University Hospital Dubrava
Avenija Gojka Suska 6, Zagreb

Zagreb, 1 March 2019

EASL | ENDORSED EVENT

# ADRIATIC LIVER FORUM 2019

## Liver and the Infections

## Dear colleagues and friends,

It is our great pleasure to announce the **5th Adriatic Liver Forum** (ALF) conference to be held on **1st March 2019 in Zagreb**, Croatia. The topic of this monothematic conference will be **Liver and the infections**. As in previous years the conference is co-organised by the University Hospital Dubrava and Croatian Society of Gastroenterology.

We are witnessing global efforts to eradicate viral hepatitis which still represent significant burden in terms of liver related morbidity, mortality and costs for health systems. Wheras effective vaccines for HBV and antiviral drugs for HCV have generally resulted in decreasing incidence and prevalence of viral hepatitis, it is estimated that at least 3.2 million of people in EU have viremic HCV. Hepatitis B and C infections account for 96% of the global mortality from hepatitis-related end stage liver disease. Patients with cirrhosis, particulary decompensated are under increased risk of developing bacterial infections with an incidence 4 times higher as compared general population. In these patients infections increase mortality 4-fold reaching 63% at 1 year. Therefore, severe bacterial infection occuring in patient with decompensated cirrhosis has been suggested to represent a distinct stage in natural history of cirrhosis with most worrisome prognosis. In addition, there is still significant gap between the number of patients who die from liver failure and organs availible for transplantation. These aspects will be discussed in depth at the upcoming meeting.

The speakers will be eminent experts in the field from eleven European countries including Bosnia & Herzegovina, Croatia, Czech Republic, Hungary, North Macedonia, Poland, Romania, Russian Federation, Serbia, Slovakia and United Kingdom. From its foundation Adriatic Liver Forum has been well accepted by hepatologists from the wider geographic area of Central-South-Eastern Europe as the platform for exchange of knowledge and establishing collaboration in hepatology, all in spirit of peace and friendship. In this line, we are very happy over the fact that tight connection has been established with the Central European Hepatology Collaboration, which is going to held its meeting in Zagreb the day after ALF conference and we share many Faculty members.

The scientific value of ALF conference has been recognized by the most eminent national and international professional organizations and we are proud to announce endorsements by Ministry of Health of the Republic of Croatia, European Association for the Study of the Liver (EASL), Croatian Society for Ultrasound in Medicine and Biology of the Croatian Medical Association, University of Zagreb School of Medicine and Faculty of Pharmacy and Biochemistry.

Participation at the conference will be accredited according to regulations of Croatian Medical Chamber and all participants will be granted certificate of attendance.

Looking forward to meeting you in Zagreb!

Presidents of the Adriatic Liver Forum 2019 conference

Assoc. prof. **Ivica Grgurevic**, MD PhD  Assoc. prof. **Tajana Filipec Kanizaj**, MD PhD

## ALF 2019 FACULTY:

1. Bende F ..... RO
2. Filipec Kanizaj T ..... HR
3. Flisiak R ..... PL
4. Grgurevic I ..... HR
5. Hrstic I ..... HR
6. Husic Selimovic A ..... BH
7. Jarcuska P ..... SK
8. Kardum D ..... HR
9. Krznaric Z ..... HR
10. Kukla M ..... PL
11. Ladic D ..... HR
12. Lalovac M ..... HR
13. Ljubicic N ..... HR
14. MacDonald D ..... UK
15. Majerovic M ..... HR
16. Manolev A ..... MK
17. Matic V ..... HR
18. Milić S ..... HR
19. Milovanovic T ..... SRB
20. Moga T ..... RO
21. Mustapic S ..... HR
22. Novak K ..... SLO
23. O'Brien A ..... UK
24. Ostojic R ..... HR
25. Papp M ..... HU
26. Pavlov C ..... RUS
27. Pinzani M ..... UK
28. Puljiz Z ..... HR
29. Salkić N ..... BH
30. Skladany L ..... SK
31. Sperl J ..... CZ
32. Stojsavljevic S ..... HR
33. Tomasiewicz K ..... PL
34. Tsochatzis E ..... UK
35. Turcic P ..... HR
36. Vince A ..... HR
37. Virovic Jukic L ..... HR

# SCIENTIFIC PROGRAMME

**08:00-08:30** **OPENING CEREMONY**

**08:30-10:00** **SESSION I: Viral hepatitis** | **Chairs:** MacDonald D, Ostojic R, Tomasiewicz K

1. Effectiveness of DAA therapy: Real life data from Central Europe (Flisiak R, PL)
2. On the road to eradicate hepatitis C: Croatian national strategy (Vince A, HR)
3. Post SVR follow-up in chronic HCV: When is it necessary? (MacDonald D, UK)
4. Hepatitis B: should we stop NUCs and when? (Husic Selimovic A, BH)
5. HBV reactivation in the immunocompromised patient (Milovanovic T, SRB)

**10:30:12:00** **SESSION II: Role of microbes in noninfective liver conditions** | **Chairs:** Jarcuska P, Ladic D, Kardum D

1. Type and prognostic impact of infectious agents in patients with cirrhosis (Grgurevic I, HR)
2. Infections in severe alcoholic hepatitis (Pavlov C, RUS)
3. The role of gut microbiota in the progression of NAFLD to HCC (Kukla M, PL)
4. Predictive value of gut dysbiosis on ACLF mortality (Milic S, HR)
5. Liver in sepsis (Salkic N, BH)

