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Resistance to ketolide antibiotics by coordinated expression of rRNA methyltransferases in a bacterial producer of natural ketolides

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Ketolides are promising new antimicrobials effective against a broad range of Gram-positive pathogens, in part because of the low propensity of these drugs to trigger the expression of resistance genes. A natural ketolide pikromycin and a related compound methymycin are produced by *Streptomyces venezuelae* strain ATCC 15439. The producer avoids the inhibitory effects of its own antibiotics by expressing two paralogous rRNA methylase genes *pikR1* and *pikR2* with seemingly redundant functions. We show here that the *PikR1* and *PikR2* enzymes mono- and dimethylate, respectively, the N6 amino group in 23S rRNA nucleotide A2058. *PikR1* monomethylase is constitutively expressed; it confers low resistance at low fitness cost and is required for ketolide-induced activation of *pikR2* to attain high-level resistance. The regulatory mechanism controlling *pikR2* expression has been evolutionary optimized for preferential activation by ketolide antibiotics. The resistance genes and the induction mechanism remain fully functional when transferred to heterologous bacterial hosts. The anticipated wide use of ketolide antibiotics could promote horizontal transfer of these highly efficient resistance genes to pathogens. Taken together, these findings emphasized the need for surveillance of *pikR1/pikR2*-based bacterial resistance and the preemptive development of drugs that can remain effective against the ketolide-specific resistance mechanism.

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Incidence and characterization of multi-drug resistance *Acinetobacter Baumannii*

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Objectives: *A. Baumannii* is a common cause of infections associated with high mortality and morbidity. It is an important multi-drug resistant microorganism worldwide. The aim of this study is to investigate the incidence and characterization of *A. Baumannii* in a tertiary Hospital in Jordan.

Methods: Retrospective study using data available on Vitek 2 compact system and patients files from 2010 to 2016 in Specialty Hospital, Amman. Demographic, clinical, isolates information and antibiotics sensitivity patterns were collected and analyzed using appropriate statistical tests.

Results: 622 *A. Baumannii* isolates were reported during the study period with about 99% having high confidence rate. Most isolates were from male, aged 18-60 years, Jordanian, and from infected wounds in surgery and critical care departments. 76.8% of *A. Baumannii* isolates were MDR. Adults over 60, male, non-Jordanians, critical ill patients and infected wounds represented significant risk factors for MDR incidence ($P < 0.0001$), while no statistical significant risk associate with years ($P = 0.3933$). Resistance pattern indicated high resistance for most cephalosporins, carbapenems fluoroquinolones, and ampicillin, moderate resistance for trimethoprim/sulfamethoxazole and ampicillin/sulbactam low resistance for aminoglycosides and tetracyclines, and the lowest resistance rates were for colistin and tigecycline. Most strains had aminoglycosides resistant phenotype GEN-NET-AMI-TOB, GEN-TOB-AMI and TOB-GEN-NET.

Conclusion: Jordan has high rate *A. Baumannii* MDR. Adults, critically ill males with infected wounds had significant high rate of *A. Baumannii* MDR. Continued surveillance and monitoring of this critical microorganism is required.

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