	Model	HR (95% CI)	C statistic for Model
Univariate	MELD Only	1.12 (1.09-1.14)	0.74
Univariate	LA Only	1. 44 (1.35-1.53)	0.79
Multivariate MELD-LA*	MELD	1.08 (1.05-1.12)	0.84
*adj for age, gender, race	LA	1.34 (1.22-1.46)	

MELD-LA and prediction of inpatient mortality.

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ANTIBIOTIC-ASSOCIATED DISRUPTION OF MICROBIAL COMPOSITION AND FUNCTIONALITY IS RESTORED AFTER FECAL MICROBIAL TRANSPLANT IN CIRRHOSIS

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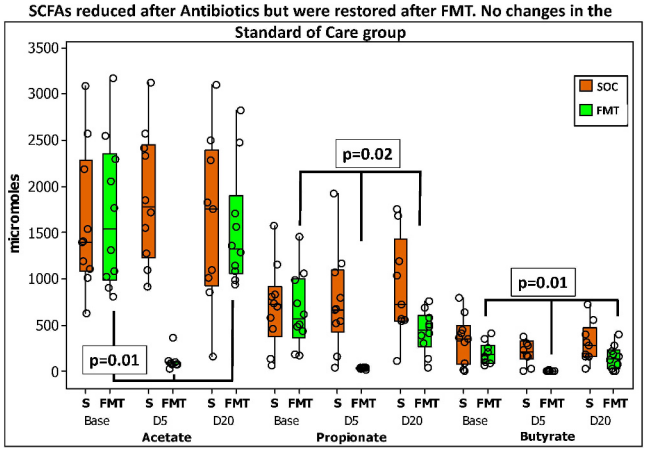
Cirrhotic patients are often prescribed antibiotics (Abx) which impact microbial diversity and functionality. These can result in antibiotic resistance and fungal infections but there are few options to restore these disruptions. Short-chain fatty acids (SCFA) and secondary bile acids (BAs) are bacterially produced molecules that help intestinal barrier function and may prevent superinfections. **Aim**: Define the impact of fecal microbial transplant (FMT) on restoring microbiota functionality after antibiotics in cirrhotic patients. **Method**: Decompensated cirrhotic pts on rifaximin were randomized 1:1 to receive standard of care(SOC) or FMT after 5 days of broad-spectrum Abx (ciprofloxacin, amoxicillin & metronidazole) as part of a trial to treat hepatic encephalopathy (HE). FMT was administered by enema (90ml) from a single well-characterized donor after pre-treatment Abx. MELD score, microbial diversity, fecal BA & SCFA profiles were studied at baseline, day 5 & day 20 in both groups. Bacterial metabolism of BAs (deconjugated/secondary BA) was evaluated. **Results:** Among 20 HE participants, 10 pts were randomized to SOC and 10 to Abx followed by FMT, in addition to SOC. Sample analysis was performed at days 0, 5 & 20 in both groups. Groups were matched on MELD score (13 vs 12) at baseline. Overall, there was a decrease in microbial diversity after Abx that recovered post-FMT (Table). MELD score increased significantly after Abx, which reduced post-FMT. Fecal BA deconjugation & secondary BA conversion capacity (Table) and fecal SCFA levels (butyrate, propionate and acetate Figure) signficantly reduced post-Abx but were restored after FMT to baseline levels. No changes were seen in the SOC group. **Conclusion:** Antibiotic-associated disruptions in microbial diversity and production of SCFAs and secondary BAs were restored to baseline with one FMT enema. FMT could be promising to restore microbiota composition and functionality disruptions in decompensated cirrhotic patients on rifaximin.

Changes in Both Groups During the Trial

Median values for fecal BAs; mean±SD for rest	Fecal Microbial Transplant			Standard of Care (no intervention)		
	Baseline	Day 5 (post-Abx)	Day 20 (post-FMT)	Baseline	Day 5	Day 20
MELD score	12.0±2.9	13.5±3.2‡	11.6±3.0†	13.2±3.7	12.5±3.4	13.4±3.8
Shannon diversity	6.46±1.07	4.59±1.67‡*	6.42±1.42†	7.23±0.77	7.21±0.95	7.34±0.86
Total BAs	3.81	4.18	3.69	3.1	3.01	2.86
Total Primary BAs	1.1	3.76‡*	1.32†*	0.20	0,31	0.69
Total Secondary BAs	0.88	0.13‡*	0.75†	0.93	0.96	1.11
Total Conjugated BAs	0.12	1.75‡*	0.21†	0.07	0.02	0.08

*p<0.05 between groups, †p<0.05 within gp compared to day 5, ‡ p<0.05 within group compared to baseline, BAs in µg/gm stool



Changes in Fecal Short-Chain Fatty Acids throughout the Trial. FMT gp in green and SOC in orange. Data presented as median (95%CI) with individual values at baseline, day 5 (after Abx in FMT) and day 20 (after FMT)

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INTEGRIN BASED ANGIOCRINE SIGNALS RECRUIT NEUTROPHILS TO DRIVE PORTAL HYPERTENSION IN CONGESTIVE HEPATOPATHY