**12:15-13:00** **LUNCH SESSION: Ultrasound for hepatologists**

1. Introductory lecture: US in liver cirrhosis: diagnosis and follow-up (Manolev A, MK)
2. Hand-on session: Bende F, Lalovac M , Matic V, Moga T, Mustapic S, Stojsavljevic S

**13:00-14:00** **LUNCH**

**14:00-15:30** **SESSION III: Infections in patients with liver cirrhosis** | **Chairs:** Hunyady B, Krznaric Z, Pinzani M

1. Hepatology: predictions for the future (Pinzani M, UK)
2. Bacterial Infections Change Natural History of Cirrhosis Irrespective of Liver Disease Severity (Tsochatzis E, UK)
3. SBP: a diagnostic algorithm for clinicians and future perspectives (O'Brien A, UK)
4. Early predictors of bacterial infection in cirrhosis: CRP and other biomarkers (Papp M, HU)
5. Proton pump inhibitors and the risk of bacterial infections in cirrhosis (Puljiz Z, HR)

**16:00-17:30** **SESSION IV: Infections in the transplantation setting** | **Chairs:** Hrstic I, Skladany L, Turcic P

1. Early infections after liver transplantation (Majerovic M, HR)
2. Drug-drug interaction potential of antiviral agents for hepatitis C in liver transplant recipients (Filipec Kanižaj T, Mijić M, HR)
3. ACLF due to bacterial infection –indications and timing for liver transplantation (Virovic Jukic L, HR)
4. Prophylaxis against CMV infection in the transplanted patients (Sperl J, CZ)

**17:30-18:00** **CONCLUDING REMARKS**

**20:00** **DINNER**

# Effectiveness of DAA therapy: Real life data from Central Europe

ROBERT FLISIAK

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Interferon free regimens based on direct acting antivirals (DAA) became available in cetral european countries in 2015. The first data from the AMBER study carried out in Polish real world experience (RWE) study with Ombitasvir/Paritaprevir/ritonavir +Dasabuvir (3D) in HCV infected patients with advanced liver disease were published in 2016 and demonstrated 99% SVR rate irrespective of any factors [1]. This study was expanded into several central european countries for studying population of post liver transplant patients and showed 100% effectiveness. Data of 2 years follow up from the original AMBER study were published recently and showed improvement in liver function and structure in large majority of patients with SVR, but also existing risk of hepatocellular carcinoma development even after succesfull treatment of HCV infection. Another RWE study was HARVEST, which demonstrated SVR rate of 94% after sofosbuvir/ledipasvir. However the most important from this study was the first in the region experience with 8-weeks regimen. Effectiveness rate of 99% after 3D therapy in failures to previous triple, interferon based and containing first generation protease inhibitors regimens was published recently by Hungarian collegues [2]. The same regimen with 100% SVR rate was administered in Czech patients with the end stage renal disease. However the largest study in the region which already included 10166 patients is the EpiTer-2. Initial data from the first year on the structure of Polish patients, treatment effectiveness in cirrhotics, genotype 3 infected, and nonresponders to triple therapy were already published in 4 papers [3]. Current effectiveness calculated in more than 8000 patients with completed follow-up reached 97%, despite of suboptimal regimens available for genotype 3 patients untill mid 2018.

**References:**

1. Flisiak R et al. Aliment Pharmacol Ther 2016; 44: 946–956
2. Hunyady B et al. Clin Exp Hepatol 2018; 4, 2: 83–90
3. Flisiak R et al. J Viral Hepat. 2018; 25: 661–669

# On the road to eradicate hepatitis C: Croatian national strategy

ADRIANA VINCE

University Hospital of Infectious Diseases, Zagreb Medical School

The first Global hepatitis report published in 2017 indicated that 1.34 milion persons died from the consequences of viral hepatitis in 2015, mostly due to cirrhosis and hepatocellular carcinoma as the sequelas of chronic HBV and HCV infection. In May 2016, the World Health Assembly endorsed the first Global Health Sector Strategy on viral hepatitis which calls for elimination of viral hepatitis as a public health threat by 2030 through implementation of national strategies. Elimination is defined as a 90% reduction in new infections and a 65% reduction in mortality. Countries are urged to develop national strategies appropriate to their local epidemiological circumstancies and health system capacities.

Croatia has developed a national strategy for prevention and control of viral hepatitis accordng to WHO published guidance and based on national epidemiological and disease burden data collected in 2017. National strategy defines aims, long-term goals (2030), short-term goals (2021), core indicators, activities, responsible groups, monitoring and evaluation systems and financial framework.

The initial assesment of the existing data has shown that hepatitis B and C are still pose a significant public health burden with an estimated 25,000 persons chronically infected with HBV and about 40,000 anti-HCV positive persons. People who inject drugs (PWIDs) have the highest risk for HCV infection with prevalence of 30%.

The national strategy focuses on 5 long-term goals: 1. Raising the awareness of general population and key populations on risks and protection from viral hepatitis 2. Monitoring health sector response to hepatitis 3. Reducing new infections with viral hepatitis by 90% 4. Strengthening the hepatitis A surveillance 5. Reducing the mortality from chronic hepatitis by 65%. The main objective of the goal 1 is to increase awareness of primary care physicians in screening people at-risk and to reduce stigma. To achieve the goal 2 estimates of morbidity and mortality due to chronic hepatitis B and C have to be defined and every case of cirrhosis and hepatocellular carcinoma has to be attributed to a cause. The main objective for the goal 3 is to decrease HCV incidence among PWID by strengthening the harm reduction programmes. In order to reduce the mortality by 65% at least 450 patients with hepatitis C have to be treated annualy. By implementation of national strategy Croatia as a small country has a reasonable chance to eliminate the viral hepatitis by 2030.

