MDR *P. aeruginosa*: resistance mechanisms other than MBLs, including treatment options

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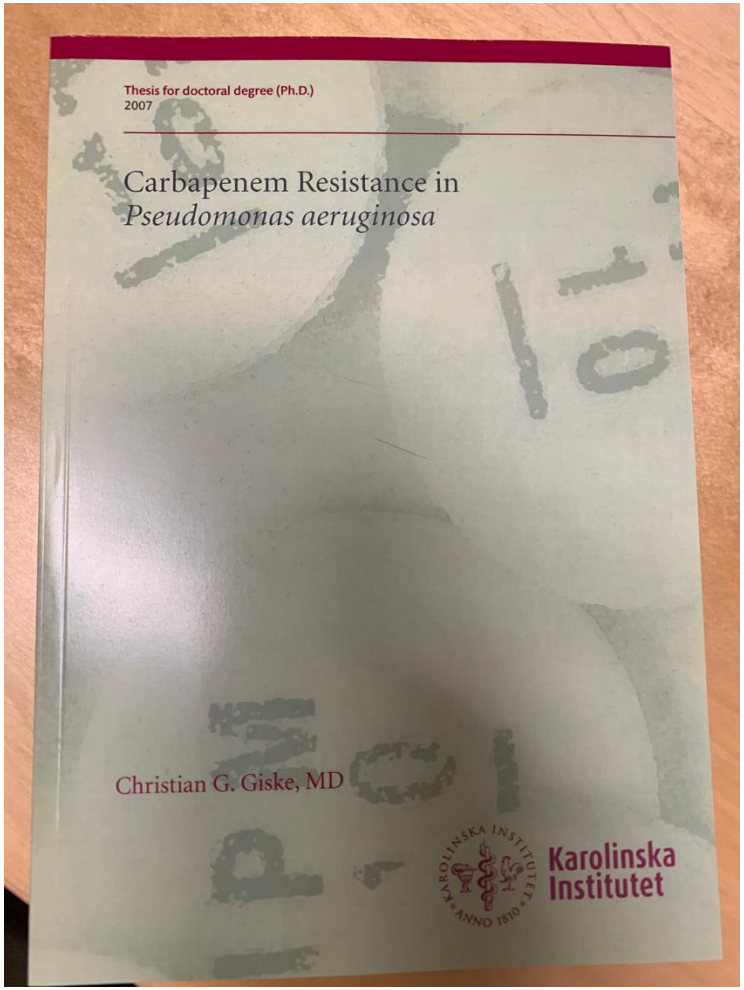
A trip down memory lane…



Multidrug-resistant *P. aeruginosa*

What is a normal antibiogram for *P. aeruginosa*?

- Piperacillin-tazobactam I (susceptible increased exposure)
- Ceftazidime I (susceptible increased exposure)
- Imipenem I (susceptible increased exposure)
- Meropenem S (susceptible)
- Ciprofloxacin I (susceptible increased exposure

Definition of MDR in *P. aeruginosa*

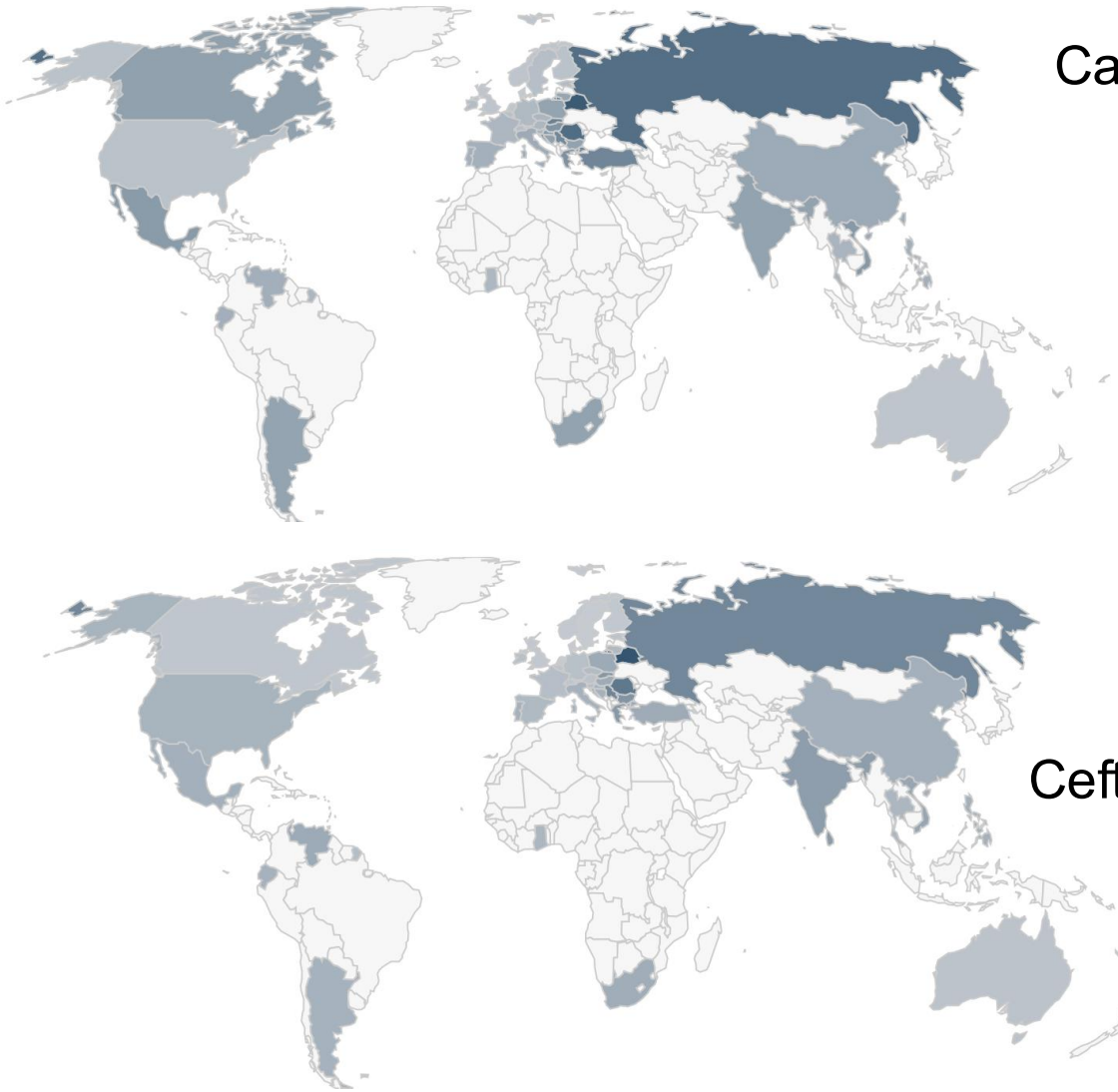
Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)
Aminoglycosides	Gentamicin	
	Tobramycin	
	Amikacin	
	Netilmicin	
Antipseudomonal carbapenems	Imipenem	
	Meropenem	
	Doripenem	
Antipseudomonal cephalosporins	Ceftazidime	
	Cefepime	
Antipseudomonal fluoroquinolones	Ciprofloxacin	
	Levofloxacin	
Antipseudomonal penicillins + β-lactamase inhibitors	Ticarcillin-clavulanic acid	
	Piperacillin-tazobactam	
Monobactams	Aztreonam	
Phosphonic acids	Fosfomycin	
Polymyxins	Colistin	
	Polymyxin B	

