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Impact of Key and Secondary Drug Resistance Mutations on Structure and Activity of β-Lactamases

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6.1 Introduction

The resistance of bacteria to various classes of antibiotics is determined by the activity of a large number of bacterial enzymes. They either represent the targets for antibiotics or modify antibiotics and their targets. The family of genes responsible for the resistance has been called "the resistome" (Wright 2007), and the family of enzymes involved in the implementation of resistance has been called "the enzystome" (Egorov et al. 2018). β-Lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams) are the most widely used in medicine and agriculture; they account for more than 60% of all used antibiotics. The rise of antibiotic resistance of the causative agents of infectious diseases in humans, animals, and the environment has become a threat and is responsible for serious problems in clinical microbiology (WHO 2018; Cassini et al. 2019). The problem became significantly complicated by the emergence of multidrug-resistant (MDR) and pandrug-resistant (PDR) Gram-negative bacteria (Davies and Davies 2010; Theuretzbacher 2017). β-Lactam antibiotics irreversibly inhibit penicillin-binding proteins (PBPs) participating in the synthesis of the cell wall, and this leads to the death of bacterial pathogens. In Gram-positive bacteria, PBPs mutated, which reduced their ability to bind β-lactams and caused the resistance. Gram-negative bacteria evolved by other means, synthesizing a new class of enzymes, β-lactamases, which catalytically hydrolyze β-lactams. This protects the bacterial cells by thousands of times more efficiently, despite the emergence of new β-lactams (Bonomo 2017). The high rate of spread of resistant pathogenic strains is explained by the localization of the β-lactamase genes mainly on the mobile genetic elements.

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