Non-selective beta-blocker use in cirrhosis: the additional benefit in preventing secondary infections

We read with interest the work by Jachs *et al*, reporting the benefits of non-selective beta blockers (NSBBs) in reducing systemic inflammation in individuals with cirrhosis, 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 on the work of Jachs *et al*, we here report a beneficial impact of NSBB on clinical and microbiological outcomes of decompensated cirrhotics in both 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 grade B/C cirrhosis attending a specialist cirrhosis outpatient clinic at St Mary's Hospital, London, over a 2-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 to 16.01, p=0.004), lower baseline Model For End-Stage Liver Disease score (OR 1.25, 95% CI 1.11 to 1.41, p=0.0001) and lower infection rates (OR 1.72, 95% CI 1.17 to 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 North American Consortium for the Study of End-Stage Liver Disease criteria,[6] with blood sampling for 16S rRNA gene count (bacterial DNA load) analysis using PCR. Further details are included in the online supplemental material. Of the 22 patients, 50%

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)	P value
Sex (%)			0.39
Male	64 (71.9)	31 (63.3)	
Female	25 (28.1)	18 (36.7)	
Age (years) (IQR)	58 (49–66)	59 (52–67)	0.47
Main aetiology (%)			0.52
Alcohol	48 (53.9)	31 (63.3)	
Hepatitis C	16 (18.0)	7 (14.3)	
Non-alcoholic steatohepatitis	6 (6.7)	6 (12.2)	
Disease severity (IQR)			
Child-Pugh Score	8 (8–10)	8 (7–10)	0.39
Model For End-Stage Liver Disease score	13.50 (11.40–15.80)	11.80 (9.40–14.40)	0.006
Ascites (%)			
None	38 (42.7)	17 (34.7)	0.12
Mild	24 (27.0)	9 (18.4)	
Moderate	18 (20.2)	11 (22.4)	
Severe	9 (10.1)	12 (24.5)	
Hepatic encephalopathy (%)	24 (27.0)	10 (20.4)	0.52
Hepatocellular carcinoma (%)	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
International normalised ratio	1.3 (1.2–1.5)	1.3 (1.2–1.4)	0.03
Platelets ($\times 10^9$/L)	96 (66–144)	127 (83–136)	0.03

NSBB, non-selective beta blocker.

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 (years) (IQR)	57 (51–68)	51 (44–56)	0.14
Gender, % (n)			0.65
Male sex	63.6 (7/11)	72.7 (8/11)	
Female sex	36.4 (4/11)	27.3 (3/11)	
Aetiology, % (n)			
Alcoholic liver disease	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
Non-alcoholic steatohepatitis	18.2 (2/11)	18.2 (2/11)	1.00
Model For End-Stage Liver Disease score (IQR)	14.9 (11.4–19.9)	14.5 (12.7–23.1)	0.72
Comorbidities, % (n)			
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, % (n)			
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

bDNA, bacterial DNA; NSBB, non-selective beta blocker.

(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 the two 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 versus the 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, were higher (109.0 pg/mL) compared with those who did not develop secondary infections (66.3 pg/mL, p=0.02).

Our findings build on 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 on 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.

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REFERENCES

1 Jachs M, Hartl L, Schaufler D, *et al*. Amelioration of systemic inflammation in advanced chronic liver disease upon beta-blocker therapy translates into improved clinical outcomes. *Gut* 2020. doi:10.1136/gutjnl-2020-322712. [Epub ahead of print: 16 Nov 2020].
2 Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 2014;61:1385–96.
3 Jalan R, Fernandez J, Wiest R, *et al*. Bacterial infections in cirrhosis: a position statement based on the EASL special conference2013.*JHepatol*2014;60:1310–24.
4 Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National hospital discharge survey. *Chest* 2003;124:1016–20.
5 Arvaniti V, D'Amico G, Fede G, *et al*. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010;139:1246–56.
6 Bajaj JS, O'Leary JG, Reddy KR, *et al*. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American Consortium for the study of end-stage liver disease (NACSELD) experience. *Hepatology* 2012;56:2328–35.
7 Bajaj JS, O'Leary JG, Reddy KR, *et al*. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology* 2014;60:250–6.