# Hepatitis B: should we stop NUCs and when?

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Long term administration of potent nucleos(t)ide analogs is the corner stone of antiviral therapy for hepatitis B, as it reduces liver related complications by efficently supressing viral replication(1).Current antiviral therapy in chronic hepatitis B provide efficient control of HBV replication but not and functional cure. The actual need is to find more active direct anti-viral agents.

Patients in serological profile experience slow HBsAg decline durring NUC therapy and have a need for life long NUCs administration. So, the future antiviral therapy has to provide shorten NUCs therapy by accelerating HBsAg clearance. NUCs are at the same time, safe, preventing the liver decompensation and development of liver cancer.

EASL guedlines are recommending discontinuation of Nas in further cases:

NAs should be dicontinued after confirmed HBsAg loss with or without antiHBs seroconversion.NAs can be discontinued in non cirrhotic HBeAg-positive HBV patients who achive stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is waranted.Discontinuation of NAs in selected non cirrhotic HBeAg-negative patients who have achieved long term ( ≥ 3 years) virological supression under NAs may be considered if close post NAs monitoring can be garanteed (2).

Although there is agreement that the best and safest stopping rule in HbeAg –neg patients is hepatitis B surface antigen (HBsAg)loss, it remains highly debated whether NAs discontinuation before HBsAg loss can be recommended.

**Conclusions:**

Therapy can be discontinuited in selected subgroups of HBeAg-ve non cirrhotic patients with undetectable HBV DNA for et least three years durring therapy. Withdraval of Nas frequently results in ALT flares and HBV rebound, thats why, close, early and longterm monitoring is necesarry fore safe NAs discontinuation.Virological and biochemical flares are ofter transient and may represent a trigger for inducing long term immune control.Younger age, low baseline HBsAg at the stop of NAs seems to be associated with viral clearence (3).

**References:**
1. Lampertico P, Berg T. Less can be more – A Finite Treatment Approach For HBeAg-Negative Chronic Hepatitis B. Hepatology 2018;10.1002/hep.29821
2. Clinical Practice Guidelines on the management of hepatitis B virus infection EASL Guidelines,2017.
3. Berg T,Simon KG. Long term response after stopping tenofovir disoproxil fummarate in non cirrhotic HBeAg-neg patients. J.Hepatol.2017,67,918-924.

# HBV reactivation in the immunocompromised patient

TAMARA MILOVANOVIĆ

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Reactivation of hepatitis B viral infection is a potentially serious complication of immunosuppression, which can be identified and efficiently prevented. Taking into account that more than two billion people around the world have been infected by hepatitis B virus (HBV), there is also an increasing number of reactivations of HBV infections recognized and it becomes a challenging issue with increasing use of immunosuppressive agents and cytotoxic chemotherapy for varied medical conditions, including cancers. The spectrum of HBV reactivation in the setting of immunosuppression may vary from asymptomatic reactivation to liver failure and death. HBV reactivation may hamper the course of planned therapies, and diminish the effects of therapies. Also, it adversely affects the prognosis of the original disease and the survival of the patients. Assessment of the risk of reactivation relies on the HBV status and drugs used. So, the aim of this presentation will be presentation of recommendations and modalities for prevention and management of HBV reactivation in immunocompromised patients.

**References:**
1. Guo L, Wang D, Ouyang X, Tang N, Chen X, Zhang Y, Zhu H, Li X. Recent Advances in HBV Reactivation Research. Biomed Res Int. 2018 Dec 26;2018:2931402.
2. Su YC, Lin PC, Yu HC, Wu CC. Antiviral prophylaxis during chemotherapy or immunosuppressive drug therapy to prevent HBV reactivation in patients with resolved HBV infection: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2018 Sep;74(9):1111-1119.
3. Viganò M, Serra G, Casella G, Grossi G, Lampertico P. Reactivation of hepatitis B virus during targeted therapies for cancer and immune-mediated disorders. Expert Opin Biol Ther. 2016 Jul;16(7):917-26.

# Type and prognostic impact of infectious agents in patients with cirrhosis

IVICA GRGUREVIC

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Bacterial infections have become increasingly prevalent in patients hospitalized for decompensated liver cirrhosis (DC). This is due to multiple factors including liver dysfunction, portosystemic shunting, gut dysbiosis, increased bacterial translocation, cirrhosis-associated immune dysfunction (AID) and genetic factors. In patients with cirrhosis, infections increase mortality almost 4-fold. 30% of patients hospitalized for DC die within 1 month after infection and another 30% die by 1 year. Whereas temporal trends reveal decrease in mortality of cirrhotic patients with bacterial infections, this holds true only for 1-month mortality, as 1-year mortality remained unchanged, around 60%. Therefore bacterial infectious complications occurring in DC has been proposed

