

Risk stratification in the management of portal vein thrombosis in cirrhosis

To the Editor,

In the Baveno VI consensus, a new section regarding anticoagulation and portal vein thrombosis (PVT) in cirrhosis has been incorporated [1]. It recommends that anticoagulation should be considered in potential candidates with thrombosis of the main portal vein trunk or progressive PVT. Similarly, our recent systematic review with meta-analysis of observational studies also suggested that patients receiving anticoagulation therapy had a significantly higher rate of complete portal vein recanalization and a significantly lower rate of thrombus progression than those without any anticoagulation treatment (pooled odds ratio [OR]=4.16, 95% confidence interval [CI]=1.88-9.20, $P=0.0004$; OR=0.061, 95%CI=0.019-0.196, $P<0.0001$) [2]. Notably, neither heterogeneity nor publication bias was statistically significant, suggesting that the benefit of anticoagulation was relatively stable. In addition, no lethal complications were recorded among studies, and major complications were rarely observed (pooled rate=1.4%, 95%CI=0.3%-3.4%). In spite of these positive findings, the level of relevant evidence is low and the grade of recommendation is weak. However, several major unresolved issues need to be outlined regarding the progression of PVT in liver cirrhosis (Fig. 1).

Firstly, as disclosed by the title of Baveno VI workshop, stratifying risk and individualizing care for portal hypertension has become one of the most important current topics [1]. Likewise, the risk stratification of PVT should be also assured. The accumulated evidence suggested that not all PVT could positively influence the prognosis of liver cirrhosis [3]. This consideration was explained by the fact that only occlusive and/or extensive PVT, but not partial PVT, could increase the technical difficulty of liver transplantation and post-operative mortality of liver recipients [4]. Indeed, as the severity of PVT was missing, statistical analyses might be confusing and suggested that PVT might improve the survival of liver cirrhosis [5]. Recently, we have proposed a new term “clinically significant PVT” to clarify the necessity of management in only a subgroup of cirrhotic patients [6]. Additionally, the primary prevention from silent PVT to clinically significant PVT should be considered.

Secondly, several studies have recently demonstrated the possibility of spontaneous recanalization of partial PVT in liver cirrhosis without any anticoagulation treatment [7-9]. Such conditions should be termed as “transient PVT”. The prevention and treatment of transient PVT should never be worthwhile. Instead, further studies should pay more attention to the prediction of spontaneous portal vein recanalization.

Thirdly, with regard to cirrhotic patients without any prior PVT, the only randomized controlled trial suggested that anticoagulation therapy could significantly prevent the

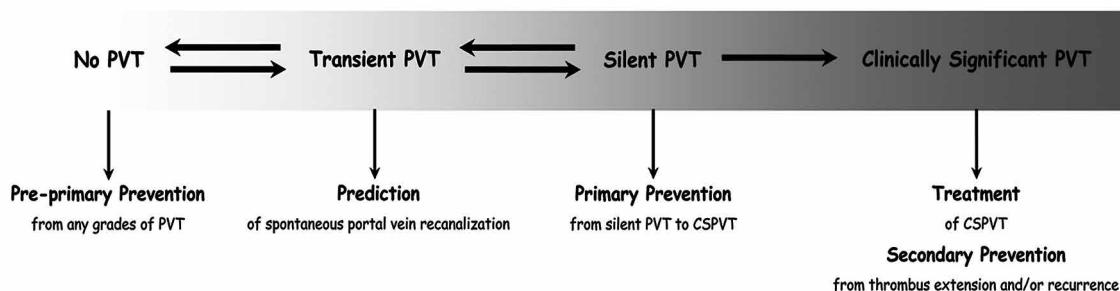


Fig. 1. Unresolved issues in the management of PVT in liver cirrhosis.

development of de novo PVT [10]. However, as mentioned above, the effect of any grade PVT on the prognosis of liver cirrhosis remained controversial. Thus, the importance of pre-primary prevention deserved further investigation.

In conclusion, the notion of risk stratification and individualized care should be expanded to the management of PVT in liver cirrhosis. According to the management of varices and variceal bleeding in liver cirrhosis, future research agenda regarding the management of PVT should also include the pre-primary prevention, primary prevention, secondary prevention, and treatment.