Criteria for defining MDR, XDR and PDR in *Pseudomonas aeruginosa*
MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories.
XDR: non-susceptible to ≥1 agent in all but ≤2 categories.
PDR: non-susceptible to all antimicrobial agents listed.
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

Magiorakos et al.
Clin Microbiol Infect 2012; 18:268–281

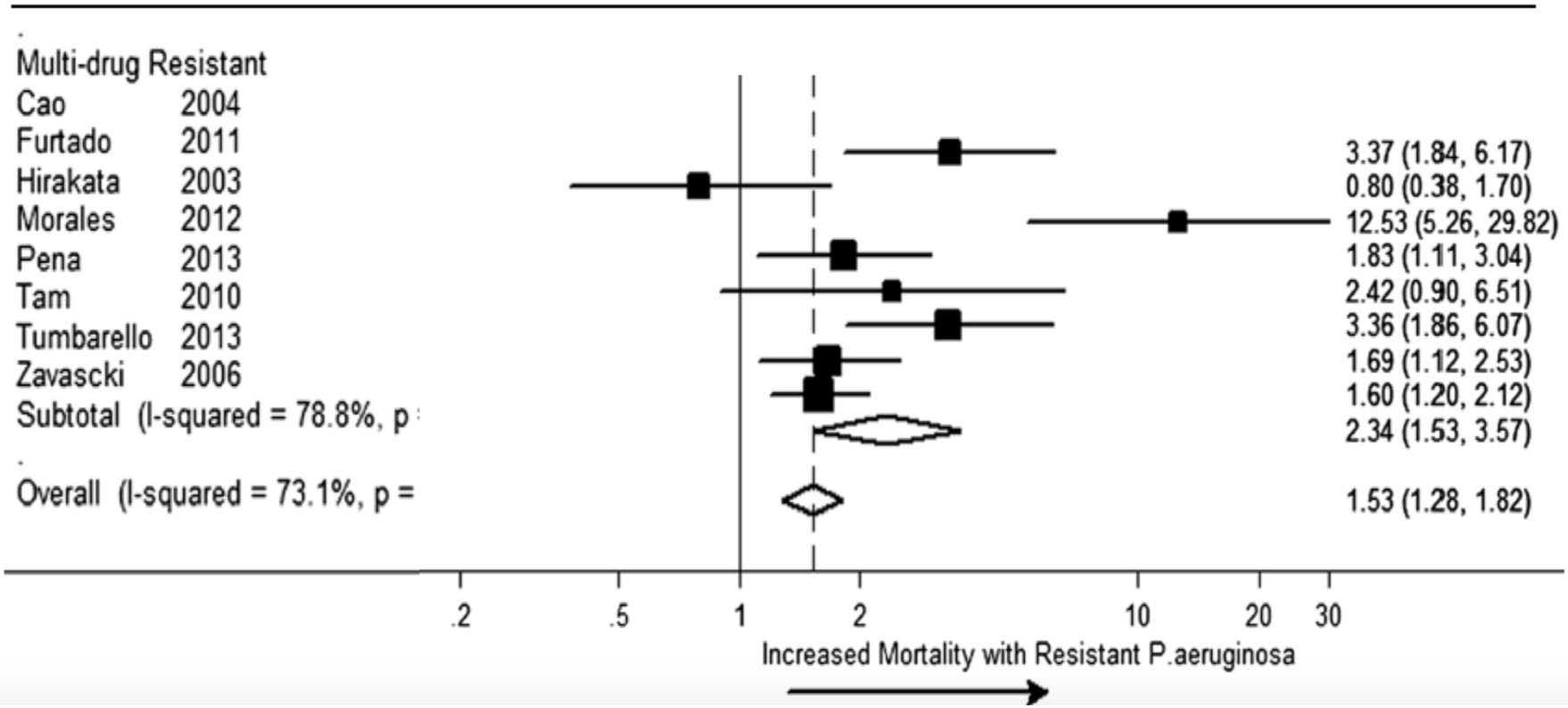
Problem:
-S is often I (or absent, or bracketed…)
-Non-susceptible is not a relevant term anymore

