1952. Bacteriophage Treatment Improves Survival of Mice Infected with Carbapenem-Resistant Klebsiella pneumoniae.

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Background. Bacteriophage (phage) therapy is being considered as a treatment option for patients with multi-drug-resistant bacterial infections. However, there is a dearth of controlled clinical data to support therapeutic phage efficacy. As a first step toward addressing this deficiency, we tested the ability of two well-characterized phages, alone and in combination, to kill carbapenem-resistant Klebsiella pneumoniae (ST258) in blood and rescue mice from lethal ST258 infection.

Methods. Wild-type C57BL/6J mice were infected with a lethal inoculum of ST258 by intraperitoneal (IP) injection followed 1 hour later by IP administration of lytic phage P1, P2, or P1+P2 at a multiplicity of infection (MOI) estimated at 1. Survival of each group of mice was tracked for 10 days. In separate experiments, mice were sacrificed at 1 hour, 24 hours, and 48 hours post-phage treatment. Mouse blood and tissues were collected at each time point for enumeration of bacteria and phage, screening for phage resistance, and histopathology.

Results. ST258 survival in mouse blood in vitro was significantly less after 1 hour of incubation with P1 or P1+P2 (MOI 1) compared with the control group (no phage). Consistent with the in vitro data, none of the mice (0/15) in the control group (no phage) survived to 10 days post-infection, whereas 12/15, 14/15, and 15/15 mice survived in the P1, P2, and P1+P2-treated groups, respectively (P < 0.0001).

Conclusion. Prompt, systemic administration of lytic bacteriophages rescued mice from lethal ST258 infection. These data support the potential of phage therapy to effectively treat infections caused by ST258. It will be important to assess whether, for other phage-bacteria combinations, in vitro lysis in blood correlates with in vivo treatment efficacy and therefore may have predictive utility.

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1954. In vivo Efficacy of Delayed Therapy with the Novel Inositol Transacylase Inhibitor Fonmanogepix (APX001) in a Murine Model of Candida auris Invasive Candidiasis.

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Background. Candida auris is an emerging pathogen associated with antifungal resistance and high mortality. The novel antifungal manogepix (APX001) prevents glycosylphosphatidylinositol-anchored protein maturation through inhibition of the inositol transacylase Gwt1 enzyme, and has demonstrated in vitro and in vivo activity against numerous pathogenic fungi, including C. auris. We evaluated the efficacy of the prodrug fonmanogepix (APX001) following delayed initiation of therapy in a murine model of C. auris invasive candidiasis.

Methods. Neutropenic outbred mice (10 per cohort) were inoculated intravenously with C. auris (minimum inhibitory concentrations [MICs]: manogepix 0.03 mg/mL, fonmanogepix 0.16 mg/mL, caspofungin 0.25 mg/mL). Treatment with placebo, fonmanogepix (104 or 130 mg/kg by intraperitoneal injection [IP]) three times daily, or 260 mg/kg [P] twice daily), fonmanogepix (20 mg/kg/day orally), or caspofungin (10 mg/kg/day [IP]) began 1 day later and continued for 7 days. Mice were followed post therapy until day 21 to assess survival. Kidneys and brains were collected on day 8, on the days that mice succumbed to infection, or on day 21. Fungal burden was assessed by colony-forming units (CFU).

Results. Survival was significantly improved at each dose level of fonmanogepix (median >21 days; 90–100% and high dose caspofungin >21 days; 90% compared with placebo (5 days; 10%; P < 0.0001). On day 8 post-inoculation, kidney and brain fungal burdens were significantly reduced in mice treated with fonmanogepix 260 mg/kg [IP] compared with placebo in mice treated with caspofungin (Table I). In the survival arm, fungal burden in kidneys and brains was significantly lower at each dose level of fosmanogepix and with high dose caspofungin compared with placebo. In contrast, no improvements in survival or reductions in fungal burden were observed with fluconazole.