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***Clostridium difficile* infection in hospitalized cirrhotic patients with hepatic encephalopathy**

To the Editor,

During the last two decades there has been a dramatic change in the epidemiology of *Clostridium difficile* infection (CDI) worldwide with an increase in both the incidence and severity of disease [1, 2]. Although broad-spectrum antibiotics are the major risk factors for CDI, other important ones are older age, hospitalization, chemotherapy, immunosuppression, multiple comorbidities, use of proton pump inhibitors (PPIs), and emergence of a hypervirulent strain of the bacterium known as NAP1 (North American pulse field type 1) in some North-American and European areas [3-5]. Patients with inflammatory bowel disease (IBD), especially those with ulcerative colitis, have higher rates of CDI than those reported in the general population, and several studies have demonstrated worse clinical outcomes including mortality in a combination of IBD and CDI than either of these diseases alone [6].

Recently, there has been an increased interest in CDI in another at-risk population, namely patients with liver cirrhosis [7, 8] who have many of the above mentioned risk factors for CDI: frequent and prolonged hospitalizations, multiple comorbidities, antibiotic therapy and consequently altered gut microbiota, PPI use, and an immunocompromised system.

We read with interest the study by Stoica et al. published in the last issue of JGLD evaluating the incidence and risk factors for CDI in cirrhotics hospitalized with hepatic encephalopathy (HE) [2]. The authors found that 7.3% of cirrhotics hospitalized for an episode of HE developed CDI, while by multivariate logistic regression analysis, antibiotic therapy, age over 65 years, and hepatorenal syndrome remained significantly related to the development of CDI. Since 2009, we have faced with a dramatic increase of cases of CDI, most of them being severe and often accompanied by potentially life threatening complications. The majority of these cases were associated with hypervirulent strains of *Clostridium difficile* (*C. difficile*) infection, ribotype 027, respectively. We had two patients recently hospitalized with cirrhosis and HE who had similar features as the group of patients described by the authors in their analysis. Both patients were under treatment with lactulose and rifaximin for HE secondary prophylaxis and had had a history of recurrent hospital admissions and systemic antibiotic use in the previous three months.

It should be mentioned that diarrhea in hospitalized cirrhotic patients with HE may represent a side-effect of the therapy used for HE, mostly lactulose [9], and this may lead to undertesting for *C. difficile* and thus to the worsening of underlying disease mainly due to the lack or delay in diagnosis of CDI in some cases.

We fully agree with the authors' recommendation that clinicians should be aware of the risk for CDI in cirrhotic patients with HE. A high index of suspicion for this infection is essential for its rapid diagnosis and prompt therapy.

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Causes of hospitalization and characteristics of UC in a population-based cohort in Romania (2014-2015): are there any differences in comparison with the Hungarian population?

To the Editor,

We read with great interest the paper by Golovics et al. providing population based data from the Veszprem Hungarian cohort with regard to the prevalence and predictors of

hospitalization and re-hospitalization in ulcerative colitis (UC) [1]. The paper has shown that the rates of hospitalization and re-hospitalization were relatively high, but early hospitalization was not predictive for the later disease course. Many studies have investigated the need for colectomy in UC patients especially in the pre-biologics era, but the population-based data with regard to surgery-related or other UC-related causes is scarce especially from Eastern European Countries, where IBD is now emerging as a challenging new pathology.

In Romania, the epidemiology of IBD is changing, in parallel with the environmental and lifestyle changes of the Romanian population. Previous epidemiological data have shown a very low incidence of IBD in Romania, compared to other Southern and Eastern European populations [2], but more recent data indicates an ascending trend [3]. Although they are neighboring countries, there are considerable differences between the Romanian and Hungarian populations, probably supported by a different genetic and environmental background. Medical care for patients with IBD in Romania is still referral center-related. A hospital-based registry (IBDPROSPECT) has been established in Romania beginning with 2006, collecting data from referral centers nationwide and comprising 1,918 IBD cases to date. This registry has already provided an interesting insight into the IBD epidemiology for Romania [4, 5].

However, in order to have robust epidemiological data in the Romanian population, a population-based registry was initiated in 2014 (EPIROM), including all patients diagnosed with IBD in the Bucharest urban region and suburbs (covering approximately 2 mil. inhabitants), in referral centers as well as private practice centers. We used the model of the French registry Epimad, with the support of our French colleagues. So far the registry comprises 211 patients, 55.02% diagnosed with CD, 44.02% with UC, and 0.96% IBD-U. Analyzing the medical setting in which the diagnosis of the patients was made, 94.23% of cases were diagnosed and followed-up in public referral centers. A percentage of 88.2% of these newly diagnosed UC patients have had a subsequent hospitalization within one year from the diagnosis.