Multidrug-resistant *P. aeruginosa*



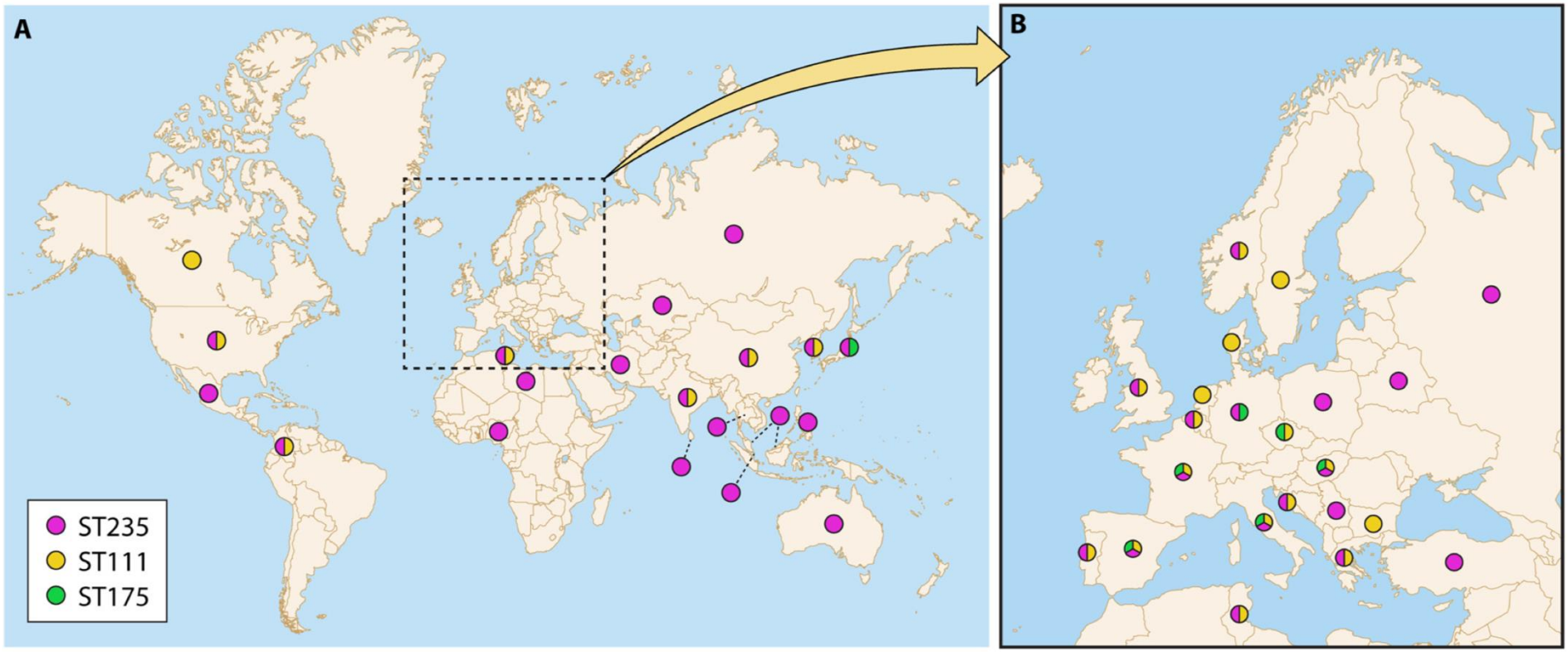
resistancemap.cddep.org

MDR *P. aeruginosa* causes higher mortality



Nathwani et al. Antimicrobial Resistance and Infection Control 2014, 3:32

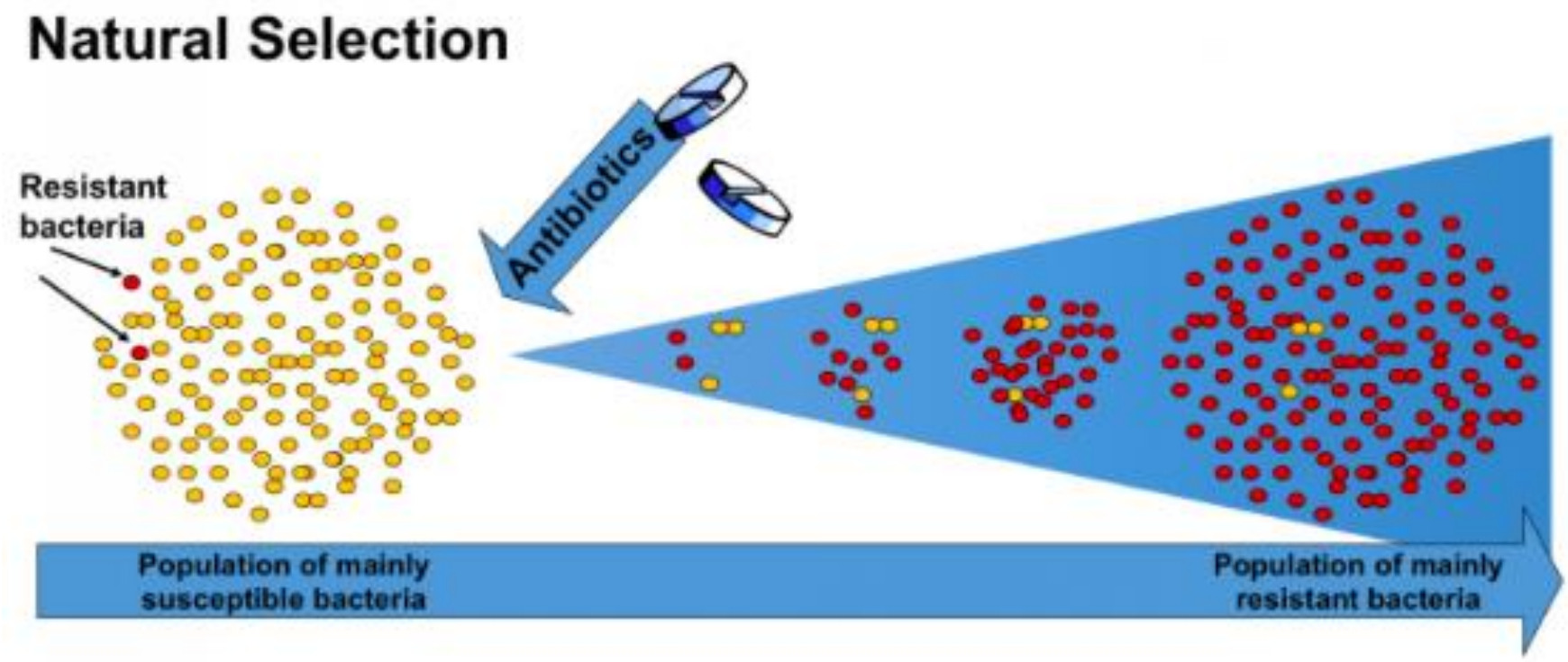
Some specific clones dominate among MDR *P. aeruginosa*



