Faecal Microbiota Transplantation, a novel treatment to tackle Antimicrobial Resistance in Chronic Liver Disease – induces phage network remodelling and enteric pathogen reduction, enhances intestinal barrier function and immunometabolism, altering mucosal IL-17 immunity.

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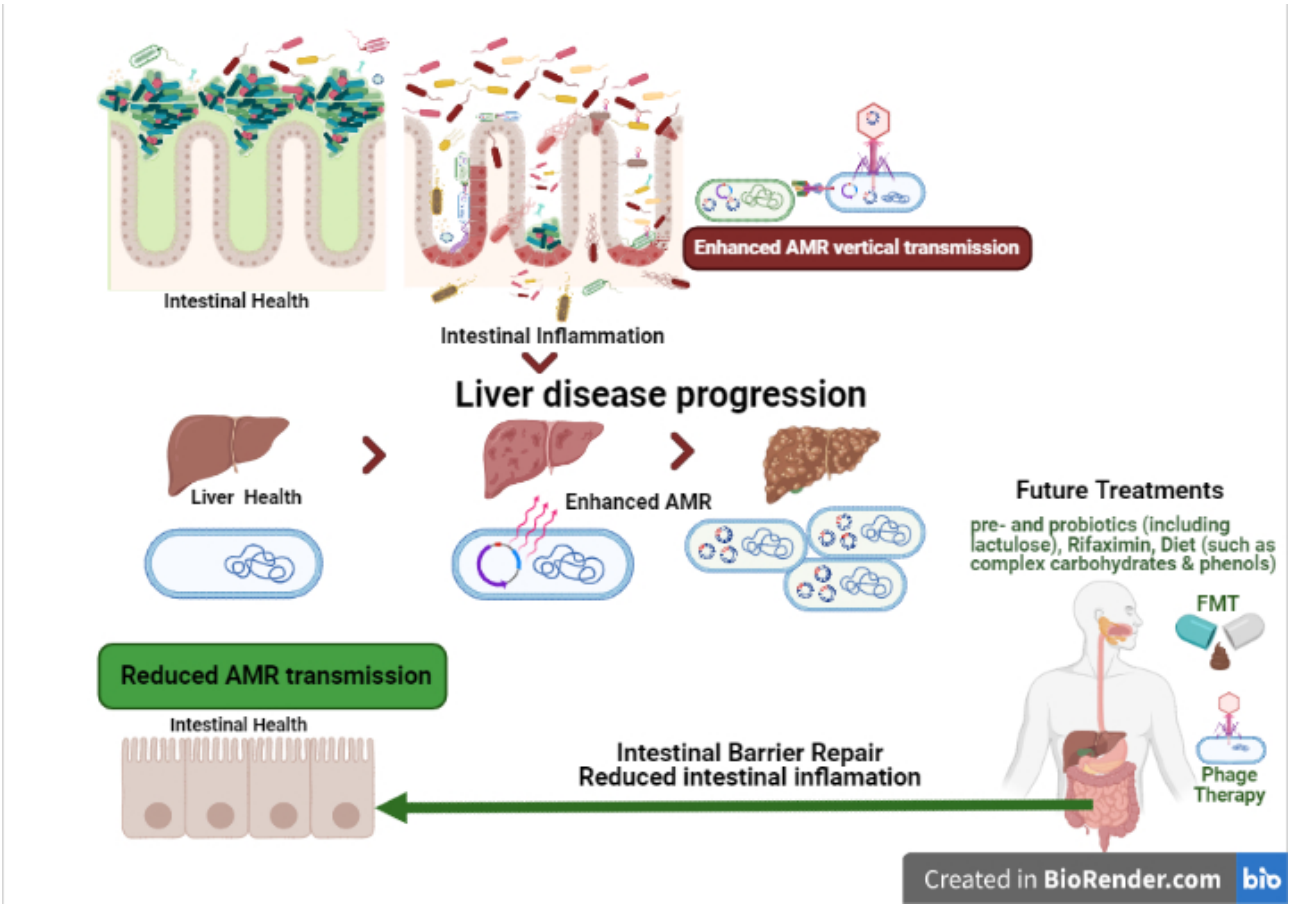
Background: The World Health Organization states that Antimicrobial Resistance (AMR) is still "the biggest threat to global health". Patients with chronic liver disease (CLD) are particularly susceptible to infections and AMR resulting in hospitalisation, organ failure and potential death. Susceptibility to infection results from gut-barrier-damage (GBD), microbiota perturbations, and translocation of bacteria and their products across the gut-epithelial-barrier, inducing innate immune dysfunction. We hypothesised modifying the gut microbiota with faecal microbiota transplant (FMT) may enhance intestinal barrier function and mucosal immunity.

Methods: We conducted a prospective, randomised, single-blinded, feasibility trial evaluating FMT (n=15) against placebo (n=6) [NIHR-NCT02862249]. Patients were administered FMT/placebo into the jejunum within 7 days of baseline. We assessed efficacy in modulating the patient's own microbiome and inflammatory status: stool was collected at baseline and 7, 30 and 90 post-FMT/placebo. Assessing cytokine production and barrier integrity markers (electrochemiluminescence/ELISA) and metabolite profile (^{1}H-NMR).

Results: Deep metagenomic sequencing confirmed FMT increased recipient species richness with significant donor engraftment, enhancing *F.prausnitzii* a metabolizer of immunosuppressive metabolites. 20% of patients recruited were colonised with Multi-Drug-Resistant-Organisms, administering FMT significantly reduced stool carriage of pathobionts such as *E.faecalis* [*p=0.000006*] and *E.coli* (EPEC) [p=0.0025] alongside AMR gene (ARG) carriage. *E. faecalis*/EPEC cause toxin and contact-mediated GBD, Inflammation/GBD increases ARG carriage. Phase-Genomics-ProxiMeta™-Metagenome-Deconvolution, captures co-located-DNA enabling strain-level assignment of phages/ARGs within microbes, not previously possible. A bacteriophage reservoir found worldwide suggests a healthy gut phagosome.[1] Lysis of bacteria drives microbial diversity and evolution, stabilizing microbial populations[2,3] correlating with health.[4] We observed within a healthy donor *Oscillospiraceae* and a respective beneficial phage network. In contrast, dsDNA phages, such as *E.faecalis*-strain-V583 prophages, positively correlate with dysbiosis and GBD.[3,5] Post-FMT, we see phage network remodelling. Faecal proteomics quantified 301 proteins, 154 human and 147 of bacterial origin. Mainly human/microbial enzymes involved in host/microbial immuno-metabolism. FMT also reduced proteins involved in bacterial virulence and AMR. FMT reduced biomarkers of inflammation, particularly luminal IL-17A and increased markers associated with gut barrier repair.

Conclusions: These data support FMT as playing an important role in phage network remodelling, enteric pathogen reduction, altering the gut-microbiota to promote inflammatory restoration of the gut barrier, and reducing AMR.

Figure:



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