First report of an OXA-48-producing multidrug-resistant *Proteus mirabilis* strain from Gaza, Palestine

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**Background**

- Emergence of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant public health threat as there are fewer, or even sometimes no, effective antimicrobial agents available for infections caused by these bacteria.

- The problem of increasing antimicrobial resistance is even more threatening when considering the very limited number of new antimicrobial agents that are in development.
MDR, XDR, PDR

- **MDR** is defined as acquired *non-susceptibility* to at least one agent in three or more antimicrobial categories.

- Bacterial isolates that are MDR will have many different resistance profiles because by definition, non-susceptible results for even a single agent in only three antimicrobial categories defines an organism as MDR.

- For example, two *E. coli* isolates, one resistant to trimethoprim-sulphamethoxazole, cefazolin and ciprofloxacin and the other to ertapenem, gentamicin and tigecycline, will both be characterized as MDR even though the agents are different.
MRD, XDR, PDR

- **XDR** is defined as *non-susceptibility* to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories)

- Initially, the term XDR was created to describe extensively drug-resistant *Mycobacterium tuberculosis* (XDR MTB)

- **PDR** is defined as *non-susceptibility* to all agents in all antimicrobial categories.

CRE

- Carbapenem-resistant *Enterobacteriaceae* have been reported worldwide and caused a significant public health alert. Our understanding of the dissemination of CRE in Gaza strip is limited.

- It is mandatory to maintain the clinical efficacy of carbapenems (imipenem, ertapenem, meropenem, doripenem), which have become antimicrobial drugs of last resort.

- Three classes of these genes were reported (Class A, B and D carbapenemases)
1. Class A Carbapenemases

- KPCs are the most clinically common enzymes in this group.
- Mainly endemic in USA, Puerto Rico, Colombia, Greece, Israel, and China.
- KPC producers are usually multidrug resistant, and therapeutic options for treating KPC related infections remain limited.

2. Class B Metallo-β-Lactamases (MBLs)

- MBLs are mostly of the Verona integron-encoded metallo-β-lactamase (VIM), Imipenemases (IMP) types and, more recently, of the New Delhi metallo-β-lactamases (NDM) types.
3. Class D Enzymes of the OXA-48 Type

- The first identified OXA-48 producer was from a K. pneumoniae strain isolated in Turkey in 2003.
- Now includes countries in Europe, the Mediterranean Sea, and Africa.
- The OXA-48-type producers are likely the most difficult carbapenemase producers to be identified.

Material and Methods

- 320 non-duplicate GN isolates from Al Shifa hospital in Gaza from March to May 2012;
- Isolation information, including time, source and departments were recorded;
- All isolates were tested by PCR/sequencing for carbapenemase genes, including \( \text{bla}_{KPC}, -\text{NDM}, -\text{VIM}, -\text{IMP}, -\text{OXA23}, -\text{OXA40}, -\text{OXA51}, -\text{OXA58}; \)
- Selective isolates were further tested by MLST and plasmids characterization.
**Material and Methods**

- In this study, we used next-generation sequencing to characterize the genomes of the OXA-48-producing *P. mirabilis* strain (*Pm-OXA-48*) and the *blaOXA-48*-harboring plasmid using a MiSeq Desktop Sequencer (Illumina, San Diego, CA).

- Susceptibility testing was performed by CLSI broth microdilution.

- Analyses of acquired antimicrobial resistance genes were performed using ResFinder 2.1

- A BLAST search was done to find all completely sequenced *blaOXA-48*-harboring plasmids in GenBank (http://www.ncbi.nlm.nih.gov/GenBank/)

**Results**

- The strain exhibited resistance to multiple antimicrobial agents, including: Cefotaxime, cefepime, ticarcillin-clavulanate, imipenem, doripenem, ciprofloxacin, levofloxacin, gentamicin, tobramycin, amikacin, minocycline, doxycycline, trimethoprim-sulfamethoxazole, colistin, polymyxin B, and tigecycline.
Results

- Using whole genome sequencing of Pm-OXA-48, we identified 16 antimicrobial resistance genes encoding resistance to:
  1. β-lactams (blaOXA-48, blaCTX-M-14, and blaTEM-1)
  2. aminoglycosides [aph(3=)-Ia, aadA1, aac(3)-IIa, aph(3=)-VIb, strA, and strB]
  3. fluoroquinolones (qnrD),
  4. streptothricin (sat-1),
  5. phenicols (catA1 and cat),
  6. tetracycline [tet(J)],
  7. sulfonamide-trimethoprim (sul2 and dfrA1)

- Moreover, 27 genes related to antiseptic and toxic compound resistance, including arsR (arsenic resistance), cutEF (copper resistance), merA (mercury resistance), and emrD (benzalkonium resistance).

- Also, mutations in the quinolone resistance-determining region (QRDR) genes (gyrA, gyrB, parC, and parE) were detected (ciprofloxacin and levofloxacin resistance).
Plasmids in OXA-48 carrying P. mirabilis

Structures of bla_{oxa-48} harboring IncL/M plasmids
Summary

• This study describes the first report of a carbapenemase-producing *P. mirabilis*.

• To the best of our knowledge, it is also the first description of *blaOXA-48* in *Proteus* spp.

• The pan-resistant nature of *P. mirabilis* strain *Pm-OXA-48* underlies the significance of detection and mitigation of *OXA-48* and other carbapenemases in our country/region before either the strains or the plasmids have the opportunity to spread further.

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Thank you