as the distinct and the most advanced stage in natural history of cirrhosis. In 2014 EASL issued position paper on the management of bacterial infection in patients with cirrhosis. It recommended early distinction between patients with community acquired (CA) and nosocomial (NC) infections, the former should be treated by third generation of cephalosporins, amoxicillin-clavulonic acid and quinolones according to the site of infection, whereas more extended spectrum coverage (piperacillin/tazobactam, carbapenems/ceftazidime±glycopeptide) should be applied in the latter group due to higher rate of multidrug resistant (MDR) bacteria expected. However, even with this approach failure of empirical antibiotic treatment occur in majority of patients (60% in MDR infections, 90% in XDR infections and 37% in pts with an infection due to non multi-resistant pathogen). MDR bacteria encounter for 34-38% of infections in patients hospitalized for cirrhosis. Prevalence and type of resistant organisms differ markedly among centers, but Enterobacteriaceae are most prevalent in general. European multicentric study identified independent predictors of MDR infection: nosocomial infection (OR: 2.74), ICU admission (OR: 2.09), and recent hospitalization (OR: 1.93). Antibiotic resistance negatively impact prognosis as it is associated to lower resolution rate of infections, higher incidence of septic shock and ACLF and higher mortality and to failure of antibiotic strategies based on third-generation cephalosporins or quinolones. For these reasons strategies aimed at preventing the spread of antibiotic resistance in cirrhosis are urgently needed.

**References:**

1. Arvaniti V et al. Gastroenterology 2010;139:1246–1256
2. Piano S at al. Gastroenterology 2018
3. Fernandez J et al. Journal of Hepatology 2019; doi.org/10.1016/j.jhep.2018.10.027

# The role of gut microbiota in the progression of NAFLD to HCC

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Hepatocellular carcinoma (HCC) is the third leading cause of worldwide cancer mortality. HCC almost exclusively develops in patients with chronic liver disease (CLD) of different origin, driven by a vicious cycle of liver injury, inflammation, angiogenesis and regeneration. Nonalcoholic fatty liver disease (NAFLD) is the commonest CLD disease in western countries, strictly associated with obesity, type 2 diabetes and metabolic syndrome. HCC can develop on every stage of NAFLD, both in the case of simple steatosis and advanced fibrosis. The gut-liver axis has been obtaining growing attention as a pivotal pathophysiological mechanism responsible for progression of CLD and development of HCC. Essential mechanisms by which the gut microbiota facilitates and promotes hepatic fibrosis and hepatocarcinogenesis, focus on the leaky gut, bacterial dysbiosis, microbe-associated molecular patterns and bacterial metabolites as key pathways that drive cancer-promoting liver inflammation, fibrosis and genotoxicity. Accumulating evidence from preclinical studies, suggest the intestinal-microbiota–liver axis to be a promising, potential target for the simultaneous prevention of CLD progression and HCC development in patients with advanced liver disease.

Intestinal dysbiosis and increased bacterial translocation through disrupted gut barrier contribute to endotoxemia. Breakdown in intestinal barrier function and bacterial overgrowth seem to be main events in HCC development. Disturbed gut barrier and bacterial overgrowth result in high absorption of bacterial products which can enter to the liver with portal blood and accelerate inflammatory process through specific receptors localized on hepatic stellate cells, macrophages and sinusoidal endothelial cells. On the other hand, commensal bacteria may be important regulators of antitumor immunity. Some of bacterial species up-regulate hepatic CXCR6+ natural killer T (NKT) cells upon antigen stimulation, leading to NKT cells mediated liver-selective tumor inhibition. NKT cell accumulation was regulated by CXCL16 expressed by liver sinusoidal endothelial cells. Gut microbiome used bile acids as a messenger to regulate chemokine CXCL16 level.

A large body of literature has demonstrated that targeting the gut-microbiota–liver axis can inhibit the development of HCC in mice and rats. Unfortunately, majority of these promising findings from these preclinical studies in mice and rats have not yet been translated to clinical settings. Targeting the gut–liver axis by nonabsorbable antibiotics such as rifaximin might not only prevent the development of HCC in patients with CLD, but additionally reduce other complications and improve overall survival.

**References:**

1. Yu LX, Schwabe RF. The gut microbiome and liver cancer: mechanisms and clinical translation. Nat Rev Gastroenterol Hepatol 2017; 14(9):527-539. doi: 10.1038/nrgastro.2017.72.
2. Schramm C. Bile acids, the microbiome, immunity and liver tumors. N Engl J Med 2018; 379(9):888-890. doi: 10.1056/NEJMcibr1807106.
3. Ma C, Han M, Heinrich B et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science 2018; 360(6391). pii: eaan5931. doi: 10.1126/science.aan5931

# Predictive value of gut dysbiosis on ACLF mortalitiy

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Acute-on-chronic liver failure (ACLF) is a specific, but complex and multifactorial form of acute decompensation of cirrhosis and is characterized by an extraordinary dynamic natural course, rapidly evolving organ failure, and high short-term mortality. Nowadays, it is accepted that patients with cirrhosis have altered salivary and enteric microbiome, characterized by the presence of dysbiosis. This altered microbiome along with small bowel bacterial overgrowth, through translocation across the gut, is associated with the development of decompensating complications like ACLF and others. In general, stool and saliva dysbiosis with reduction of autochthonous bacteria in patients with cirrhosis incites changes in bacterial defenses and higher risk for bacterial infections, such as spontaneous bacterial peritonitis, and sepsis. Specifically, microbiome dysbiosis has been introduced either as a reduced ratio of autochthonous to non-autochthonous taxa (CDR) or as inversion of the Firmicutes/Bacteroidetes ratio.Gut microbiome has even been associated with oncogenic pathways and under circumstances might promote the development of hepatocarcinogenesis. Lately, the existence of the oral-gut-liver axis has been related with the development of decompensating events and ACLF. This link between the liver and the oral cavity could be via the gut through impaired intestinal permeability that allows direct translocation of bacteria from the oral cavity to the systemic circulation. ACLF patients had lower abundance of Bacteroidaceae, Ruminococcaceae, and Lanchnospiraceae, but higher abundance of Pasteurellaceae, Streptococcaceae, and Enterecoccaceae. Abundance of Lachnospiraceae was decreased in ACLF patients with HE. Gut dysbiosis in ACLF has predictive value for mortality and could represent diagnostic biomarker. Overall, the contribution of the microbiome to pathogenesis becomes more pronounced with progressive disease and therefore may represent an important therapeutic target in the management of cirrhosis and also ACLF.