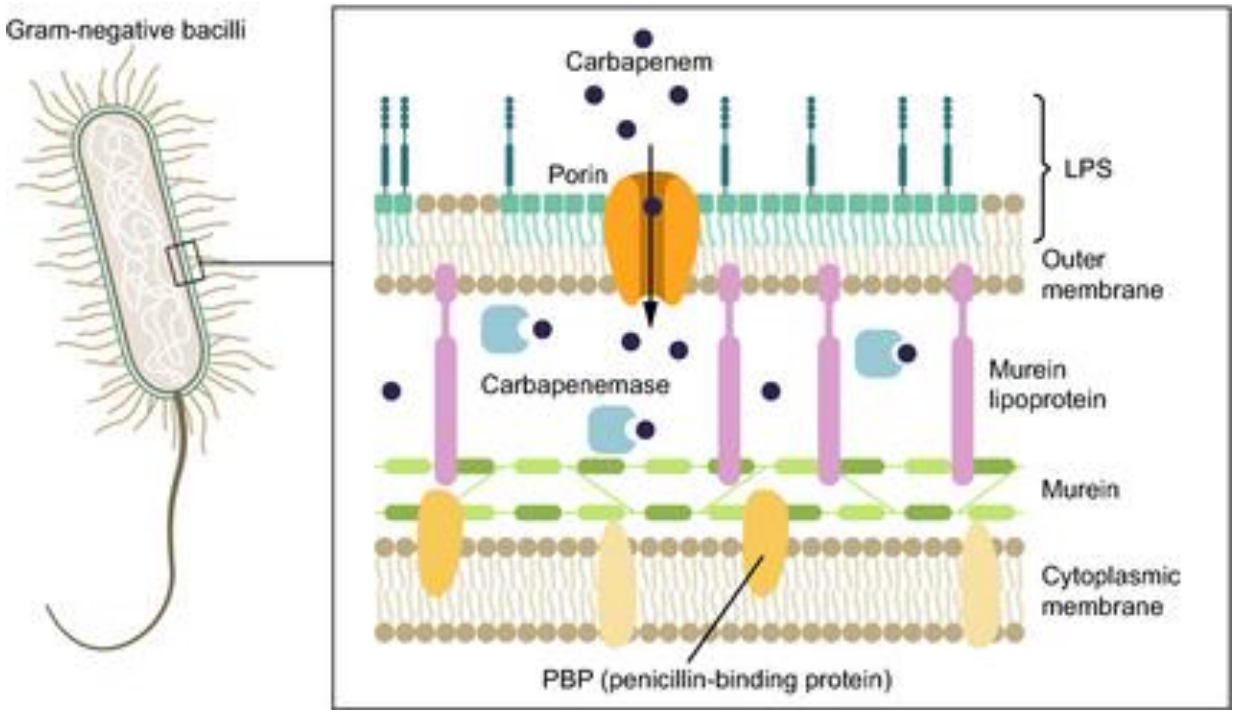
Horcajada et al. Clin Microbiol Rev 2019; 32:e00031-19

What are the mechanisms?

