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THE IMPACT OF THE DELETION OF THE MMP-1 GENE ON THE EXPRESSION OF SYMPTOMS AND THE EFFECTIVENESS OF TREATMENT IN PATIENTS WITH PULMONARY TUBERCULOSIS

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The objective of the study is to examine the impact of the deletion of the MMP-1 gene on the development, expression, dynamics of clinical syndromes and the effectiveness of treatment in patients with pulmonary tuberculosis.

73 patients with pulmonary tuberculosis, receiving treatment in the hospital of the state health care facility "Regional TB Dispensary" in the city of Astrakhan. Depending on the genotype of MMP-1, three groups were formed: the first group — with G1/G1 — 15 people (20.5%), the second — with G2/G1 — 27 people (50.7%) and the third one — with G2/G2 — 21 people (28.8%).

During the treatment, the disappearance of symptoms of intoxication and bronchopulmonary disorders in patients of the 1st and 2nd groups occurred earlier than in the 3rd group ($\chi^2 = 11.5$, $p = 0.02$). Dissolving of infiltration in the lung tissue also started earlier in the first and second groups ($\chi^2 = 9.2$, $p < 0.05$). The discharge of *Mycobacterium tuberculosis* (MBT) stopped earlier in patients of the 1st group. After four months of treatment, MBT were not determined by any method in 94.6% of the patients in the 2nd group and in 90.4% in the 3rd group ($\chi^2 = 9.9$ $p = 0.07$). Closure of decay cavities after 2 months of treatment was observed in 70% of cases in patients of the 1st group, in 53.6% of cases — of the second and in 15.6% of cases — of the third. In 47.4% of patients with G2/G2, destructive changes persisted for more than 4 months of treatment ($\chi^2 = 10.3$, $p = 0.03$).

Patients with genotype G2/G2 have a tendency to a protracted tuberculosis. The study of the polymorphism of the MMP-1 gene in patients with pulmonary tuberculosis can be used as a prognostic criterion of the clinical course of tuberculosis, correction of specific therapy, and justification for prescribing drugs affecting collagen metabolism.

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IN VITRO ACTIVITY OF BEDAQUILINE AGAINST NON-TUBERCULOUS MYCOBACTERIA

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Infections caused by non-tuberculous mycobacteria (NTM) have become more frequent in the last years since they have emerged as important pathogens in immune-compromised patients. Unfortunately, their treatment is long, toxic and often with poor results. Bedaquiline (BDQ) (trade name Sirturo; Janssen Therapeutics, Inc.) has been approved for the treatment of multidrug-resistant tuberculosis and there is increasing interest in its potential use for treating NTM infections.

The aim of this study was to determine the Minimum Inhibitory Concentration (MIC) and the Minimum Bactericidal Concentration (MBC) of BDQ against clinical isolates of NTM obtained from different hospitals. We investigated the possible role of gene mutations on the activity of BDQ against NTM by sequencing the *atpE* gene.

The MIC was determined by the broth dilution method in 7H9 medium supplemented with OADC and glycerol using the resazurin microtiter assay (REMA). The MBC was determined by conventional 7H10 plate agar dilution method.

Range concentration of BDQ in REMA was assessed from 2 to 0.0035 μg/ml. Each experiment was performed in triplicate. The MIC of BDQ was found at ≤ 0.015 μg/ml. The MBC of all NTM tested was found to be higher than 4 times the MIC. No nonsynonymous mutations in the *atpE* gene that conferred BDQ resistance in all NTM tested were identified.

BDQ exhibited a strong inhibitory effect against all the NTM clinical isolates tested. These promising results indicate that BDQ could be potentially useful for the treatment of NTM. However, according to the MBC data it lacks bactericidal activity. Nevertheless, BDQ could still have excellent potential for use in patients with NTM infections and further investigation is needed.

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EMERGING OPPORUNISTIC PATHOGEN *MYCOBACTERIUM ABSCESSUS* IN SLOVENIA: MOLECULAR ANALYSIS OF RESISTANCE GENES COMPARED TO MIC METHOD

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Mycobacterium abscessus complex (MABSC) is a group of three closely related subspecies: *M. abscessus* subsp. *abscessus* (MAA), *M. abscessus* subsp. *bolletii* (MAB) and *M. abscessus* subsp. *massiliense* (MAM). Correct species identification is important, especially for patients with cystric fibrosis (CF), due to distinct molecular resistance profiles among subspecies. Gene *erm(41)* with T/C polymorphism at nucleotide 28 is responsible for inducible macrolide resistance (only in MAA and MAB, in MAM gene is not functional), meanwhile mutation in *rrl* gene causes high-level macrolide resistance. Amninoglycoside resistance occurs with mutation in *rrs* gene.

We aimed to diferentiate Slovenian MABSC isolates to subspecies level and to assess their molecular resistance profile. Selected isolates were further tested with microdilution method to to obtain full phenotypic resistance profile.

Molecular analysis was performed on 37 clinical isolates recovered from 37 patients in the period 2000–2017 from Slovenian National Mycobacterial Collection. GenoType NTM-DR (Hain Lifesciences, Nehren, Germany) was used to identify subspecies and resistance mutations. Antimicrobial susceptibility testing (AST) was performed on selected isolates with reference microdilution method using Sensititre RAPMYCO microplates (TREK Diagnostic Systems, Cleveland, Ohio, USA). Susceptibility and resistance were assessed according to CLSI guidelines.

GenoType NTM-DR showed the highest prevalence rate for MAA 72.9% (27/37), followed by MAB 16.2% (6/37) and MAM 10.8% (4/37). Resistance profile showed that T28 polymorphism in *erm(41)* gene is present in all MAB and MAM isolates and in 88.8% (24/27) MAA iso-