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Non-selective Beta-Blocker use in cirrhosis: the additional benefit in preventing secondary infections.

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We read with interest the work by Jachs *et al.*, reporting the benefits of non-selective beta blockers (NSBB) in reducing systemic inflammation in cirrhotics, with an associated reduced rate of acute decompensation and mortality (1). Systemic inflammation is a hallmark of cirrhosis-associated immune dysfunction, representing pathological translocation of bacteria and/or bacterial products from the gut (2).

Cirrhotics have an increased risk of developing infection (3), with substantially increased mortality when such infections occur (4,5). Secondary infections significantly contribute to this, and predict 30-day mortality independently of disease severity (6,7). Extending upon the work of Jachs *et al.*, we here report a beneficial impact of NSBB on clinical and microbiological outcomes of decompensated cirrhotics both in a specialist outpatient setting and inpatients. We also report the novel finding of a reduction in circulating bacterial DNA (bDNA) levels in a subset of cirrhotics with primary infections on NSBB.

We retrospectively analysed 138 patients with Child-Pugh (CP) grade B/C cirrhosis attending a specialist cirrhosis outpatient clinic at St Mary's Hospital, London, over a two-year period. Patients were included at the point of clinic attendance, with records of adverse events (including hospitalisation) and mortality collected from electronic notes. Baseline characteristics of this cohort are shown in **Table 1**. The indication for NSBB for all patients in this cohort was for either primary or secondary prophylaxis of varices. NSBB use (89/138) was associated with improved survival ($p=0.01$), lower 1-year incidence of infection requiring

hospitalisation ($p=0.03$), and reduced need for all-cause admission ($p=0.02$). On binary logistic regression, factors independently associated with 1-year survival were NSBB use [OR 5.18 (95% CI: 1.67-16.01), $p=0.004$], lower baseline MELD score [OR: 1.25 (1.11-1.41), $p=0.0001$] and lower infection rates [OR: 1.72 (1.17-2.58), $p=0.007$].

Subsequently, we prospectively investigated the impact of NSBB use on bDNA levels and the 28-day incidence of secondary infection. We assessed bDNA levels in 22 consecutive cirrhotics admitted with primary infection with follow-up at day 28. At this point they were assessed for secondary infection development, defined as per the NACSELD consortium criteria (6), with blood sampling for 16S rRNA gene count (bacterial DNA load) analysis using PCR. Further details are included in the **Supplementary Material**. Of the 22 patients, 50% of patients ($n=11$) were already established on NSBB therapy at enrolment and 50% were not ($n=11$). There was no significant difference in Median MELD scores between both groups. Demographic and clinical details are summarised in **Table 2**.

Disease severity stratified by MELD score correlated with bDNA concentrations (Spearman's $r=0.550$, $p=0.0145$), and also with C-reactive protein (Spearman's $r=0.543$, $p=0.0162$). Notably, circulating levels of bDNA at baseline were significantly lower in the NSBB group vs non-NSBB group (73.0 pg/ml of whole blood vs 133.8 pg/ml, $p=0.01$).

The incidence of secondary infection development at 28 days was 22.7% (5/22), comparable to previous studies (6). Circulating levels of bDNA at baseline in patients who developed secondary infection, all of whom were not on NSBB, was higher, 109.0 pg/ml compared to those who did not develop secondary infections, 66.3 pg/ml, ($p=0.02$).

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Our findings build upon those from Jachs *et al.*, suggesting that NSBB therapy within the context of a specialist decompensated cirrhosis service can benefit patients by reducing mortality, need for admission and infection rates. Additionally, we have shown that NSBB therapy can result in lower levels of bDNA during episodes of primary infection and may protect against the development of secondary infections. More broadly, our data support the concept that NSBB may have added beneficial effects beyond the pure reduction of portal pressures. Mechanisms may include NSBB-related improvement in gut barrier integrity, potentially via an impact upon gut motility. Finally, we agree with Jachs *et al.* that in clinical trials involving cirrhotic patients, where inflammatory/infective outcome measures are being assessed, consideration needs to be given to patient stratification by NSBB use to allow optimal study design and interpretation of results.

Table 1: Baseline characteristics of NSBB users and non-users attending a specialist cirrhosis clinic at St Mary's Hospital, London, UK.

