Microbiome Metabolic Therapies (MMTs) reduce pathogen colonization in *ex vivo* testing of intensive care unit patient microbiomes

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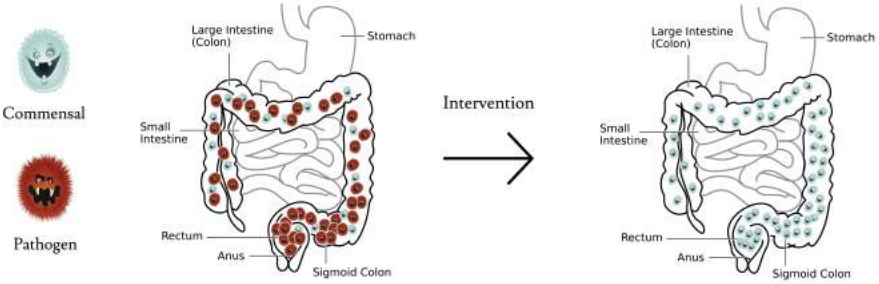
BACKGROUND

Mutidrug resistant (MDR) pathogens remain problematic in intensive care unit (ICU) populations. Carriage of MDR bacteria substantially increases the risk of infection and transmission rates. MMTs selectively enhance the growth of commensal taxa, allowing commensals to outcompete pathogens for resources. Reducing pathogen abundance via MMTs may decrease infection rates and maintain healthy microbiome function during periods of critical care.



METHODS

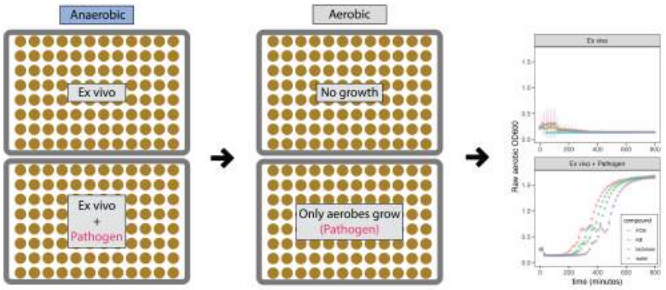


Figure 1: Our high-throughput screen allows for rapid assessment of MMT utilization by pathogens. Fecal slurries are anaerobically incubated for 24-42 hours with or without pathogen. Then, samples are transferred to selective media and aerobic growth curves are measured.

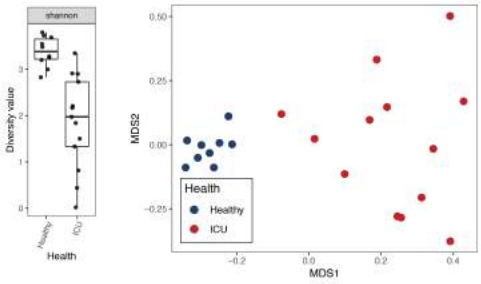


Figure 4: Microbiome samples from ICU patients receiving antibiotics are categorically different from healthy subjects. Above, fecal community composition of healthy and ICU donors before MMT intervention.

RESULTS

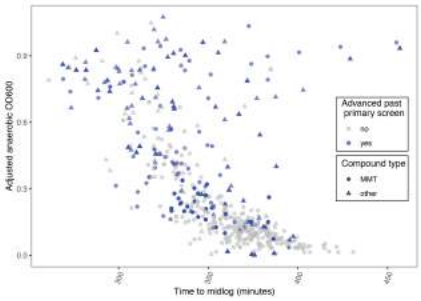


Figure 2: Anaerobic OD600 and time to midlog, calculated from aerobic growth curves, allow selection of MMTs that exclusively support commensal growth (i.e. high anaerobic OD600 and high time to midlog). Above, results from our initial screening effort show a wide range of pathogen reduction and commensal support. 115 of 413 compounds were selected for further investigation.

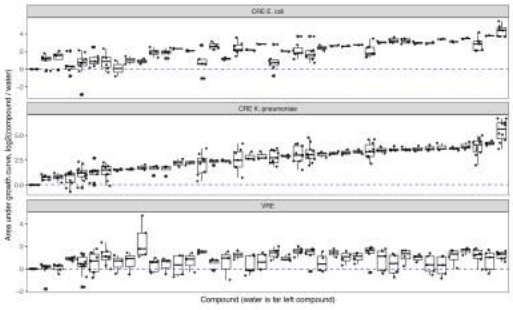


Figure 3: Grown in isolation, selected MMTs do not support pathogen growth. Above, each point represents the area under the growth curve for a strain grown on a compound in minimal media. Compounds supporting single strain pathogen growth were excluded from candidate consideration.

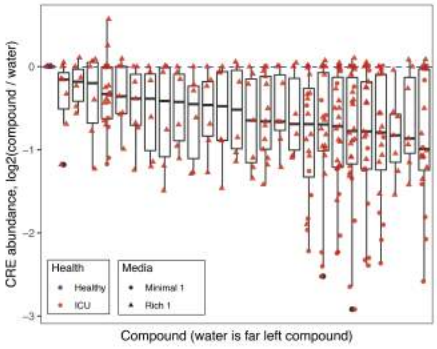


Figure 5: Despite low diversity starting communities, ICU samples experience upwards of 8X reduction in spiked CRE after intervention. Right, each point represents a patient sample across media and experiments.

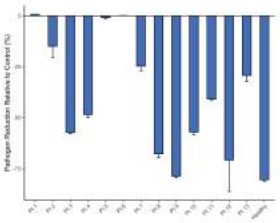


Figure 6: MMT reduces pathogen burden in 10 of 13 ICU donors, with a maximum reduction of 80% and median of 45%.

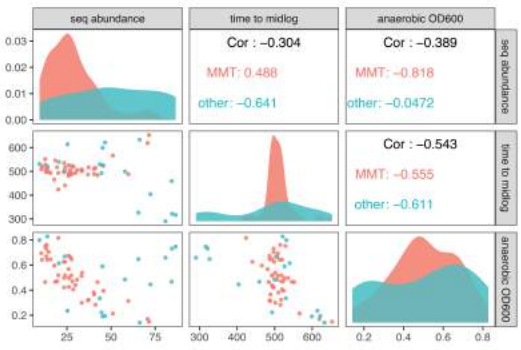


Figure 7: MMTs promote the absolute abundance of commensals and not pathogens. Right, Pearson correlation plots comparing CRE relative abundance assessed via sequencing, anaerobic OD600, and aerobic time to midlog.

CONCLUSIONS

These results suggest intervention with MMTs reduce CRE and VRE colonization and support further evaluation. Based on this data, we have selected several MMT leads for additional evaluation and expect to initiate a clinical study in colonized subjects in the first half of 2019.

Acknowledgements:
Arrow cartoon: created by unfimicon (Noun Project)
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