Inhaled bacteriophage therapy in a porcine model of ventilator-associated pneumonia caused by pseudomonas aeruginosa.

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Abstract

Background and Purpose. Pseudomonas aeruginosa is a main cause of ventilator-associated pneumonia (VAP) with drug-resistant bacteria. Bacteriophage therapy has experienced resurgence to compensate for the limited development of novel antibiotics. However, phage therapy is limited to a compassionate use so far, resulting from lack of adequate studies in relevant pharmacological models. We used a pig model of VAP caused by P. aeruginosa that recapitulates essential features of human disease to study the antimicrobial efficacy of nebulized-phage therapy. Experimental Approach. (i) Lysis kinetic assays were performed to evaluate in vitro phage antibacterial efficacy against P. aeruginosa and select relevant combinations of lytic phages. (ii) The efficacy of the phage combinations was investigated in vivo (murine model of P. aeruginosa lung infection). (iii) We determined the optimal conditions to ensure efficient phage delivery by aerosol during mechanical ventilation. (iv) Lung antimicrobial efficacy of inhaled-phage therapy was evaluated in pigs, which were anesthetized, mechanically ventilated and infected with P. aeruginosa. Key Results. By selecting an active phage cocktail and optimizing aerosol delivery conditions, we were able to deliver high phage concentrations in the lungs, which resulted in a rapid and marked reduction in P. aeruginosa density (1.5 Log reduction, $p<0.001$). No phage was detected in the sera and urines throughout the experiment. Conclusion and Implications. Our findings demonstrated: (i) the feasibility of delivering large amounts of active phages by nebulization during mechanical ventilation, (ii) rapid control of in situ infection by inhaled bacteriophage in an experimental model of VAP with high translational value.

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