

The deleterious effects of non-selective beta-blockers on cirrhotic patients: the confused clinician!

To the Editor,

We read with great interest the editorial “Cross-talk between the liver, heart and kidney - another piece in the puzzle” by Krag and Gluud published in the last issue of the *J Gastrointestin Liver Dis* [1]. During the cross-talk, the voices of the kidney (history and diagnostic criteria of hepatorenal syndrome) and the heart (cirrhotic cardiomyopathy with its electrophysiological abnormalities, and the value of natriuretic peptides as another piece in the puzzle) are louder, while that of the liver is more quiet. We must confess that we expected the initiators of the wellknown “window hypothesis” for beta-blocker therapy to offer more light on the ongoing debate concerning the potential harmful effect of non-selective beta-blockers (NSBBs) on cirrhotic patients. Thirty-three years ago, Lebrech et al performed the first randomized clinical trial, which documented that propranolol significantly reduced the risk of rebleeding from oesophageal varices [2]. Since then, over 600 articles (including RCTs and meta-analyses) have been published on the use of NSBBs in cirrhosis, establishing propranolol as the first-line pharmacotherapy in the primary and secondary prevention of variceal bleeding. Moreover, NSBBs have proved beneficial in the prevention of other complications of cirrhosis such as hepatorenal syndrome, refractory ascites, and spontaneous bacterial peritonitis (SBP) [3]. Therefore, NSBBs are still considered to be the cornerstone of the medical therapy in cirrhosis. Four years ago, Serste et al [4] published an article about the deleterious effects of beta-blockers on the survival of patients with cirrhosis and refractory ascites and concluded that propranolol should be contraindicated in such patients. Recently, Mandorfer et al [5] showed that in patients with cirrhosis and SBP, NSBBs were associated with reduced transplant-free survival and increased risks for hepatorenal syndrome and acute kidney injury; their provocative article ends with the recommendation that such patients should not receive NSBB therapy. Both studies support the “window hypothesis” for beta-blocker therapy by

Krag et al [6], who suggested that NSBBs may be effective and improve survival only within a narrow clinical window in the course of liver cirrhosis, and are harmful outside of this window. According to this hypothesis, the presence of refractory ascites or development of SBP closes the window of opportunity for NSBB therapy. It is in this context that these two studies suggesting that NSBBs have deleterious effects on patients with advanced cirrhosis generated significant controversies among clinicians as they are difficult to reconcile with those of many previously published articles showing the beneficial role of NSBBs in preventing both refractory ascites and SBP in cirrhotic patients. This has added complications to a subject of therapy which is becoming confused, making it more difficult for a disoriented clinician to take the right decision in current clinical practice: to initiate or not the NSBBs treatment, or continue/discontinue NSBBs in such patients.

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Reply,

When to stop non-selective beta-blockers: the window hypothesis in clinical practice

We thank Drs. Trifan and Stanciu for their interest and comments on our editorial [1]. We agree that the controversy regarding non-selective beta-blockers (NSBBs) in advanced cirrhosis is important. Numerous letters and comments have debated the use of NSBBs in advanced cirrhosis, but only a few studies are published [2-5]. No randomised controlled trials (RCTs) have evaluated the question and we therefore cannot make strong conclusions or recommendations. In previous RCTs on NSBBs versus placebo, no intervention or endoscopic therapy were designed to evaluate the prevention of variceal bleeding. Patients with advanced liver disease have a poor prognosis and are difficult to include in RCTs. Accordingly, they were excluded from RCTs or trials that only included a small number of these patients [6, 7]. However, an international multicenter RCT may be conducted if ethical issues regarding the design and variceal prophylaxis can be dealt with. A large number of clinical sites would have to participate to obtain the sufficient sample size.

Two retrospective single center studies and one cohort single center study have evaluated the effect of NSBBs in advanced cirrhosis [2, 3, 5]. One additional epidemiological population based study has been published in abstract form [8]. The studies were conducted rigorously, but the design entails a risk of bias. Confounding factors cannot be completely eliminated through statistical analyses. In a clinical setting, patients who are treated with NSBBs will differ from those who are not. One of the main problems therefore includes confounding by indication. Although the evidence is inconclusive, the data suggest that there are serious concerns regarding severe adverse effects of NSBBs on patients with advanced liver disease. In particular, the concerns refer to patients with refractory ascites and spontaneous bacterial peritonitis. There is no international consensus regarding the use of NSBBs in these patients. Based on our interpretation of the evidence, we believe that the safety of NSBBs in patients with advanced liver disease should be considered in clinical practice as well as research. As described in our paper on the window hypothesis, the potential detrimental effects in advanced disease may outweigh the beneficial effects [9]. We recommend that patients with end stage liver disease and refractory ascites should be considered for liver transplantation or transjugular intrahepatic portosystemic shunt (TIPS). Patients with refractory ascites, a low mean arterial pressure or increased creatinine (Type 2 hepatorenal syndrome) or previous spontaneous bacterial peritonitis have a short survival

