# رقم البحث: ( ٤ )

**عنوان البحث باللغة الانجليزية**:

First penicillin-binding protein occupancy patterns for 15 β-lactams and β-lactamase inhibitors in *Mycobacterium abscessus*

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**المؤلفين**

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## ABSTRACT

*Mycobacterium abscessus* causes serious infections that often require over 18 months of antibiotic combination therapy. There is no standard regimen for the treatment of *M. abscessus* infections, and the multitude of combinations that have been used clinically have had low success rates and high rates of toxicities. With β-lactam antibiotics being safe, double β-lactam and β-lactam/β-lactamase inhibitor combinations are of interest for improving the treatment of *M. abscessus* infections and minimizing toxicity. However, a mechanistic approach for building these combinations is lacking since little is known about which penicillin-binding protein (PBP) target receptors are inactivated by different β-lactams in *M. abscessus* We determined the preferred PBP targets of 13 β-lactams and 2 β-lactamase inhibitors in two *M. abscessus* strains and identified PBP sequences by proteomics. The Bocillin FL binding assay was used to determine the β-lactam concentrations that half-maximally inhibited Bocillin binding (50% inhibitory concentrations [$IC_{50}$s]). Principal component analysis identified four clusters of PBP occupancy patterns. Carbapenems inactivated all PBPs at low concentrations (0.016 to 0.5 mg/liter) (cluster 1). Cephalosporins (cluster 2) inactivated PonA2, PonA1, and PbpA at low (0.031 to 1 mg/liter) (ceftriaxone and cefotaxime) or intermediate (0.35 to 16 mg/liter) (ceftazidime and cefoxitin) concentrations. Sulbactam, aztreonam, carumonam, mecillinam, and avibactam (cluster 3) inactivated the same PBPs as cephalosporins but required higher concentrations. Other penicillins (cluster 4) specifically targeted PbpA at

2 to 16 mg/liter. Carbapenems, ceftriaxone, and cefotaxime were the most promising β-lactams since they inactivated most or all PBPs at clinically relevant concentrations. These first PBP occupancy patterns in *M. abscessus* provide a mechanistic foundation for selecting and optimizing safe and effective combination therapies with β-lactams.