Chromosomal resistance: selection of resistant mutants

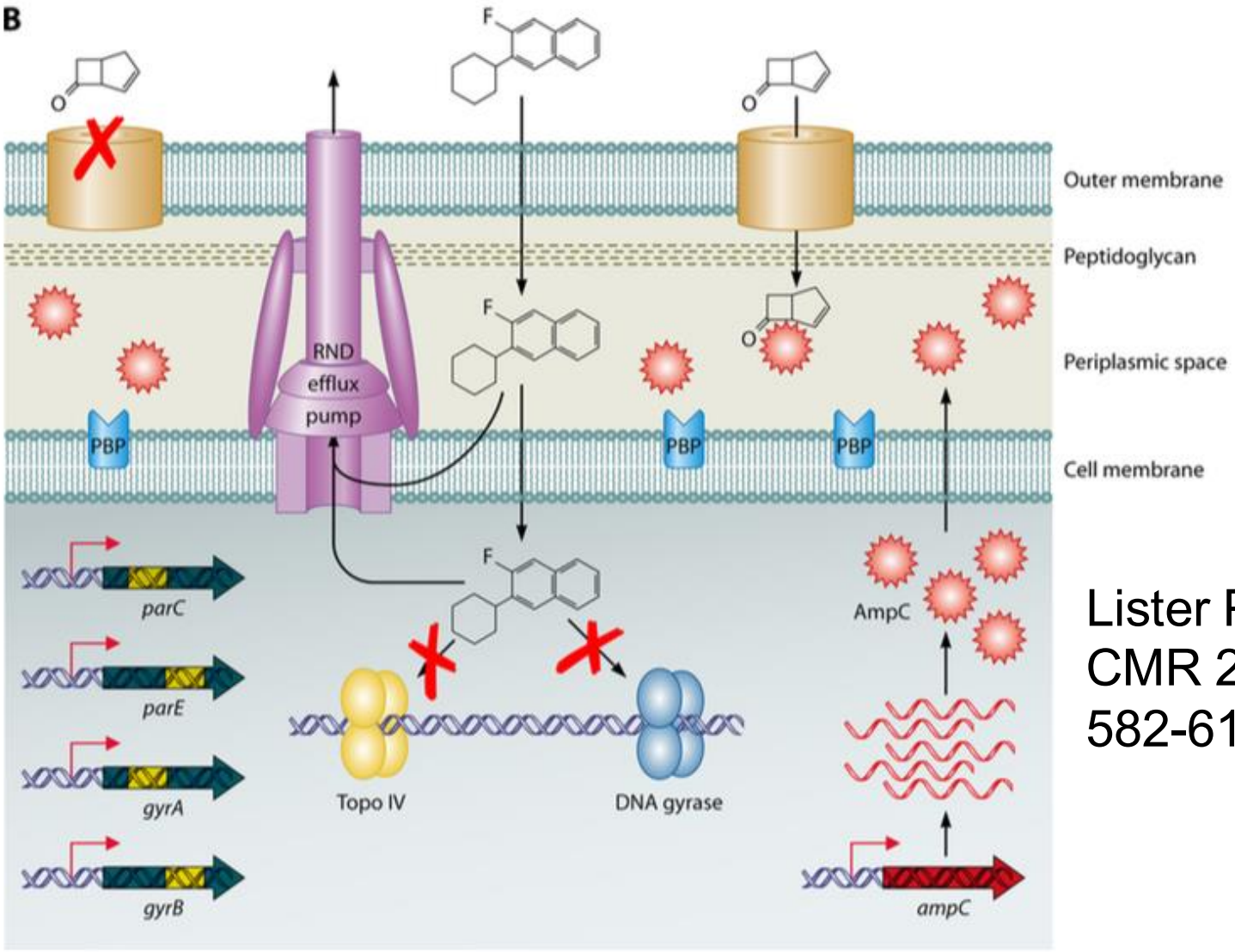


Resistance mechanisms: cell wall



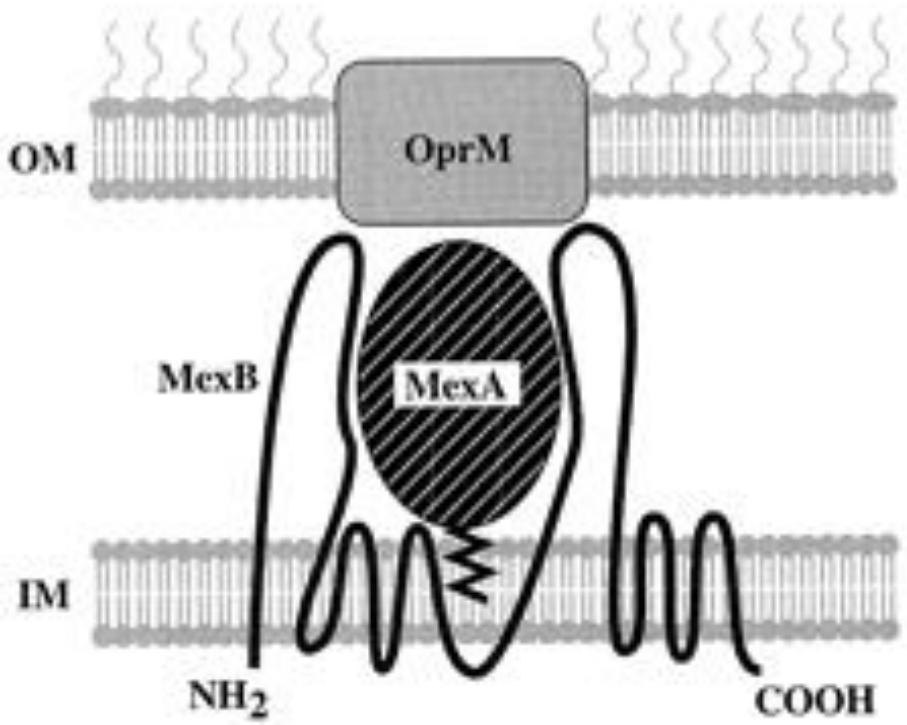
Tängdén T and Giske CG. J Intern Med. 2015;277(5):501-12.

Resistance mechanisms (cont.)