without transplantation. If these patients develop large varices, primary prevention with ligation alone should be first choice [7]. In secondary prophylaxis, the addition of NSBBs to banding reduces risk of rebleeding, but does not affect mortality [6]. The combination of NSBBs and banding ligation should be avoided or monitored closely. Endoscopic surveillance and repeated ligations should be performed. During acute illness such as acute variceal bleeding, sepsis and hepatorenal syndrome NSBBs should generally be discontinued to enable cardiac compensatory tachycardia (if necessary) [10-12].

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Epidemiology and predictors of recurrence of *Clostridium difficile* infection in a North Italian tertiary care hospital

To the Editor,

Clostridium difficile is considered to be the main cause of bacterial infectious diarrhoea in nosocomial setting. Over the last 20 years, a two- to fourfold increase in the incidence of severe *Clostridium difficile* infection (CDI) has been observed worldwide [1, 2]. The rate of recurrences represents perhaps one the most challenging aspects in the management of CDI. In fact, after a successful first-line treatment with standard therapies around 20-30% of patients may experience a second event [2]. Only limited data are available on CDI epidemiology in Italy. Here we report a retrospective analysis of all patients

with CDI admitted from January 2009 to December 2012 to the Santa Maria Misericordia University Hospital, a 1,200 bed tertiary care hospital located in Udine, Italy. All in-patients whose stool samples were sent to the hospital Microbiology laboratory for *C. difficile* toxin detection were included in the analysis. In the stool samples the presence of toxin A and B was tested by enzyme immunoassays (EIA) for A/B toxins. A CDI episode was considered as a positive *C. difficile* toxin assay in a stool sample. The study was approved by the local Institutional Review Board.

A total of 354 CDI episodes were identified on 4,098 stool samples tested (8.6%). The demographic characteristics are described in Table I. A large proportion of CDI cases involved elderly patients: the ≥ 60 year-old age group experienced 199 episodes of CDI (56.2% of cases). The majority of CDI episodes were found in the internal medicine department (163

Table I. Demographics, clinical characteristics and risk factors of the studied patients.

Variables	Overall patients, n 354	Patients with only one episode, 328 (92.7 %)	Patients with recurrent episodes, 26 (7.3 %)	p value
Age, years, mean (SD)	60 (25)	60 (24)	63 (26)	0.54
Male, n (%)	174 (49.2)	161 (49.1)	13 (50)	0.93
Therapy and co-morbidities, n (%)				
steroids	153 (43.2)	140 (42.7)	13 (50)	0.47
chronic renal failure	57 (16.1)	50 (15.2)	7 (26.9)	0.12
hemodialysis	15 (4.2)	15 (4.6)	0	0.27
transplant	68 (19.2)	65 (19.9)	3 (11.5)	0.30
radiotherapy	15 (4.2)	14 (4.3)	1 (3.8)	0.91
chemotherapy	81 (22.9)	78 (23.8)	3 (11.5)	0.15
diabetes	46 (13.0)	41 (12.5)	5 (19.2)	0.33
cancer	118 (33.3)	109 (33.2)	9 (34.6)	0.89
cirrhosis	20 (5.6)	19 (5.8)	1 (3.8)	0.68
HIV	15 (4.2)	15 (4.6)	0	0.27
Previous hospitalization in the last year, n (%)	280 (79.1)	258 (78.7)	22 (84.6)	0.47
Days of hospitalization at the time of CDI, mean (SD)	20 (22)	19 (19)	27 (33)	0.05
Ward where CDI was diagnosed, n (%)				
Medicine	163 (46.0)	153	10 (6.1)	
Paediatrics	88 (24.9)	87	1 (1.1)	
Onco/hematology	40 (11.3)	36	4 (10)	
Surgery	34 (9.6)	27	7 (20.6)	
Intensive care unit (ICU)	23 (6.5%)	22	1 (4.3)	
Long term care/rehab (LTCF)	6 (1.7%)	3	3 (50.0)	
Patients treated with antibiotics in the previous 3 months, n (%)	280 (79.1)	257 (78.4)	23 (88.5)	0.22
Days of antibiotic treatment before CDI, mean (SD)	17 (21)	16 (19)	24 (26)	0.04
Type of antibiotic used (in the previous 3 months) n (%)				
Quinolones	144 (40.7)	133 (40.5)	11 (42.3)	0.86
Cephalosporins	85 (24.0)	78 (23.8)	7 (29.9)	0.72
Carbapenems	101 (28.5)	91 (27.7)	10 (38.5)	0.24
Beta-lactams with BLI	144 (40.7)	132 (40.2)	12 (46.2)	0.55
Clindamycin	2 (0.6)	2 (0.6)	0	0.69
Others	153 (43.2)	141 (43.0)	12 (46.2)	0.75
Use of PPI, n (%)	278 (78.5)	257 (78.3)	21 (80.8)	0.77
Type of treatment for CDI (first episode) n (%)				
No treatment	28 (7.9)	26 (7.9)	2 (7.7)	0.96
Vancomycin	127 (35.9)	119 (36.3)	8 (30.8)	0.57
Metronidazole	142 (40.1)	130 (39.6)	12 (46.2)	0.51
Vancomycin + metronidazole	57 (16.1)	53 (16.2)	4 (15.4)	0.92
Duration of CDI treatment, days, mean (range)	12 (6-18)	11 (5-17)	14 (4-24)	0.02