**References:**

1. Bajaj JS, Heuman DM, Hylemon P et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 2014;60:940-947.
2. Chen Y, Guo J, Qian G et al. Gut dysbiosis in acute-on-chronic liver failure and its predictive value for mortality. J Gastroenterol Hepatol 2015;30:1429-1437.
3. Oikonomou T, Papatheodoridis GV, Samarkos M et al. Clinical impact of microbiome in patients with decompensated cirrhosis. World J Gastroenterol 2018; 24: 3813-3820.

# Liver in sepsis

NERMIN SALKIC

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Despite the progress made in the clinical management of sepsis, sepsis morbidity and mortality rates remain high. Only recently has the role of the liver in sepsis begun to be revealed. During sepsis, the liver plays a key role. It is implicated in the host response, participating in the clearance of the infectious agents/products.

Liver dysfunction induced by sepsis is recognized as one of the components that contribute to the severity of the disease. Nevertheless, the incidence of liver dysfunction remains imprecise, probably because current diagnostic tools are lacking, notably those that can detect the early liver insult. In clinical practice, there is no standardized diagnostic panel that would allow for an early, clear diagnosis of acute liver dysfunction, and there is no therapeutic panel enabling the full restoration of damaged liver function.

According to the Surviving Sepsis Campaign (SSC) Guidelines, the diagnosis of liver dysfunction during sepsis is based on the increase in bilirubin concentration >34.2 mcrmol/l and the occurrence of coagulation disorders with INR > 1.5. The lack of specificity and ability to distinguish acute liver failure from previous liver dysfunction disqualifies bilirubin as a single parameter reflecting the complex liver function. Clinical manifestations of sepsis-associated liver dysfunction include hypoxic hepatitis, sepsis-induced cholestasis and dysfunction of protein synthesis manifesting with, e.g., coagulopathies. To determine a liver dysfunction in a critically ill patient, the concept of shock liver may be used. It is a complex syndrome of hemodynamic, cellular, molecular and immunologic changes leading to severe liver hypoxia.

In this review, the epidemiology, diagnostic tools, and impact on outcome as well as the pathophysiological aspects, including the cellular events and clinical picture leading to liver dysfunction. Finally, therapeutic considerations with regard to the weakness of the pertinent specific approach are examined.

# US in liver cirrhosis: diagnosis and follow-up

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Cirrhosis is the pathologic and-stage of chronic liver disease and most commonly results from chronic hepatitis C and B, alcohol consumption, nonalcoholic fatty liver disease etc. Cirrhosis is characterized by fibrosis and nodule formation of the liver, secondary to a chronic injury. It`s main complications are related to the development of liver insufficiency and portal hypertension, include ascites, varicose hemorrhage, jaundice, hepatorenal and hepatopulmonary syndromes and the development of hepatocellular carcinoma.

Most of this conditions can be assessed by ultrasonography as a cheap and available image modality. US assessment with standard B mod allows visualization of the liver parenchyma, changes of structure, size and shape, surface and presence of nodules and fibrosis. Vascular US assessment as a routine part of liver assessment and is important for confirming presence of portal hypertension, porto-systemic collateral vessels and signs of thrombosis of portal

vein or hepatic veins. Good understanding of the liver anatomy and vessels (hepatic artery, portal vein, hepatic veins, lienal, vein) is needed for defining the extent of liver damage as well as, opportunity to follow therapeutic effectiveness. Furthermore, vascular US is needed for preoperative assessment in candidates for liver transplantation as therapeutic solution in liver cirrhosis and follow up of transplanted hepatic vessel flow. Ultrasonography combined with elastography (fibroscan) can play an important role in quantifying of steatofibrosis and led to early prediction of liver cirrhosis.

**References:**

1. EFSUMB – European Course Book, Editor: Christoph F. Dietrich. Ultrasound of the liver. Christoph F. Dietrich, Carla Serra, , Maciej Jedrzejczyk
2. Boris Brkljacic, Vaskularni ultrazvuk, 2010, 380-04/38-10-4

# Bacterial infections change natural history of cirrhosis irrespective of liver disease severity

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Patients with cirrhosis are at increased risk of bacterial infections, which represent one of the most common causes of decompensation, hospitalization and death[1]. In addition to the increased bacterial translocation from the gut, the susceptibility to bacterial infections is related to impairment of the immune defensive response, which becomes more severe as cirrhosis progresses from a compensated stage to a decompensated one. Despite the advances achieved in the last decades in their prevention, diagnosis and management, the clinical outcome after an infectious episode is still very poor. Indeed, there is now evidence that both the short and long-term survival of patients with cirrhosis is significantly impaired after a single episode of bacterial infection, even if this is resolved and irrespective of the liver disease severity. In a meta-analysis of 178 studies, we showed that infections increase mortality in cirrhosis 4-fold, with 30% of patients dying within one month after infection and 30% dying within one year [2]. In a subsequent study of 501 consecutive patients over a 2-year period with a median time of over 1 year, we showed that patients with cirrhosis who become infected have a greater risk of death even if they survive the acute episode of infection, independently of the severity of their underlying liver disease [3]. Importantly patients with MELD scores <15 and infection, have a mortality rate very similar to those with MELD score ≥15 and no infection. Our findings suggest that the occurrence of infection, even with recovery, should be regarded as a prognostic stage of cirrhosis beyond the decompensated stages and the term critically ill cirrhotic could be used for such patients.

