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| **Novel intranasal phage-CaEDTA therapy effectively treats Pseudomonas aeruginosa lung infection** |
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| **Introduction/Aim:** Given the rise of multidrug-resistant (MDR) Pseudomonas aeruginosa infections, alternative treatments are needed. Anti-pseudomonal phage therapy shows promise, but its clinical application is limited due to the development of resistance and a lack of biofilm penetration. Recently, adjuvants like CaEDTA have shown the ability to enhance the effectiveness of combined antimicrobial agents. To address this and provide conceptual validation, localized intranasal therapeutic combinations of phages, CaEDTA, and antibiotics were evaluated in vitro and in vivo.  **Methods:** Myoviridae phage-KPP10 was used to target planktonic and biofilm of MDR clinical isolates of P. aeruginosa (n=27). We tested a phage-adjuvant combination and demonstrated the effectiveness of intranasally inhaled phage (KKP10) + CaEDTA in addition toceftazidime/avibactam (CZA) in vitro and in vivo using a clinically relevant model of chronic P. aeruginosa lung infection.  **Results:** The combination of KKP10 + CaEDTA significantly reduced bacterial viability compared to ceftazidime/avibactam + CaEDTA or KKP10 + ceftazidime/avibactam (p<0.05). The addition of ceftazidime/avibactam to this combination resulted in a significant reduction in planktonic P. aeruginosa viability (< 102 CFU), with no bacterial regrowth observed (p<0.01). It also eliminated mature P. aeruginosa biofilms and significantly reduced bacterial viability (<98%) within biofilms (p<0.01). Remarkably, single intranasal inhalation of KPP10 + ceftazidime/avibactam + CaEDTA completely cleared the bacterial infection in the lung, ensuring 100% survival in treated mice (p<0.01).  **Conclusion:** This promising approach shows potential as a therapy for P. aeruginosa chronic respiratory tract infections.  **Grant Support:** Chulalongkorn University (Second Century Fund- C2F Fellowship). |