cases, 46.0%), followed by paediatrics (88, 24.9%), oncology/hematology (40, 11.3%), surgery (34, 9.6%), ICU (23, 6.5%) and long term care/rehabilitation (LTCF) (6, 1.7%) departments. The overall incidence rate per 10,000 patient-days was 2.4, increasing from 1.7 in 2009 to 3.0 in 2012. Incidence rate rose up particularly in the oncology/hematology units, ICU and LTCF.

Patients who experienced at least one recurrent episode were 26, accounting for 7.3 % of the total with the highest incidence in LTCF (3/6, 50%) and surgery (7/34, 20.6%). At univariate analysis a higher number of days of antibiotic treatment before CDI and a longer duration of antibiotic treatment of the first CDI episode were significantly associated with the risk of recurrence ($p=0.04$ and 0.02 , respectively).

The increasing incidence rate of CDI in our hospital represents a matter of concern. In Europe, this continuous increase has been associated with outbreaks, firstly described in the United Kingdom then in other European countries [3]. Very limited data are available regarding CDI epidemiology in Italy. Mellace et al recently reported a cumulative incidence of 2.56 per 100 hospitalizations and an incidence rate of 23.3 per 10,000 patient-days [4]. As observed in that study, where CDI episodes mostly occurred in medical wards (80%) and in patients > 60 years of age (77%), we similarly documented an important incidence of CDI in elderly patients admitted to Internal Medicine wards and having one or more underlying diseases. We observed that commonly prescribed antibiotics before the onset of CDI were quinolones and beta-lactams. A recent study confirmed a significant association between CDI cases and previous use of fluoroquinolones and also a significant role of 3rd-generation cephalosporins [5].

In our analysis, the proportion of patients with at least one episode of recurrence was 7.3%, lower than the incidence reported in a similar European analysis, where the rate was around 20% [5]. This difference could be related to the study design: we excluded all positive samples collected within 25 days after the first positive result for any individual patient (as considered part of the same episode) and all positive samples collected from asymptomatic patients after the first episode.

In conclusion, a progressively increasing incidence of CDI episodes was documented over the years in our hospital. These data represent a matter of concern for clinicians. Improvements in the surveillance systems and infection control programs are required.

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An extremely rare primary gallbladder myxoid liposarcoma associated with amplification of *DDIT3* gene

To the Editor,

A 70-year-old otherwise healthy woman presented with one week of severe right upper quadrant abdominal pain. No significant abnormal laboratory result was detected. Computerized tomography demonstrated a well-defined, 6 x 6 cm mass surrounding the gallbladder wall, consisting of abnormal fat (Fig. 1). A cholecystectomy was performed to completely excise the mass. Gross examination revealed an enlarged and asymmetric gallbladder which measured 13 x 8 x 5 cm. A well-circumscribed myxoid mass occupied nearly the entire wall. The mass had heterogeneous yellow and tan fatty cut surface. On microscopic examination, the gallbladder was diffusely involved by a tumor displaying hypocellular, monomorphic, stellate or fusiform cells without atypia and occasional signet-ring lipoblasts in the background of myxoid stroma containing a delicate, arborizing, and "chicken-wire" capillary vasculature. These features are characteristic of a myxoid liposarcoma (MLS) (Fig. 2). No necrosis, increased cellularity or round cell component were identified. Fluorescence in situ hybridization assay demonstrated amplification of the 12q13 region containing the *DDIT3* (*CHOP*) gene in 100% of tumor nuclei (Fig. 3). *DDIT3* gene rearrangement was not identified. The post-operative staging by radiologic imaging did not reveal any metastatic lesion.



