Evaluation of the synergism of phage therapy with antibacterial drugs in relation to *Pseudomonas aeruginosa* in biofilms

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Background: *P. aeruginosa* is a dangerous human pathogen causing various infections, especially in immunocompromised individuals. The ability of *P. aeruginosa* to form biofilms makes its treatment ineffective and therefore contributes to the development of chronic infections, including chronic lung infections in people with cystic fibrosis. Therefore, the development of new effective antibacterial drugs and alternative treatment options is an urgent task of modern pharmaceutics. Phages, viruses of bacteria, seem to be one of such alternatives. Although the efficiency of phages in combination with antibacterial drugs has been shown in many works, the high strain-specificity of phages requires screening of new ones for development of phage cocktails.

Materials and methods: *P. aeruginosa* strains ATCC 27853, 190158 and bacteriophages Ka1, Ka2 isolated from Baikal Lake were used in this work. The minimum inhibitory concentration (MIC) of antimicrobial agents was determined by broth microdilution assay. Cell viability was evaluated in resazurin test. Full-genome sequencing of bacteriophage genomes was performed on the Illumina-SOLEXA (MiSeq) platform.

Results: The Ka1 genome consists of 46092 nucleotides and has maximum identity with the genome of the bacteriophage *Pseudomonas* phage PSA37 (95 % with 79 % coverage), belonging to the family *Podoviridae*. The Ka2 genome consists of 66310 nucleotides and has maximum identity with the genome of the *Pseudomonas* phage S50 (97 % at 99 % coverage), belonging to the family *Myoviridae*. The electron microscopy confirmed that the ultrastructure of Ka1 and Ka2 fits with those of podoviruses and myoviruses, respectively. Ka1 exhibited synergy with amikacin, gentamicin, colistin, meropenem. In combination with bacteriophage, the MIC of amikacin on different test strains was 4-16 times lower, of colistin 16-32 times lower, of meropenem 4 times lower. The bacteriophage Ka2 reduced 4-8-fold the MIC of amikacin, 8-fold of gentamicin, 4-8-fold of Colistin and 4-fold of meropenem.

Conclusions: Ka1 and Ka2 bacteriophages can be used as part of phages cocktails for treatment of infections caused by *P. aeruginosa*.

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