We further analyzed the main reasons for hospitalization and re-hospitalization during the first year in our UC inception cohort. In our setting, there are three main reasons for hospitalization: biological treatment-related hospitalizations (one-day hospitalizations for biologic therapy for controlled disease) (48.8%), diagnostic procedures (28.4%), disease flares or UC-related complications (22.7%).

In our UC inception cohort, during the short-term follow-up (1 year), there were neither UC-unrelated nor surgery related hospitalizations. In contrast, the Hungarian cohort has indicated at one year 44.8% UC unrelated-hospitalizations and 4.8% surgery related hospitalizations. In the Hungarian cohort, 46.2% of all colectomies were performed in the first year after diagnosis, indicating, in comparison with our cohort, a definite increased need for colectomy in the Hungarian patients, possible due to more severe cases. However, there was a relatively low need for anti-TNF (7.5%). The comparative epidemiological data in Hungarian and Romanian cohorts is presented in Table I. We emphasize the significant differences with regard to the family history of IBD, incidence of arthritis, drug exposure (steroids, azathioprine, biologics). There are

Table I. Comparison between disease characteristics of ulcerative colitis in Romanian and Hungarian population-based cohorts.

	Veszprem UC inception cohort	EPIROM UC inception cohort	EPIROM UC cohort
Male/Female	200/147	23/10 (%: 69.07 / 30.3)	56/36 (%: 60.87/39.13)
Age at presentation (years)	36, IQR: 26-50	40.3, IQR: 36.4-44.3	34.73, IQR: 32.06-37.40
Duration (years)	7, IQR :4-10	1.47, IQR: 1.23-1.71	5.9, IQR: 1-35.6
Familial IBD	65 (18.7%)	0 (0%)	2 (2.17%)
Location at diagnosis			
1 proctitis	97 (27.8%)	8 (25%)	20 (22.22%)
2 left colitis	154 (44.3%)	14 (41.38%)	44 (48.2%)
3 pancolitis	96 (27.8%)	11 (31.03%)	28 (29.63%)
Arthritis	52 (14.9%)	3 (9.09%)	8 (8.7 %)
Steroid use	135 (38.8%)	7 (21.21%)	24 (26.09 %)
Topical steroid use		2 (6.06%)	7 (7.61 %)
Azathioprine use	59 (17%)	4 (12.5%)	23 (25.6 %)
Biological use			
Total	26 (7.5%)	4 (12.12%)	17 (18.67%)
Infliximab		4 (12.12%)	10 (10.98%)
Adalimumab		0 (0%)	7 (7.69%)
Smoking habits at diagnosis			
No	223 (64.3%)	17 (51.52%)	55 (59.78 %)
Ex-smokers	81 (23.3%)	15 (45.45%)	30 (32.61 %)
Yes	43 (12.4%)	1 (3.03%)	7 (7.61 %)

IQR: interquartile range; UC: ulcerative colitis.

not significant differences between the two populations with regard to disease extension, sex ratio, age at presentation and smoking habits.

A question that arises is whether repeated hospitalizations for biologic infusion have been taken into account in the Hungarian cohort or if these have been excluded from the analysis as having been conducted on an outpatient basis. In the multivariate analysis, the need for an anti-TNF was the second most important predictor for the first UC-related hospitalization. Subsequent hospitalization for anti-TNF could be an indicator of controlled disease, as biologics are potentially disease course modifiers.

Comparative epidemiological studies in neighboring populations such as Romania and Hungary, emphasizing environmental exposures and genetic factors could bring interesting new insights in IBD epidemiology.

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Reply,

We are thankful to Dimitriu et al. for commenting on our article "Does hospitalization predict the disease course in ulcerative colitis? Prevalence and predictors of hospitalization and re-hospitalization in ulcerative colitis in a population-based inception cohort (2000-2012)" published in the *J Gastrointest Liver Dis* [1].

There are still relatively few data available on hospitalization and re-hospitalization rates in ulcerative colitis (UC) from population-based studies especially in Eastern European countries. The recent EpiCom study with inception cohorts, initiated in 2010 and 2011 involving centers from Romania and Hungary, evaluating the disease phenotype, hospitalization and colectomy rates in UC patients did not differ between Eastern and Western European countries during the first year of the disease. In the 2010 ECCO-EpiCom cohort [2], 14% vs. 8%, while in the 2011 ECCO-EpiCom cohort [3], 16% vs. 16% of the UC patients in Western vs. Eastern Europe were hospitalized. However, in contrast to the EPIROM and the Hungarian cohort, diagnosis-related hospitalizations were excluded from the analysis. The colectomy rate was low in the Eastern European region with 2 (1%) UC patients being colectomized in the 2010 inception cohort, while no UC patients underwent colectomy in the 2011 inception cohort during the first year after diagnosis. The same tendency was observed in Western Europe, where 4% and 1% of the UC patients from the 2010 and the 2011 inception cohorts underwent colectomy.