Conclusion. Fonmanogepix demonstrated potent in vivo activity against invasive candidiasis caused by C. auris even with delayed initiation of treatment. Improvements in both survival and reductions in fungal burden within the kidneys and brains were observed. These data demonstrate the potential utility of fonmanogepix against C. auris infections.

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Background. Enterococcus causes 14% of all hospital-associated infections (HAIs) according to Centers for Disease Control and Prevention (CDC) data. 35.5% of these HAIs are caused by Vancomycin-resistant Enterococci (VRE) including highly fatal bacteremia, surgical site infections, and urinary tract infections. We present a novel synthetic compound, HSD 03-21 that could make VRE completely susceptible in vitro.

Methods. HSD 03-21 was synthesized de novo from a hydroxybenzylidene – indolinone backbone in our laboratory. The minimum inhibitory concentration (MIC) of HSD 03-21 and vancomycin against VRE were determined according to clinical laboratory standards institute (CLSI) guidelines. The standard checkerboard assay was used to determine vancomycin-HSD 03-21 interactions against VRE. Briefly, HSD 03-21 and vancomycin at 10 μg/mL were prepared and diluted serially along the ordinate and abscissa of 96-well microtiter plates, respectively. Bacteria was standardized using the 0.5 McFarland standard, diluted (1:100), aliquoted into respective wells and incubated at 37°C for 18–20 hours. All assays were run in triplicates. The fractional inhibitory concentration (FIC) index was calculated for each combination. The FIC of either agent was calculated as: FIC (vancomycin) = MIC of vancomycin in combination/ MIC of vancomycin alone and FIC (HSD 03-21) = MIC of HSD 03-21 in combination/ MIC of HSD 03-21 alone. The cumulative FIC index ∑FIC = FIC (vancomycin) + FIC (HSD 03-21) was then calculated as: ∑FIC = (MIC of vancomycin) + (MIC of HSD 03-21). The calculated ∑FIC indices were interpreted as synergistic if ∑FIC ≤ 0.5.

Results. The MIC of vancomycin for VRE faecalis was 256 μg/mL1 while that of HSD 03-21 was 128 μg/mL1. When vancomycin was combined with HSD 03-21 at 8 μg/mL1 (1/16 MIC), there was a reduction in MIC of vancomycin to 0.5 μg/mL1. The combination showed excellent synergy with ∑FIC of 0.06. HSD 03-21 reduced the MIC of vancomycin from 256 to 0.5 μg/mL1. This has an immense potential of changing the way we use vancomycin and in the treatment of VRE infections. Translation of this novel compound could save thousands of lives from VRE and the failures and inherent toxicities of current doses of vancomycin.

Conclusion. This has an immense potential of changing the way we use vancomycin and could be de-labeled. Adult patients with BLA are more likely to receive broader-spectrum antimicrobials and experience worse health outcomes than nonallergic patients. Similar studies on the impact of BLA on antimicrobial use and clinical outcomes are limited in pediatrics. Our objective was to compare antimicrobial use, and clinical and economic outcomes between hospitalized children with and without BLA.

Methods. This was a retrospective cohort of pediatric patients hospitalized at an Intermountain Healthcare (IH) hospital from 2007 to 2017. IH has 22 hospitals including one children’s hospital. Patients aged 30 days-17 years who received ≥1 dose of an antimicrobial during hospitalization were included. The exposure variable was the presence of BLA (penicillins or cephalosporins) in the allergy field of the medical record. Patients with BLA were matched to nonallergic controls on age, sex, race, clinical service line, admission date, children’s hospital or other hospital, and co-morbid conditions. We used multivariable log-transformed linear and logistic regression models to compare patients with BLA to controls in terms of antibiotic selection and total antimicrobial days, antimicrobial cost, length-of-stay (LOS) and 30-day readmission. For antibiotic selection we examined the odds of receiving the following broader-spectrum agents individually and in composite: vancomycin, fluoroquinolones, clindamycin, carbapenems, and macrolides.

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