Lister PD et al. CMR 2009; 22: 582-610

Efflux



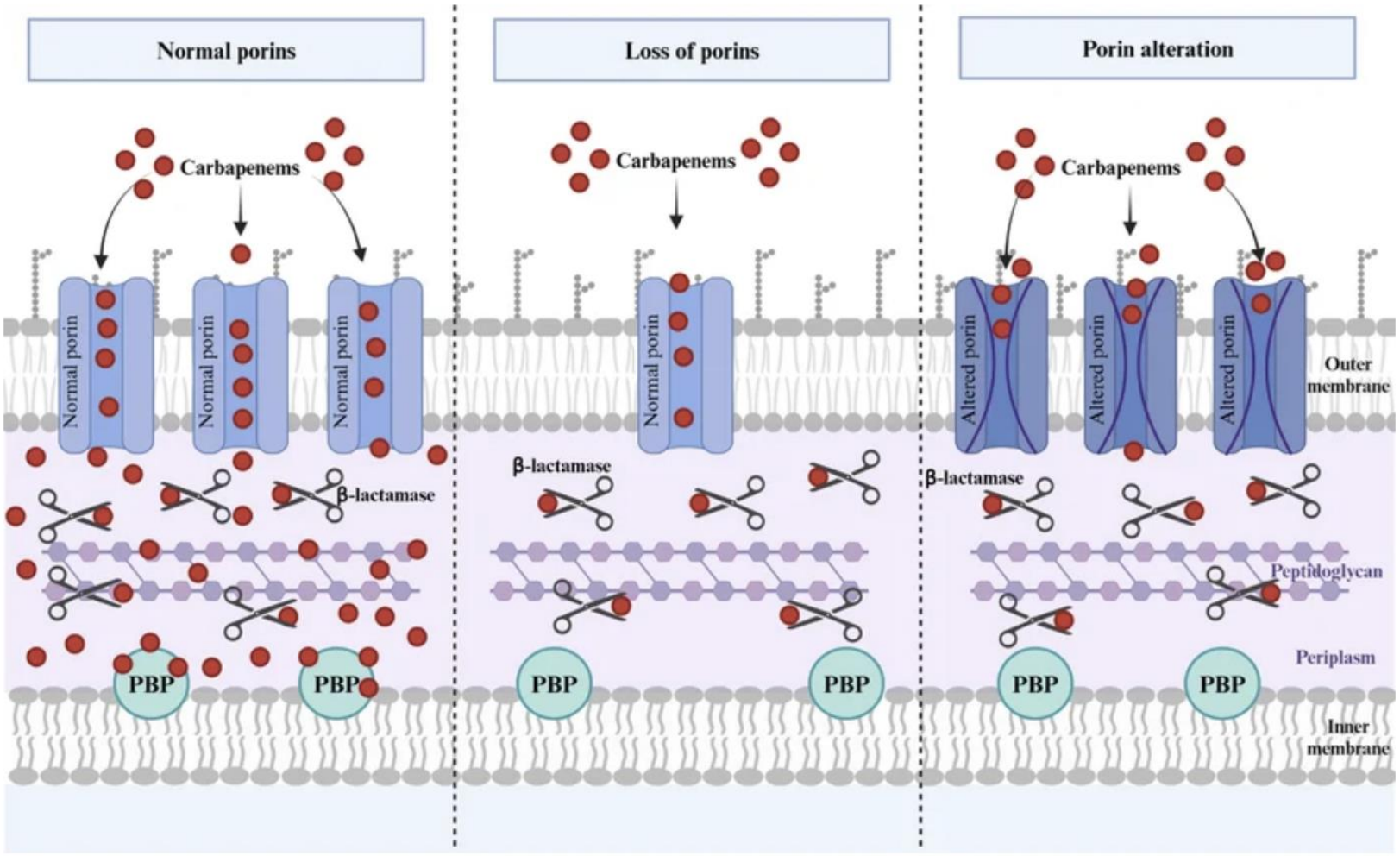
Heavy metals Dyes
Solvents Antimicrobials

Pump (MexB)
Channel (OprM)
Fusion protein (MexA)

Baseline expression: intrinsic resistance

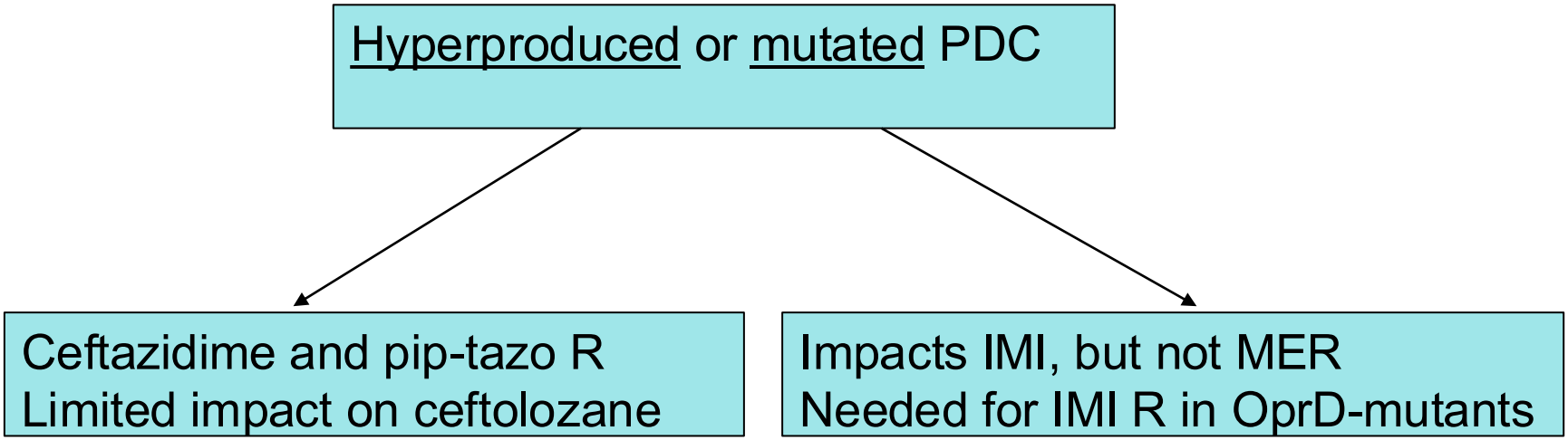
Hyperexpression: resistance to antipseudomonal beta-lactams and FQ

