 58.3% of these isolates were ciprofloxacin resistant, respectively. Also, *oqxAB* was present in 87.5% (14/16) of international ESBL-producing *K. pneumoniae* isolates.

Our survey indicates that OqxAB, an efflux pump found in isolates of veterinary origin, is highly prevalent in diverse clinical MDR *K. pneumoniae* strains isolated from humans, including KPC-producing *K. pneumoniae* isolates of ST 258. Furthermore, its presence in *K. pneumoniae* isolated more than a decade ago suggests widespread dissemination. The association of the OqxAB efflux pump with a diverse set of substrates, including fluoroquinolones, commonly used in humans, may contribute to the MDR profile of *K. pneumoniae*. The occult dissemination of this efflux pump gene adds to the constellation of resistance determinants already circulating in *Enterobacteriaceae*.

ACKNOWLEDGMENTS

This work was supported by funds and facilities provided by the Louis Stokes Cleveland Department of Veterans Affairs Medical Center, by the VISN 10 Geriatric Research, Education and Clinical Care Center (VISN 10) of the Department of Veterans Affairs, and by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH) under award numbers R01AI072219, R01AI063517, and R01AI100560 to R.A.B. B.N.K. is supported by the NIH under award numbers R01AI072219, R01AI063517, and R01AI100560 to R.A.B. B.N.K. is supported by the NIH under award numbers R01AI090155 and R21AI06551. F.P. and D.V.D. are supported by the National Center for Advancing Translational Sciences (NCATS) component of the NIH and NIH Roadmap for Medical Research. P.N.R. is supported by Merit Review and Research Career Scientist awards from the Department of Veterans Affairs.

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