**References:**

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014; 383(9930): 1749-61.
2. 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(4): 1246-56, 56 e1-5.
3. Dionigi E, Garcovich M, Borzio M, et al. Bacterial infections change natural history of cirrhosis irrespective of liver disease severity The American journal of gastroenterology 2017; 112: 588-96.

# Spontaneous bacterial peritonitis: a diagnostic algorithm for clinicians and future perspectives

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Cirrhosis patients with acute decompensation or Acute-on-Chronic-Liver Failure are highly prone to bacterial infection secondary to immune dysfunction and bacterial infection is a leading cause of death in these patients.

Spontaneous bacterial peritonitis (SBP) is the most common serious infection and carries significant morbidity and mortality. There are no immune restorative therapies and the only available strategy is prophylactic antibiotic treatment. While antibiotic prophylaxis to prevent further infection has been established for those with a prior episode of SBP, there remains considerable uncertainty over primary prophylaxis for SBP. This represents an important gap in our knowledge as 90% of SBP cases present with no previous episode and so all current guidelines focus on the minority of patients. Prophylaxis with norfloxacin or ciprofloxacin for ascitic fluid protein concentration <1.5 g/dL is recommended until the ascites has resolved, but evidence for this is dated and the duration of prophylaxis has not been established.

The benefits of antibiotic prophylaxis must be balanced against the risk of selecting drug resistant organisms and *Clostridium difficile* associated diarrhoea (CDAD). Yet this risk is unknown, as published data have been from small single or dual centre studies with anti-microbial resistance (AMR) data only examined during treatment period (6 months to 1 year), and most were performed in an era pre-dating the rise in AMR.

Co-trimoxazole is a narrow spectrum antibiotic that is well tolerated, and effective with a vast literature of prophylaxis in HIV. We shall shortly commence our 550 patient randmisosed controlled trial at 30 sites in the UK, ASEPTIC (Primary **A**ntibiotic prophylaxis using co-trimoxazole to prevent **S**pontan**E**ous bacterial **P**eritoni**TI**s in **C**irrhosis). The primary objective is to determine whether treatment reduces the incidence of SBP compared to placebo in cirrhosis and ascites over a 2-year trial period.

**References**

1. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis . J Hepatol 2018; 69 (2): 406-460.
2. Fernández J et al. Antibiotic prophylaxis in cirrhosis: Good and bad. Hepatology 2016; 63:2019-2031.
3. West R et al. Spontaneous bacterial peritonitis: recent guidelines & beyond. Gut 2012; 61:297-310.

# Early predictors of bacterial infection in cirrhosis: CRP and other biomarkers

MARIA PAPP

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In cirrhosis, accurate prediction, early recognition and prognostication of bacterial infections are essential to surmount complications, delay progression and diminish mortality, however these are challenging in the clinical practice.

Pathological bacterial translocation (BT) is incrementally increasing with diseases severity and has an important role in the development of systemic infections. Inflammatory state sustained by BT is sufficient alone to elevate inflammatory markers to a significant level, even in the absence of overt infection. Accordingly, of the acute phase proteins (APPs) namely low-grade increases in the level of C-reactive protein (CRP) and lipopolysaccharide-binding protein were established as risk factors for developing of systemic bacterial infections. Recently, IgA type serological antibodies directed against gut innate immune proteins or intestinal microorganisms were reported as reliable markers of infectious risk in this patient population. Presence of target specific IgA antibodies could be a clue of an excessive mucosal immune response due to extended microbial challenge or dysregulation thereof.

In the clinical practice, conventional biomarkers such as CRP and procalcitonin(PCT), are used most frequently in the diagnosis of bacterial infection. However, several diseases specific pitfalls attenuate the diagnostic accuracy of these APPs in cirrhosis. Firstly, if the main source of the APP is the liver, synthesis of protein can be affected by liver failure and its severity. Secondly, depending on molecular weight renal failure and also renal replacement therapy can be confounding factors. Acute kidney injury is frequent in cirrhosis, especially in bacterial infections. Novel markers, such as presepsin or mid-regional pro-adrenomedullin have also some drawbacks. Excessive elevation in the level of certain APPs, particularly PCT or anti-inflammatory response related molecules (sCD163, suPAR, monocyte HLA-DR loss or sTNF-R) are associated with higher risk of short-term mortality during bacterial infections and supposedly represent the deleterious effect of the exaggerated inflammatory processes.

**Conclusions:** Novel biomarkers being devoid of the limitations of classic APPs are highly needed to optimize the rule in and rule out processes necessary for the diagnosis and also for the severity assessment of bacterial infections. Furthermore they may help the identification of patients at high risk for developing systemic infections and those that mostly have advantage from prophylactic measures.

