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Pseudomonas aeruginosa Resistance to Beta-lactams

Note: Chart is meant as a general teaching tool for common and advanced mechanisms of antimicrobial resistance (AMR).
Resistance in *P. aeruginosa* is complex and various mechanisms may be simultaneously present, impacting *in vitro* activity of each agent.

Minimally impacted by AMR mechanism
Heavily impacted by AMR mechanism **R**=Resistant
Some AMR impact
Possible association

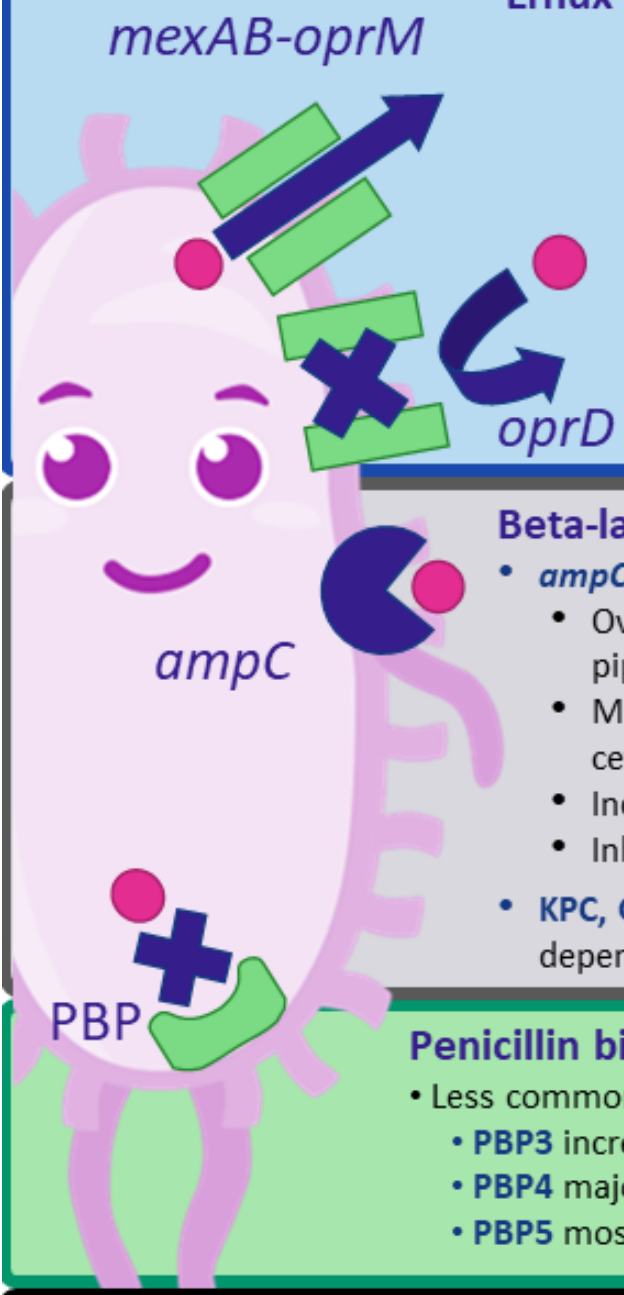
	Porin Channels	Efflux Pumps	AmpC	Carbapenemases Minor AMR contributor
Standard Agents				
Ceftazidime	↑ MIC Loss of OprF	↑ MIC or R Upregulated MexAB-OprM		
Cefepime	↑ MIC Loss of OprF	↑ MIC or R Upregulated MexAB-OprM, MexXY-OprM, MexCD-OprJ	↑ MIC or R Overexpression	
Piperacillin-Tazobactam	↑ MIC Loss of OprF	↑ MIC or R Upregulated MexAB-OprM		
Imipenem	R Loss of OprD		↑ MIC Overexpression	
Meropenem	↑ MIC Loss of OprD	↑ MIC or R Upregulated MexAB-OprM & MexXY-OprM		
MDR Agents				
Ceftazidime-Avibactam	↑ MIC Loss of OprF	↑ MIC or R Upregulated MexAB-OprM	↑ MIC or R AmpC mutants	Inhibits some carbapenemases rarely found in PsA, does not inhibit MBL
Ceftolozane-Tazobactam			↑ MIC or R AmpC mutants	
Imipenem-Relebactam		↑ MIC or R (Relebactam only) Upregulated MexAB-OprM & MexEF-OprN		Inhibits some carbapenemases rarely found in PsA, does not inhibit MBL
Meropenem-Vaborbactam	↑ MIC Loss of OprD	↑ MIC or R Upregulated MexAB-OprM & MexXY-OprM		Inhibits some carbapenemases rarely found in PsA, does not inhibit MBL
Cefiderocol	↑ MIC Mutation of Iron Transport system		↑ MIC or R AmpC mutants	Active vs KPC, MBL, GES ↑ MIC for NDM

SIDP Breakpoints Podcast Episode #59 Resistance in *P. aeruginosa*: Pearls & Perils - Hosted by Dr. Erin McCreary, featuring Drs. Maggie Monogue and Antonio Oliver

Pseudomonas aeruginosa
Mechanisms of Resistance

Breakpoints
The SIDP Podcast

Episode #59: Resistance in *Pseudomonas aeruginosa*: Pearls and Perils



Efflux pumps: β-lactams and aminoglycosides most affected
- ***mexR*** repressor gene mutation increases expression of ***mexAB-oprM*** (cefepime, ceftazidime, piperacillin, and meropenem)
- Relebactam less likely to be effluxed than avibactam
- ***mexXY*** induction of aminoglycoside resistance

Porin channel mutations:
- ***oprD:*** carbapenems (imipenem > meropenem)
- ***oprF:*** low-level, broad β-lactam effect

Beta-lactamases:
- ***ampC***: can hydrolyze most antipseudomonal β-lactams
  - Over expression is a major mechanism of resistance for piperacillin-tazobactam and ceftazidime
  - Mutations in the catalytic center of *ampC* can lead to ceftolozane-tazobactam and ceftazidime-avibactam resistance
  - Induced by: imipenem, piperacillin, and tazobactam
  - Inhibited by: avibactam, relebactam
- **KPC, GES, metallo-β-lactamases**: less common but heavily dependent on geographic region

Penicillin binding protein site mutations:
- Less common than other resistance mechanisms.
  - **PBP3** increases MIC to cefepime, aztreonam, and meropenem
  - **PBP4** major *ampC* regulator, mutation causes *ampC* overexpression
  - **PBP5** most common PBP, can function as a β-lactamase enzyme

Takeaway:
- **Local epidemiology is important for predicting resistance mechanisms in *Pseudomonas aeruginosa***
- **Knowledge of underlying resistance mechanisms is important for determining optimal treatment**

Featured Speakers: Maggie Monogue, PharmD and Antonio Oliver, MD
Host: Erin McCreary, PharmD
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