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Fecal transplant to mitigate hyperammonemia and hepatic encephalopathy in animal models

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Article commented:

Shen TC, Albenberg L, Bittinger K, Chehoud C, Chen YY, Judge CA, Chau L, et al. Engineering the gut microbiota to treat hyperammonemia. *J Clin Invest* 2015; 125: 2841-50.

Comment:

The paper by Shen, *et al*. reports on efforts to engineer the gut microbiota to treat hyperammonemia by decreasing the levels of urease positive gut bacteria.[1] After treatment of mice with oral antibiotics and PEG to deplete indigenous bacteria, mice were inoculated with a consortium of 8 bacteria with low urease gene content. This new gut microbiota was relatively stable for up to 120 days. The established of a new gut microbiota with less urease activity was associated with decreased morbidity and mortality of a liver injury mouse model. Interestingly, no adverse effects on the mice body weight or mortality for over 1 year after fecal microbiota transplant (FMT) was noted. However, perturbations of the microbiome by antibiotics can select for bacterial resistance. Nevertheless, FMT, which introduces a healthy bacterial community into selected patients, has great promise to treat diseases related to the microbiome that are otherwise difficult to treat. This has been used for *Clostridium difficile* and is being vigorously investigated for inflammatory bowel disease.[2]

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As noted by the authors, ammonia reduction as a result of selected transplanted gut microbiota, demonstrated a clear benefit by reducing morbidity and mortality in this mouse model. However, the authors noted that a humanized version of FMT in animal models should be further tested for safety before human studies. The extension of these findings into humans may be challenging given potential barriers to FMT in this decompensated stage of cirrhosis.[3,4] Most current therapies for HE, such as rifaximin, lactulose and probiotics, focus on the gut milieu and indeed have variable effects on the gut microbiota that range from compositional and functional (probiotics) to largely functional (lactulose/rifaximin).[5-8] Therefore, the current standard of care already involves modulating gut microbiota as the backbone of HE therapy.[9] However, the results by Shen, *et al*. are provocative and give hope to the promise of a scientifically driven microbiota that can reduce hyperammonenia.

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