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P1531 First comprehensive penicillin-binding protein (PBP) occupancy patterns of beta-lactams in Acinetobacter baumannii (AB)

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Background: All beta-lactam antibiotics bind to and thereby inactivate the PBPs as their high affinity target sites. A few prior studies presented PBP binding data for selected beta-lactams in AB, but a comprehensive binding dataset is lacking. We aimed to generate the first comprehensive PBP binding dataset for 12 chemically diverse and clinically relevant β-lactams in AB.

Material/Methods: PBP binding by β-lactams was assessed using Bocillin FL fluorogenic binding assay in AB ATCC 19606. Bacteria were lysed by sonication and membrane fractions isolated via ultracentrifugation. Binding reactions were conducted over a wide concentration range. Antibiotics were incubated with the membranes at 35°C before adding BOCILLIN FL. The membranes were then analyzed on SDS-PAGE and scanned directly by an imager. Binding data ('IC50s') were reported as the beta-lactam concentration which half-maximally decreased the Bocillin FL signal.

Results: Mecillinam had high affinity for PBP2. Carbapenems bound PBP1a and PBP2 at concentrations <=0.125 mg/L and PBP1b and PBP3 at slightly higher concentrations. Ceftazidime bound PBP1a at low and PBP3 at higher concentrations. Cefepime and cefpirome bound PBPs more evenly.

	IC50 of the indicated drug (mg/L)[a]							
	IPM	MEM	DOR	FEP	CPO	CAZ	ATM	MEC
PBP 1a	0.06	<0.03	<0.03	<0.03	<0.03	<0.06	0.5	256
PBP 1b	1	0.5	0.5	1	2	8	2	256
PBP 2	0.125	<0.03	<0.03	0.25	0.25	32	4	<0.06
PBP 3	1	0.125	0.125	0.5	1	0.5	0.5	64

[a] Concentration of β-lactam that inhibits 50% of Bocillin FL compared to a control containing no drug. IPM, imipenem; MEM, meropenem; DOR, doripenem; FEP, cefepime; CPO, cefpirome; CAZ, ceftazidime; ATM, aztreonam; MEC, mecillinam.

Conclusions: This study provided the first comprehensive PBP binding data of beta-lactams in AB. The carbapenems, cefepime and cefpirome bound PBP1a and PBP2 at low concentrations, as well as PBP1b and PBP3 at higher concentrations. These PBP binding data enable the development and rational optimization of double beta-lactam and beta-lactam / beta-lactamase inhibitor combinations in AB.