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# Proton pump inhibitors and the risk of bacterial infections in cirrhosis

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Proton pump inhibitors (PPIs) are very often prescribed drugs in liver cirrhosis (LC). A benefit of therapy is well known in peptic ulcer disease and as a prevention of rebleeding after endoscopic ligation of varices. Overprescription and lack of indications are evident in many other cases. Recently, PPIs have been studied due to their possible harmful adverse effects. Results of four meta-analyses showed statistically significant association between PPIs use in cirrhosis and spontaneous bacterial peritonitis (SBP). Only one conducted prospective and multicenter study didn't confirm it. Retrospective study from Taiwan revealed increased SBP after more than 180 days of PPIs use. The mechanism of action on SBP hasn't been clarified. Results of two recent studies have shown significant impact of PPIs on the gut microbioma structure. Change in microbioma can result in chronic infection due to impaired gut surface barrier. Prolonged activity of PPIs due to impaired liver function can decrease acidity and induce bacterial translocation from proxymal to distal gastrointestinal tract. These drugs are associated with small intestine bacterial overgrowth (SIBO) but that mechanism is not clear. More well designed studies are neccessary to elucidate the role of PPIs use in LC.

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# Risk factors for early viral infections after liver transplantation

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Immunocompromised patients are susceptible to infections that healthy immune systems usually conquer. The risks and types of infections encountered differ based upon the timing after orthotopic liver transplantation (OLT).

In the context of early viral infections, i.e. in the first 180 days post-OLT, the infection can be either due to the direct transfer of donor's unrecognised active infection at the time of organ procurement, reactivation of latent infections, either donor or patient-derived, or can be newly acquired.

In clinical practice, we most commonly encounter reactivation of latent viral infections.

While unusual in the first post-OLT month, except in the case of HSV, reactivation of opportunistic viruses, in the absence of prophylaxis, is common during the second and third month when immunosuppression is at its maximum. CMV, EBV, VZV, HHV-6 and adenovirus infection/disease can cause significant morbidity, including graft loss, elevated risk of other infections or even malignant diseases, e.g. post-transplant lymphoproliferative disorder.

The risk of reactivation can be stratified by the serologic status of the donor and the recipient. The highest risk occurs in the seronegative recipient who received an organ from a seropositive donor. The risk is moderate in seropositive recipients, regardless of the donor's status. Seronegative recipients who receive an organ from a seronegative donor are considered at low risk, although it should be borne in mind that these patients are at risk of primary infection that may carry grave consequences.

Female recipients are at higher risk of viral infections in general while other recognised risk factors include enhanced immunosuppressive regimens, T-helper/suppressor (H/S) ratio of ≤2.8 and CVVH after OLT.

Also, the flare of chronic HCV or untreated HBV infection can be expected in this period.

After risk assessment, appropriate measures should be undertaken, including vaccination, prophylactic or pre-emptive therapy.

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# The drug-drug interaction potential of antiviral agents for the treatment of chronic hepatitis C infection in liver transplant recipient

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The advent of safe and highly effective DAAs has had huge implications for the hepatitis C virus (HCV) transplant field. After transplantation some DAAs have a limited use because of their drug to drug interactions (DDI) with various immunosuppressants (IS) as well as the many other drugs liver transplant (LT) recipients are often prescribed. In addition, some DAAs should be avoided in case of severe renal failure, which is not an unusual complication after LT.

According to EASL Recommendations on Treatment of Hepatitis C in 2018, LT recipients should be treated with the fixed-dose DAA combination according to their stage of liver and kidney disease:

1. without or with compensated cirrhosis, for 12 weeks:

a. sofosbuvir+ledipasvir (SOF/LDV) in genotype 1, 4, 5 or 6

b. sofosbuvir+velpatasvir (SOF/VEL) in all genotypes

1. with decompensated cirrhosis, for 12 weeks:

a. SOF/LDV in genotype 1, 4, 5 or 6

b. SOF/VEL in all genotypes

both with daily weight-based ribavirin

2. with an eGFR <30ml/min/1.73m2 and without or compensated liver disease

a. glecaprevir and pibrentasvir (G/P) for 12 weeks.

SOF/LDV and SOF/VEL regimens are not related with significant DDI with IS. SOF exposure is increased in patients with severe renal impairment including those on dialysis. In this patients, combination of G/P is recommended. These drugs are strong substrates of CYP3A4 and inhibitors of transport by P-gp, BCRP and OATP1B1/3 with strong influence on DDI potential. Calcineurin inhibitors are metabolized by CYP3A4 and have very narrow therapeutic interval. It is recommended that, during treatment with protease inhibitors-based regimens, IS drug levels need to be closely monitored and adjusted as needed, during and after the end of DAA treatment.

LT candidates and recipients should be treated in centers with experience in IS management. Before starting of DAA treatment all possible DDI should be checked and concomitant therapy adjusted to DAA therapeutic regimen requirements. Due to risk od side effects, DDI, and decline in IS levels in association with viral clearance, liver and renal function including IS level should be closely monitored and IS dosage adjusted during treatment.