According to the EPIROM data, the rate of the early hospitalization was exceedingly high (88.2% in the year of diagnosis) including hospitalizations due to biological therapy. As high as 48.8% of all hospitalizations were related to biological therapy during the first year of the disease, which at least partly should reflect the improving access to biological treatment in this region. In the recent study by Rencz et al. [4] on the access of biological treatment in Central and Eastern Europe, the percentage of biological-treated UC patients was 2.1% of the total UC patients in Romania, compared to 3.5% in Hungary. Interestingly, the rate of biological therapy was lower in CD compared to UC in Romania, which was exceptional among the investigated countries.

The main difference between the EPIROM and our population-based study was that in Romania almost half of the hospitalization events occurred for the administration of biological therapy, while Hungarian inflammatory bowel disease (IBD) patients receive biological infusion on an outpatient basis.

Therefore, it is questionable whether mandatory hospitalizations due to the reimbursement policy as biological therapy-related hospitalizations should be included as real hospitalization events, which may also lead to difficulties in the interpretation of hospitalization rates due to the inclusion of administrative rather than clinical causes. Furthermore, in voluntary registries the completeness of the data is ambiguous, therefore an extensive validation of the data is necessary.

In conclusion, both EPIROM and the Hungarian population-based inception cohort from Veszprem County are important initiatives to gain a better insight into current trends in the epidemiology, therapeutic and monitoring strategy and disease outcomes in IBD in Eastern European countries. Further population-based studies are warranted to assess the disease characteristics and also economic burden of IBD in the region. Finally, recent publications confirm that the rate of hospitalizations continues to be high and that hospitalization remains to be an important outcome measure and a major cost driver in IBD.

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The orientation of the gastric biopsy specimen for the gastric atrophy assessment is important

To the Editor,

It was with great interest that we read the article by Isajevs et al. on the pattern of inflammatory and atrophic changes in the stomach, recently published in the *Journal of Gastrointestinal and Liver Diseases* [1]. We would like to add, if we may, an aspect to the topic that we consider very important, i.e. the role of orientation of the gastric biopsy specimen in the gastric atrophy assessment.

One of the authors' findings is a moderate interobserver agreement for the assessment of gastric atrophy compared to intestinal metaplasia, which has a higher interobserver index. Gastric atrophy and intestinal metaplasia of the stomach are well-defined premalignant conditions. The risk of developing gastric cancer is increased in patients with extensive and severe gastric atrophy [2]. For this reason, the use of multiple biopsies standardized protocols for the assessment of gastric atrophy extension and severity is recommended [3]. An international group of gastroenterologists and pathologists proposed a staging system for gastric atrophy, using the extension and severity of atrophic mucosal changes [the operative link for gastritis assessment (OLGA) staging system] [4]. The highest OLGA stages correlate with an increased

risk of developing gastric cancer. The study presented by Isajevs et al. [1] is consistent with other data that show unsatisfactory interobserver agreement for gastric atrophy assessment [5]. In order to make an accurate evaluation of gastric atrophy, the pathologist needs a perpendicular (full-thickness) mucosal section [4]. This is a hazard in the biopsy samples that are not oriented before or after formalin fixation, and consequently, the proper evaluation of mucosal atrophy can be very difficult. Unfortunately, the orientation of gastric biopsy specimens is not a common practice [6]. We showed, in a recently presented study, that orientation of gastric biopsy samples could dramatically improve the interobserver agreement for OLGA staging system [7]. Two sets of biopsy samples (oriented and not-oriented) taken from the same patients were blindly analyzed by two experienced pathologists. The OLGA gastric biopsies protocol was applied [4]. Nitrocellulose filters were used before formalin fixation for gastric biopsy samples orientation. The kappa index values for oriented / not-oriented OLGA 0, I, II, III and IV stages were 0.62/0.13, 0.70/0.20, 0.61/0.06, 0.62/0.46, and 0.77/0.50, respectively.

Our conclusion was that orientation of gastric biopsy samples is very useful for the proper assessment of gastric atrophy. For this reason, the orientation of the gastric biopsy specimens taken for gastric atrophy assessment should be encouraged.

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