Permeability: OprD porin



Mammeri H et al. PloS Pathogens 2025 10.1371/journal.ppat.1012902

Pseudomonas-derived cephalosporinase (PDC)/AmpC



PDC can be inhibited: e.g. relebactam, avibactam
Restores activity to CAZ, PTZ and IMI (in strains with porin loss)
Induced AmpC: no resistance to antipseudomonal beta-lactams

Oliver A et al. CMI 2024; 30: 469

Isolated imipenem resistance

Ceftazidime I
Piperacillin/tazobactam I
Ciprofloxacin I
Meropenem S (or I)
Imipenem R

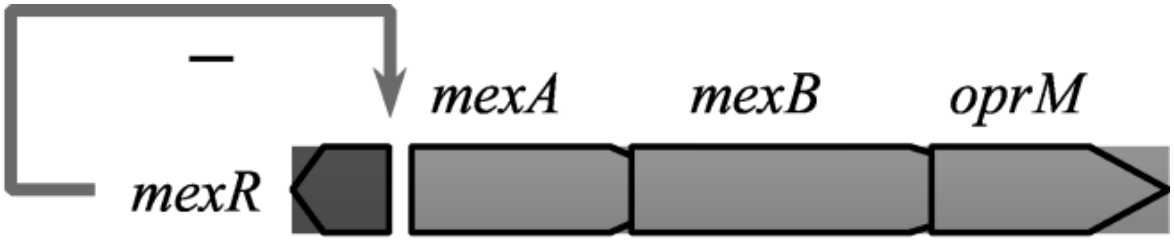
Porin loss

OprD: -Uptake of basic amino acids, imipenem and meropenem
-Imipenem MIC 8-32 mg/L (Livermore, JAC 2001)
-Meropenem MIC 2-4 mg/L
-17% mutation rate in imipenem monoterapy (Calandra et al, Lancet 1986)
-High imipenem consumption associated with significant increase of resistance in *P. aeruginosa* (Lepper et al, AAC 2002)

Meropenem and ciprofloxacin

Ceftazidime I
Piperacillin/tazobactam I
Ciprofloxacin R
Meropenem I
Imipenem I

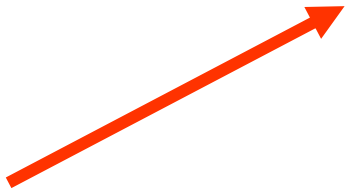
→ Efflux



Derepression selected by fluoroquinolones and meropenem
Meropenem and FQ are substrates (not imipenem)
Concomittant OprD mutation needed for full MER resistance

R to all beta-lactams

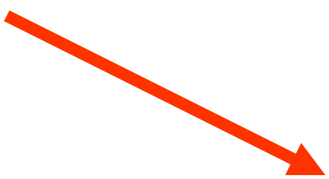
Ceftazidime R
Piperacillin/tazobactam R
Ciprofloxacin I/R
Meropenem R
Imipenem R



Efflux

Porin loss

PDC



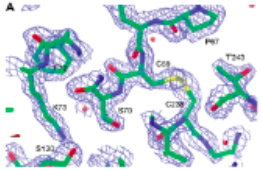
Carba-
penemase

Class B: -MBLs: NDM/VIM/IMP/SPM/GIM
-Can hydrolyze all beta-lactams except monobactams

Class A: -KPC and GES: in some parts of the world

Beta-lactamases – overview

Serine β-lactamases



Class A | **Class C** | **Class D**

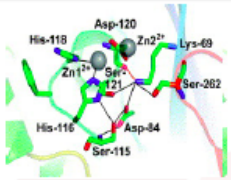
ESBLs:
CTX-M, TEM-ESBL, SHV-ESBL, PER, VEB etc.

CARBAPENEMASES:
KPC, IMI/NMC-A, SME GES-variants, FRI, BIC, SFC BKC, etc.

ESBLs:
OXA-11, OXA-13, etc.

CARBAPENEMASES:
OXA-48-like, OXA-23-like, OXA-24/-40-like, OXA-58-like, OXA-143-like, etc.

Metallo-β-lactamases (MBLs)



Class B

CARBAPENEMASES:
NDM, VIM, IMP, SPM, GIM, DIM, SIM, AIM, KHM, TMB, etc.

Most common is Pseudomonas-derived cephalosporinase (PDC) or AmpC
Class B metallo-beta-lactamases are common in some regions
Class A beta-lactamases (KPC, GES): in some parts of the world

Resistance mechanisms and typical antibiogram

Mekanism	Pip-taz	Cefta	Imip.	Merop.	Cipro.
Impermeability (porins)	I	I	R	I	I
Efflux	I	I	I	R	R
AmpC alterations or hyperproduction	R	R	I	S	I
Porin+efflux+AmpC	R	R	R	R	R
Metallo-beta-lactamase (MBL)	R	R	R	R	I
MBL+ciprofloxacin resistance mechs.	R	R	R	R	R

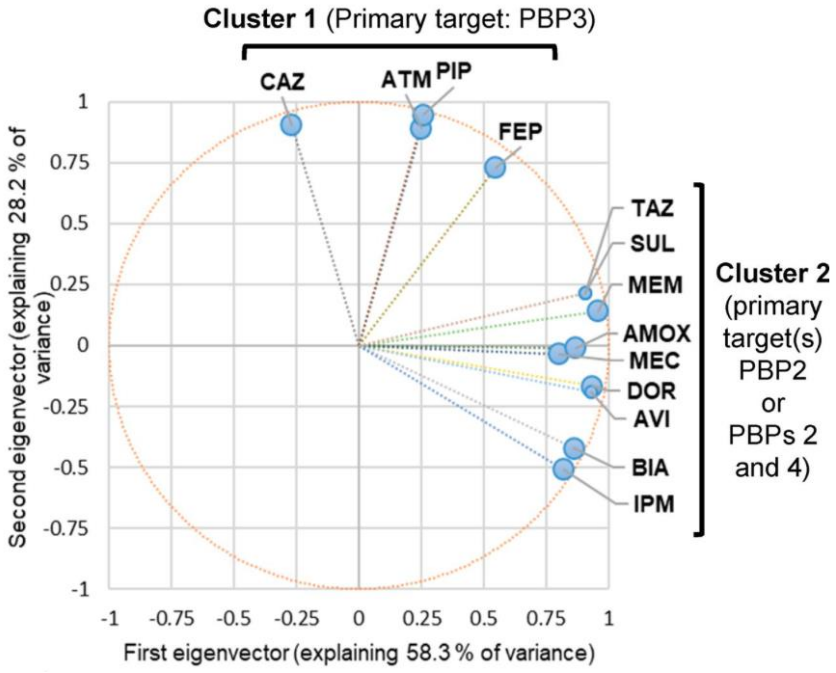
What about the new drugs?