Demographics	NSBB (n=89)	Non-NSBB (n=49)	<i>p</i> -value
Sex (%)			
Male	64 (71.9)	31 (63.3)	0.39
Female	25 (28.1)	18 (36.7)	
Age, years (IQR)	58 (49 – 66)	59 (52 – 67)	0.47
Main Aetiology (%)			
Alcohol	48 (53.9)	31 (63.3)	0.52
Hepatitis C	16 (18.0)	7 (14.3)	
NASH	6 (6.7)	6 (12.2)	
Disease Severity (IQR)			
Child-Pugh Score	8 (8 – 10)	8 (7 – 10)	0.39
MELD score	13.50 (11.40 – 15.80)	11.80 (9.40 – 14.40)	0.006
Ascites (%)			0.12
None	38 (42.7)	17 (34.7)	
Mild	24 (27.0)	9 (18.4)	
Moderate	18 (20.2)	11 (22.4)	
Severe	9 (10.1)	12 (24.5)	
HE (%)	24 (27.0)	10 (20.4)	0.52
HCC (%)	6 (6.7)	1 (2.0)	0.42
Laboratory parameters (IQR)			
Sodium, mmol/L	137 (133 – 139)	137 (135 – 138)	0.91
Creatinine, µmol/L	70 (62 – 84)	63 (57 – 73)	0.03
Albumin, g/L	29 (25 – 33)	30 (26 – 33)	0.33
Bilirubin, µmol/L	39 (23 – 59)	30 (15 – 52)	0.06
INR	1.3 (1.2 – 1.5)	1.3 (1.2 – 1.4)	0.03
Platelets, x10 ⁹ /L	96 (66 – 144)	127 (83 – 136)	0.03

Table 2: Baseline characteristics of patients with bDNA according to the use of NSBB

Demographics	NSBB group (n=11)	Non-NSBB group (n=11)	p-value
Age – yrs (IQR)	57 (51-68)	51 (44-56)	0.14
Gender – % (no)			
Male sex	63.6% (7/11)	72.7% (8/11)	0.65
Female sex	36.4% (4/11)	27.3% (3/11)	
Aetiology – % (no)			
Alcoholic Liver Disease (ALD)	54.5% (6/11)	72.7% (8/11)	0.38
Viral Hepatitis (Hepatitis B or C)	27.3% (3/11)	9.1% (1/11)	0.27
NASH	18.2% (2/11)	18.2% (2/11)	1.00
MELD Score (IQR)	14.9 (11.4 – 19.9)	14.5 (12.7 – 23.1)	0.72
Comorbidities – % (no)			
Ischaemic heart disease	9.1% (1/11)	9.1% (1/11)	1.00
Lung disease	18.2% (2/11)	18.2% (2/11)	1.00
Diabetes Mellitus	36.4% (4/11)	18.2% (2/11)	0.34
Primary Infection Site – % (no)			
Spontaneous Bacteraemia	27.3% (3/11)	36.4% (4/11)	0.65
Spontaneous Bacterial Peritonitis	18.2% (2/11)	9.1% (1/11)	0.53
Respiratory Infection	27.3% (3/11)	18.2% (2/11)	0.61
Cellulitis	-	18.2% (2/11)	-
Urinary Tract Infection	18.2% (2/11)	-	-
Other Abdominal Infections	9.1% (1/11)	18.2% (2/11)	0.53

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Supplementary Material:

Methods:

All cirrhotics admitted to hospital were screened for suitability for inclusion into the study within 72 hours of admission. Criteria for study inclusion is summarised in **Supplementary**

Table 1.

Inclusion Criteria	<ul style="list-style-type: none"> • Clinical $\pm$ biochemical $\pm$ radiology $\pm$ histological diagnosis of cirrhosis. • Hospital admission with complication of cirrhosis including alcoholic hepatitis, sepsis, variceal haemorrhage, ascites, renal dysfunction etc. • Commencement of antimicrobial therapy. • Age 18 – 80 years.
Exclusion Criteria	<ul style="list-style-type: none"> • <i>C. difficile</i> infection. • HIV antibody positive • Immunosuppression (excluding low dose steroids or steroid sparing agents for autoimmune hepatitis treatment - < 20mg or equivalent of prednisolone). • Advanced disseminated hepatocellular carcinoma or invasive carcinoma. • eGFR < 30 on screening $\pm$ randomisation • End-stage/severe cardiac, pulmonary or kidney disease • Type 1 Diabetes Mellitus • Colitis or coeliac disease • Pregnancy

	<ul style="list-style-type: none">• Already receiving Rifaximin or concomitant long-term antibiotics.
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Supplementary Table 1: Study inclusion and exclusion criteria

Data collected included patient demographic details, aetiology of cirrhosis and concomitant medication use. Whole blood samples were obtained at all study timepoints to quantify circulating levels of bacterial DNA. Bacterial DNA extraction was performed in accordance with manufacturers’ protocol using the QIAamp® DNA Blood Midi Kit (Qiagen Ltd, UK). 16S ribosomal bacterial DNA was then quantified from the purified DNA by real-time PCR using the established protocol as per *Jordan and Durso* (8). This was targeted at the V7-V9 variable region of the 16S gene.