Fig. 1. CT scan shows a well-defined 6 x 6 cm gallbladder mass (arrow).

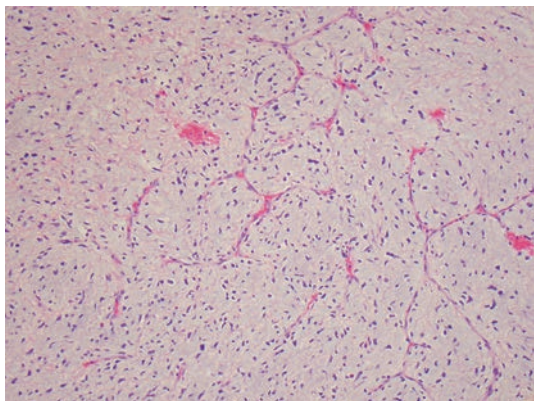


Fig. 2. The tumor displays typical features of myxoid liposarcoma (H&E, x200).

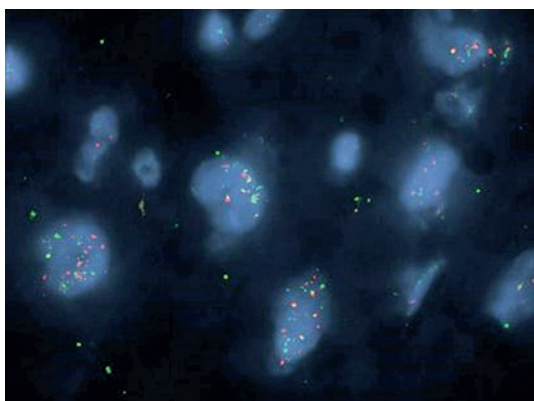


Fig. 3. FISH demonstrates amplification of 12q13 region (the red signals are 3'DDIT3 and the green signals are 5'DDIT3, x630).

Liposarcoma is one of the most common soft tissue sarcomas of adults affecting mostly extremities and the retroperitoneum. Liposarcomas arising primarily in the gallbladder are extremely rare and, to our knowledge, there have been only two cases reported [1, 2]. The first case was an intramural MLS published in the German literature in 1983 and the patient died of diffuse spread of the tumor two years later [1]. The second was a primary pleomorphic liposarcoma (PL) published in 2006 by a Japanese group. The patient developed recurrent disease and metastasis to the liver later and had two more subsequent surgeries though she was free of disease three and a half years after the first surgical treatment [2]. Since the expected outcome of primary gallbladder sarcomas is poor, the fact that both previously reported cases had metastasis may alarm physicians of an unpromising prognosis of gallbladder liposarcoma.

The World Health Organization Classification of soft tissue tumors divides liposarcomas into four subtypes: atypical lipomatous tumor (ALT), MLS, dedifferentiated liposarcoma (DL) and PL [3]. Myxoid liposarcoma accounts for 15-20% of liposarcomas that affects mostly extremities with recurrence and the metastasis determined largely by the round cell component. Myxoid liposarcoma usually contains a reciprocal translocation $t(12;16)(q13;p11)$ resulting in a chimeric *FUS/CHOP* gene in > 95% of cases. Complex amplification of regions of 12q is a key feature of ALT. The novel molecular

finding in our case: amplification of 12q13 region containing *DDIT3* gene has never been reported in MLS, so the clinical significance is unknown.

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Increased rate of spontaneous clearance of hepatitis C virus in patients infected with HIV

To the Editor,

We read with interest the paper by Kaung et al [1]. Indeed, chronic viral hepatitis C is one of the diseases that worsen the status of a patient infected with HIV, given that standard therapy for hepatitis C is poorly tolerated [2], and the rate of response to treatment with peginterferon and ribavirin is low [3].