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Background: Congestive hepatopathy (CH) which occurs in the setting of right heart failure can lead to portal hypertension (PHTN). Our prior studies revealed that mechanical stretch (MS) of liver sinusoidal endothelial cells (LSECs) upregulates the neutrophil chemokine CXCL1 through a mechanosensitive NOTCH pathway, suggesting a novel role for neutrophils in CH. This was confirmed by our finding that genetic deletion of neutrophil elastase (NE), a protease which impacts endothelial cell function, inflammation, and tissue remodeling, abrogates PHTN in our partial inferior vena cava ligation (pIVCL) model of CH. In the present study, we sought to elucidate the mechanocrine pathways which generate CXCL1 and promote PHTN in CH. **Methods and Results:** Intravital imaging in wild type (WT) mice 24 hours after pIVCL revealed sinusoidal recruitment of neutrophils and their aggregation with platelets, providing real time imaging evidence that neutrophils instigate sinusoidal thromboses in CH. To test this hypothesis, we treated WT mice with the NE inhibitor sivelestat after pIVCL and sham procedures. Sivelestat decreased portal pressure (PP) after IVC ligation (55.9% change, p=0.03). Liver lysates from sivelestat-treated mice demonstrate increased mRNA levels of endothelial nitric oxide synthase (eNOS) and decreased expression of endothelin-1, suggesting that NE may impact PP by modulating vasoregulatory molecules in LSEC. Next, we performed bile duct ligation (BDL) in $NE^{-/-}$ mice to elucidate the role of NE in an alternative model of PHTN. $NE^{-/-}$ mice again had lower PP (42.0% change, p= 0.01) compared with WT mice after BDL suggesting some parallel roles of sinusoidal thrombosis and neutrophils in varying forms of chronic liver injury. Finally, we studied the mechanosensitive pathways activated by MS in LSECs which may interface with NOTCH to contribute to the pathophysiology of PHTN in CH. To do this, we performed RNA-seq to compare network analysis of genes regulated in stretched and unstretched primary murine LSECs. This revealed a key role of integrin proteins. Indeed, inhibition of integrin signaling with RGD-peptide prevented stretch-induced upregulation of the Notch pathway (p=0.01) and CXCL1 (p=0.05), suggesting that integrins serve as initial mechanosensors which activate mechanocrine signaling in LSECs. **Conclusion:** NE deficiency abrogates PHTN in models of CH and cholestatic liver disease by regulating neutrophil function and LSEC expression of vasodilatory molecules. LSECs sense MS in the setting of passive hepatic congestion through integrins which initiate mechanocrine signaling with the NOTCH pathway to upregulate CXCL1 and recruit neutrophils to the sinusoids.

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IMPAIRED SECRETION OF RENALASE INTO BLOOD MAY LEAD TO SYMPATHETIC OVERACTIVITY AND EARLY SODIUM RETENTION IN EXPERIMENTAL LIVER CIRRHOSIS

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Introduction. Sympathetic overactivity is chief promoter of sodium retention and functional renal failure in liver cirrhosis. Renalase (REN), 38 kDa amine oxidase with just 13% aminoacid identity with monoamine oxidase A, is secreted into the blood by the kidney and is the only identified form of amine oxidase outside of the nervous system that is able to catabolize plasma catecholamines. **Aims.** To study plasma and tissue content and function of REN in experimental preascitic and ascitic cirrhosis. **Methods.** In normal rats (group G1), rats with CCl_4-dependent liver cirrhosis without ascites (G2) and with ascites (G3) we evaluated: REN levels and activity in plasma, liver and kidney; REN gene transcription and immunohistochemical localization in liver and kidney; liver histology and matrix deposition, hormonal status and kidney function. **Results.** In plasma, mature (38 kDa) REN and REN activity, well detected in normal rats, were virtually absent in rats with compensated or ascitic cirrhosis (all P<0.01 vs. G1). In G2 and G3 rats, but not in G1, we found large amount of enzymatically active high-molecular-weight (78 kDa) REN and very little 38 kDa protein in hepatocytes of regenerative nodules of the cirrhotic liver and in kidney tubules. RT-PCR confirmed higher levels of REN gene transcription in both liver and kidney of G2-3 (P<0.03 vs. G1). Rats with preascitic liver damage showed increased plasma catecholamines, normal renin-angiotensin system activation and sodium retention, while ascitic rats had both secondary aldosteronism and increased adrenergic activation. **Conclusions.** High-molecular-weight forms of functional REN accumulates in diseased liver and kidney, but tissue processing and release into blood of mature (38 kDa) REN is almost absent, contributing to increased levels of plasma catecholamines and sodium retention in both preascitic and decompensated cirrhosis.

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ACADEMIC MEDICAL CENTERS HAVE HIGHER ACUTE ON CHRONIC LIVER FAILURE ASSOCIATED MORTALITY DESPITE USING MORE RESOURCES THAN NON-ACADEMIC CENTERS

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Background: Acute on chronic liver failure (ACLF) in patients with cirrhosis has high short-term mortality due to multi-organ failure. Data comparing ACLF admissions to academic (AC) and non-academic centers (NAC) are scanty. Methods: National Inpatient Sample (2006-2014) was queried for admissions with cirrhosis and ACLF: ≥2 organ failures: cardiovascular (septic shock or need for arterial line/ pulmonary wedge pressure monitor), respiratory (mechanical ventilation), renal (renal failure or dialysis), or cerebral (hepatic encephalopathy).Analysis was performed comparing admissions to AC (teaching hospitals in urban