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O0577 Molecular determinants of response to antimicrobial combinations for the treatment of carbapenem-resistant Enterobacteriaceae (CRE)

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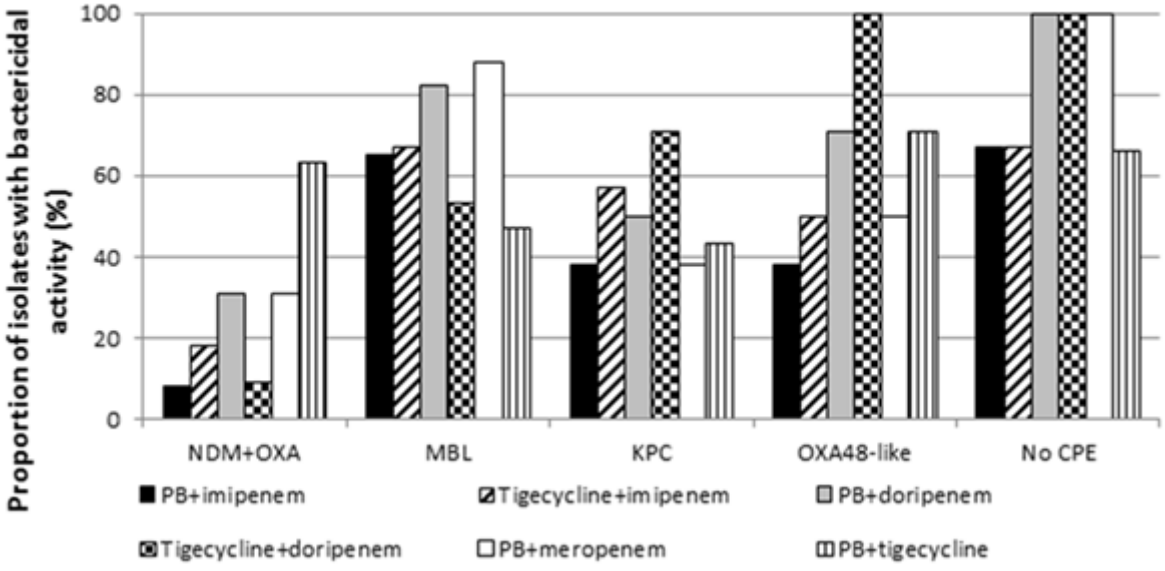
Background: CRE exhibit high genetic diversity and resistance is mediated by multiple different mechanisms. Combination therapy appears to be effective in certain instances but optimal treatment regimens remained undefined. It is unclear whether specific resistance mechanisms influence the activity of antibiotic combinations. This study aimed to evaluate the *in vitro* activity of antibiotic combinations against CRE with heterogeneous resistance mechanisms and to identify genetic markers for effective combination therapy.

Materials/methods: 49 clinical (blood, abdominal, urinary, respiratory isolates) CRE isolates were included in the study. Time-kill studies were conducted with 5 $\log_{10}$ CFU/mL baseline at clinical achievable concentrations of aztreonam, cefepime, piperacillin/tazobactam, doripenem, imipenem, meropenem in combination with polymyxin B (PB) or tigecycline. Each of the carbapenems were also evaluated in combination with ertapenem.

Results: All isolates were resistant to tested antibiotics except PB (29% resistance) and tigecycline (20% resistance). The MIC_{50}/MIC_{90} (mg/L) were ≥128/≥128, ≥64/≥64, ≥128/≥128, ≥16/≥16, 1/4, 1/8 for aztreonam, cefepime, piperacillin/tazobactam, carbapenems (ertapenem, imipenem, meropenem and doripenem), tigecycline and PB respectively. Most isolates harboured ≥ 1 ESBL/AmpC (47/49). Carbapenemases was detected in 46/49 isolates [14 metallo-beta-lactamase (MBL), 13 co-producers, 8 KPC, 8 OXA-48-like]. OmpK35 and OmpK36 loss were detected in 21 and 15 isolates respectively. Among all isolates, the combinations with the highest bactericidal (≥99.9% kill from baseline) rates were PB+doripenem (63%) and PB+meropenem (60%). The combinations with the highest bactericidal rates were tigecycline+doripenem for KPC-CRE (71%); PB+meropenem (88%) and PB+doripenem (82%) for MBL-CRE; tigecycline+doripenem for OXA-CRE (100%); PB+tigecycline (63%) for co-producer-CRE; and meropenem/doripenem plus PB/tigecycline (100%) for non-carbapenemase-CRE (Figure 1). The median (IQR) bactericidal rates of all combinations were 38%(34-47%), 44%(25-53%), 29%(17-44%), 9%(4-18%), and 67%(33-67%) for KPC-, MBL-, OXA-, coproducer- and non-carbapenemase-CRE respectively. There were significant differences between carbapenemase types and the bactericidal activity of doripenem- and meropenem-containing combinations ($p<0.05$). We did not observe any patterns between bactericidal activity and porin loss.

Conclusions:
The *in vitro* activities of various antibiotic combinations were highly variable in CRE. Carbapenemase types might have an impact on the activity of doripenem and meropenem combinations. Knowledge of carbapenemase types can provide empiric combination selection in CRE.

Figure 1.


Proportion of isolates with bactericidal activity (%)
100
80
60
40
20
0
NDM+OXA
MBL
KPC
OXA48-like
No CPE
PB+imipenem
Tigecycline+imipenem
PB+doripenem
Tigecycline+doripenem
PB+meropenem
PB+tigecycline