Therapeutic Management of Bloodstream Infection Resulting from *Pseudomonas aeruginosa* that is Non-Susceptible to Carbapenems but Susceptible to Cephalosporins and/or to Penicillins

Asaf Miller, Hadas Ofer-Friedman, Ronit Zaidenstein,
Mor Dadon, Dror Marchaim

Introduction

For bloodstream infections (BSI) caused by *Pseudomonas aeruginosa* (PA) that is non-susceptible to ≥1 group 2 carbapenem, it is debatable whether older β-lactam alternative (e.g., ceftazidime, piperacillin) can be safely used, even when the organism is supposedly susceptible.

Method

- A retrospective cohort study was conducted at Assaf Harofeh Medical Center (AHMC) from 01/2010 to 08/2014.
- Adult patients with PA-BSI with MIC > 2 to either meropenem or imipenem, but with MIC < 16 to ceftazidime, or <32 to piperacillin, or < 32/4 to piperacillin-tazobactam were enrolled.
- We compared the outcomes of patients who got (≥2 doses) of an appropriate (per in-vitro report) beta-lactam agent ("cases") to those who got (≥2 doses) of appropriate non-beta-lactam regimens ("controls").
- Patients who received agents from both study arms were excluded.
- Whole genome sequencing for one representative blood isolate was executed, and mechanisms of carbapenem resistance and genotyping (MLST) were queried.

Results

- There were 26 patients with PA BSI who met the inclusion criteria: 18 were treated with a beta-lactam: 9 with pipacillin-tazobactam, 7 with ceftazidime, and 2 patients received a combination of both agents. 8 patients were treated with non-beta-lactam regimen: 3 with a fluoroquinolone, 2 with colistin, 1 with an aminoglycoside and a fluoroquinolone, 1 with an aminoglycoside and colistin, and 1 with a fluoroquinolone and colistin.
- Patients' characteristics were similar between groups (prediction score to control for biases associated with being a "case" in not presented due to model instability).
- All clinical outcomes were similar between groups (Table).
- Molecular investigation of a representative isolate revealed a strain that belonged to MLST-137 and harbored several weak OXAs and efflux pumps (Table).

Conclusions

- Even for invasive BSI, when the PA is non-susceptible to carbapenems, it is reasonable to choose another "appropriate" (per MIC breakpoints) non-carbapenem-beta-lactam agent.
- However, larger confirmatory studies are needed.

Outcome Parameter	Beta-lactam Rx (n=18)	Non-β-lactam Rx (n=8)	OR	CI-95%	P value
In hospital mortality	11 (61)	4 (50)	1.6	0.3-8.4	0.7
14 days mortality	6 (33)	2 (25)	1.5	0.2-9.8	>0.99
30 days mortality	10 (57)	4 (50)	1.25	0.2-6.6	>0.99
90 days mortality	11 (61)	4 (50)	1.6	0.3-8.4	0.68
Functional deterioration	4 (57)	0			0.2
Additional hospitalizations in 3 months following the index infection	11 (92)	5 (83)	2.2	0.1-43	>0.99
LOS after excluding dead	11 (6-39)	11 (5-23)			0.3

Name of mechanism	Role and function of mechanism
mdtC, mdtB, mexN	efflux pump conferring antibiotic resistance; aminocoumarin resistance gene
mexC, adeA	chloramphenicol resistance gene; beta-lactam resistance gene; macrolide resistance gene; fluoroquinolone resistance gene; efflux pump conferring antibiotic resistance; trimethoprim resistance gene
mtrD, adeB, ceoB, mdsB, smeE, mexY, smeB, amrB, mexQ, acrB, adeG, acrF, mdtF, acrD, mexF, mexD, mexB, cmeB, adeJ	efflux pump conferring antibiotic resistance; tetracycline resistance gene; fluoroquinolone resistance gene
OXA-50	antibiotic inactivation enzyme; beta-lactam resistance gene
rosB	efflux pump conferring antibiotic resistance; polymyxin resistance gene
PDC-5, PDC-4, PDC-7, PDC-6, PDC-1, PDC-3, PDC-2, LRA-18, PDC-9, PDC-8, LRA-13, PDC-10	antibiotic inactivation enzyme; beta-lactam resistance gene

Correspondence: Dr. Dror Marchaim, M.D.; drormarchaim@gmail.com