Currently, the Regional HIV/AIDS Center of Constanta has 1,026 records of patients infected with HIV. Of these, 41 patients (4%) have also anti-HCV antibodies, a figure similar with non-HIV patients in Romania [4] and far below that mentioned by Kaung et al. All patients are under therapy with HAART. It is remarkable that 14 patients of the 41 with antiHCV (34%) had no detectable viremia, which may be explained by the fact that these patients had had HCV clearance, spontaneous or induced by the antiretroviral therapy. As a special feature, we mention that all these patients were treated with protease inhibitors (lopinavir/ritonavir 10 patients and saquinavir/ritonavir 4 patients). Recent studies included ritonavir as anti-HCV therapy in interferon free regimens [5, 6]. We wonder to what extent ritonavir and other protease inhibitors have facilitated HCV clearance. Recently, Stenkvist et al communicated a rate of spontaneous clearance of HCV in 21.6% of their HIV co-infected patients, a percentage lower than that found in our center. They discuss the possibility that antiretroviral therapy has a significant role in this process by immune reconstitution in patients with IL28B CC variant, a variant present in all co-infected patients who had HCV clearance [7]. Also in this year, Vispo et al communicated a

rate of 14% of spontaneous clearance of HCV in co-infected patients who followed HAART and also had the CC genotype [8]. Thus, protease inhibitors and IL28B CC variant appear to play an important role in HCV clearance in patients with HIV infection.

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Assessment of active mucosal inflammation in IBD patients in clinical remission

To the Editor,

In a recent issue of the *Journal of Gastrointestinal and Liver Diseases*, we read with great interest the article by Voiosu and colleagues entitled "Rapid fecal calprotectin level assessment and the SIBDQ score can accurately detect active mucosal inflammation in IBD patients in clinical remission: a prospective study" in which the investigators suggested that faecal calprotectin (FC) and a short inflammatory bowel disease questionnaire had a good diagnostic accuracy in

detecting mucosal inflammatory changes in inflammatory bowel disease (IBD) patients in clinical remission, and in addition, thought them both to be a practical method for monitoring disease activity in these patients [1]. However, we think that some points should be discussed.

Fecal calprotectin is a validated non-invasive biomarker in IBD. Previous studies suggested that various drugs such as aspirin, nonsteroidal anti-inflammatory drugs, immunosuppressants, anti-tumor necrosis factor drugs, and statins could alter FC levels [2, 3]. Beside these drugs, dietary supplements such as fatty acids, zinc, vitamin D, and several probiotics can alter FC levels, too [4]. The authors considered only corticosteroids as a contributing factor. We believe that the aforementioned contributing factors have to be stated to provide robust data too.

Smoking status and body mass index of the participants were shown to affect calprotectin levels [5, 6]. Also, sampling time is important to evaluate FC to prevent pre-analytical errors. Lasson et al showed that there was a great variability in the concentrations of FC in stool samples collected during a single day [7]. Jost et al suggested that pregnancy might represent low-grade signs of intestinal inflammation due to mild elevation of FC [8]. We think these contributing factors have to be stated to prevent misinterpretations.

Single measurement of FC may not be sufficient to evaluate the diseases, as the authors stated, and different biomarkers such as platelet and leucocyte count, albumin, alpha-1 acid glycoprotein, polymorphonuclear elastase, and lactoferrin may be required [9, 10]. In conclusion, clarifying the above concerns will certainly provide a clearer picture to the readers.

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Reply,

To the Editor,

The authors would like to thank Agilli et al for their interesting comments. We would like to state that no pregnant woman was included in the MAID cohort. Also, we do not recommend NSAID use in IBD patients, although over-the-counter, intermittent use is likely but very difficult to account for. In our study we did not analyze the impact of any

therapeutic agents (corticosteroids, immunosuppressants or biologics) on calprotectin levels, but given the impact of these agents on mucosal healing we believe this to be a potential confounding factor. In regard to the timing of stool sampling, we acknowledge that this might influence calprotectin levels, but repeated sampling is cumbersome for both patient and physician and likely to decrease patient overall compliance while increasing costs.

We agree that several factors might contribute to the variations of calprotectin levels, including smoking status, probiotics or dietary supplements including zinc or vitamin D. However, the influence of these factors is probably very small compared to that of active inflammation of the bowel wall, and most data in the literature do not adjust calprotectin levels for any cofactors. Furthermore, accounting for such cofactors in multivariate analysis is not technically feasible in small cohorts as the number of variables should be limited according to the size of the patient sample [1]. Combining multiple biomarkers is an attractive option for further research and we would like to explore this in the near future.

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Conflicts of interest: no conflicts of interest.

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