What about the new drugs?

Antimicrobial	PDC ↑	PDC mut.	PDC+ porin	PDC+porin +efflux	KPC or GES	MBL
Ceftolozane-tazobactam	+	+/-	+	+	-	-
Ceftazidime-avibactam	+	+/-	+	+	+	-
Meropenem-vaborbactam	+	+	+/-	-	-	-
Imipenem-relebactam	+	+	+/-	+/-	-	-
Cefiderocol	+	+	+	+	+	+

Oliver A et al. CMI 2024; 30: 469

Cefiderocol resistance

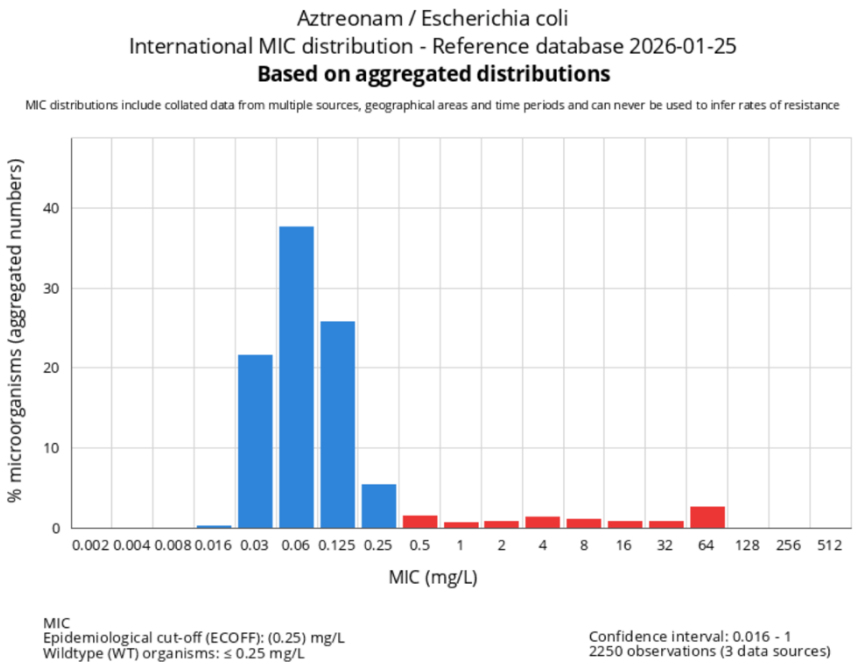


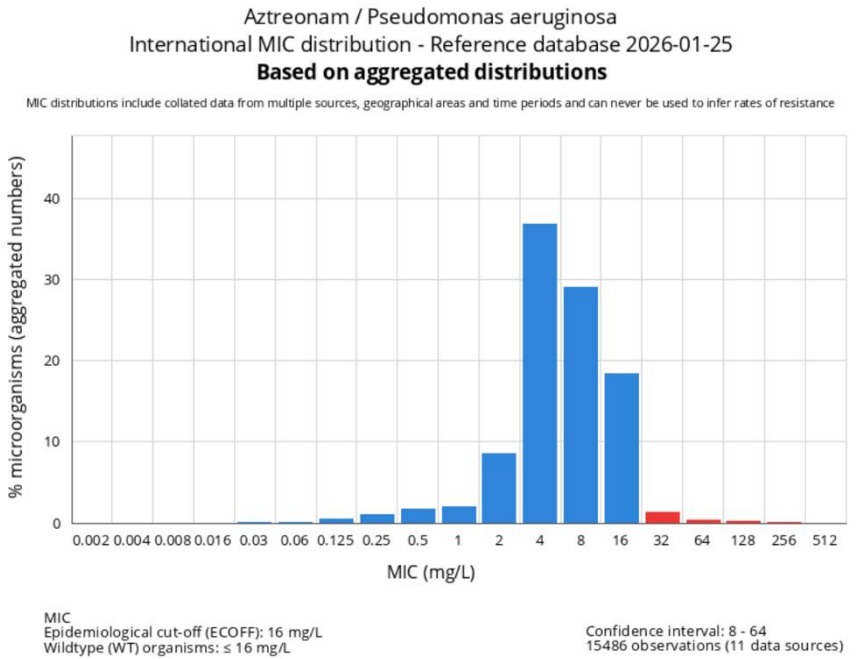
Cefiderocol: binds to PBP3

PBP3 changes can confer resistance, along with mutations in iron uptake systems

Sutaria DS, et al. Antimicrob Agents Chemother 2018; 62:e00282-18.

Why is aztreonam-avi not as active vs *P. aeruginosa*?





With aztreonam 2 g x 4 plus extended infusion you have some coverage of 16 mg/L
Aztreonam-avibactam only contains 1.5 g aztreonam
Aztreonam is also affected by efflux, which may be present in strains with MBL, and by some PDC-mutations (when protected by avibactam)

Thank you for your attention!