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3. www.hep-druginteractions.org

# Acute-on-chronic liver failure due to bacterial infection – indications and timing for liver transplantation

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Acute-on-chronic liver failure (ACLF) is characterized by an acute deterioration of chronic liver disease in combination with organ failures, which is associated with high short-term mortality. Although triggers for decompensation vary among studies and across different regions of the world, infections are common precipitating events for ACLF. In the CANONIC study, bacterial infections were the most common triggers responsible for 33% of ACLF episodes. Subsequent studies showed that patients with ACLF are also at increased risk of developing new bacterial infections; these follow-up infections are often more severe as indicated by the higher prevalence of sepsis or septic shock. Spontaneous bacterial peritonitis, urinary tract infections, pneumonia and skin or soft tissue infections are the most common types of infection. Nosocomial or healthcare associated infections and infections caused by multi-drug-resistant organisms are more common in patients with ACLF compared to patients with acute decompensation without organ failures. The prompt use of appropriate antibiotics represents a key factor in managing ACLF patients with bacterial infections. Clinical course of ACLF caused or complicated by bacterial infections is worse, transplant-free survival shorter and mortality higher than in patients with acute decompensation or ACLF without infections. Although active, uncontrolled infections require a temporary suspension from the waiting list, liver transplantation represents a life-saving strategy for ACLF patients. There is increasing evidence that patients with ACLF, including those with multi-organ failure (grade 3), have a good outcome after liver transplantation, comparable to patients with no ACLF or lower stages of ACLF, although rates of complications post-transplantation, especially infections, were higher. Critically ill patients awaiting liver transplantation should be managed in expert centers to ensure optimal treatment, regular re-evaluation and decision-making using clinical judgment and prognostic calculators to select patients and the right moment for transplantation surgery.

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# Prophylaxis against CMV infection in the transplanted patients?

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Human cytomegalovirus (CMV) represents frequent opportunistic infection among solid organ transplant (SOT) recipients increasing their morbidity and mortality. Two major types of CMV infection are known to occur in SOT recipients. Primary infection is observed in CMV seronegative recipients (R-) who receive an allograft from a CMV seropositive donor (D+). Reactivation of CMV occurs in CMV seropositive recipients on immunosuppressive treatment. CMV infection occurrence peaks 2–3 months post-transplant, but the onset can be delayed when CMV prophylaxis is administered. Late-onset CMV infection can develop after prophylaxis cessation and is more common in high-risk (D+/R–) recipients who are given prophylaxis compared with those to whom preemptive treatment is administered. Two approaches have been designed to minimize the risk of CMV infection. First, a preemptive treatment strategy, when antivirals are administered only to patients with newly positive CMV viraemia in order to prevent progression to CMV disease. Regular monitoring of CMV replication every 1–2 weeks is necessary. The second option is universal administration of CMV prophylaxis for 3–6 months post-transplant, postponing the onset of CMV infection (late-onset) and thus is effective in reducing the CMV incidence in the early post-transplant period, especially in the high-risk group (D+/R). Several risk factors increasing susceptibility to CMV have been described and involve pre-transplant CMV serostatus, type and dose of immunosuppression, acute cellular rejection in the early post-transplant period, and coinfection with other immunomodulating viruses. However, some recipients still develop CMV disease in spite of the prophylaxis, or present with CMV disease when the prophylaxis is discontinued. In SOT recipients the interaction between virus and innate immune system seems to play a crucial role since CMV-specific adaptive immune control is inhibited by immunosuppressants. Impact of both host and donor genetics on the risk of CMV infection or disease is being investigated.

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[1] Mark-Christensen et al. 2014; Endoscopy 47(3):251-61
[2] Cuesta et al. 2014; Scand J Gastroenterol. 49(3):355-61


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# EPCLUSA

IZLIJEČITE SVOJE KOMPENZIRANE BOLESNIKE S HCV INFEKCIJOM U SAMO 12 TJEDANA S PANGENOTIPSKIM JEDNOTABLETNIM REŽIMOM LIJEČENJA[1,a]

**IZGRAĐEN NA SOVALDIJU: DOKAZANOM TEMELJU ZA LIJEČENJE HCV INFEKCIJE[1–12]**

## PROŠIRITE MOGUĆNOSTI

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## IZLJEČENJE

Do 100% izlječenja HCV infekcije[1,b]

– 95-100% stopa izlječenja u fazi 3 pivotalnih studija u bolesnika s HCV GT1-6[1,c]

## JEDNOSTAVNO

Jednotabletni režim liječenja bez ribavirina i bez inhibitora proteaze za gotovo sve kompenzirane HCV bolesnike[1,a]

[a] EPCLUSA nudi jednotabletni režim bez primjene ribavirina i inhibitora proteaze za većinu HCV bolesnika, osim onih s dekompenziranom cirozom. Primjena ribavirina preporučena je za bolesnike s dekompenziranom cirozom jetre, a može biti razmotrena za liječenje HCV GT3 bolesnika s kompenziranom cirozom jetre.[1]

[b] EASL definira izlječenje kao SVR12.[4]

[c] U pivotalnim ASTRAL 1, 2 i 3 studijama u kompenziranih HCV monoinficiranih bolesnika ukupna stopa izlječenja postignuta je u 95-100% bolesnika liječenih kroz 12 tjedana lijekom EPCLUSA.[1]

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**SKRAĆENI SAŽETAK OPISA SVOJSTAVA LIJEKA**

**Naziv lijeka: Epclusa 400 mg/100 mg filmom obložene tablete. Način izdavanja:** Lijek se izdaje na recept. **Djelatna tvar:** Jedna filmom obložena tableta sadrži 400 mg sofosbuvira i 100 mg velpatasvira. **Terapijske indikacije:** Epclusa je indicirana za liječenje kronične infekcije virusom hepatitisa C (HCV) u odraslih. **ZA DODATNE INFORMACIJE POGLEDATI ODOBRENI SAŽETAK OPISA SVOJSTAVA LIJEKA.**

**Kontraindikacije:** Preosjetljivost na djelatne tvari ili neku od pomoćnih tvari navedenih u dijelu 6.1. Primjena s jakim induktorima P gp a i jakim induktorima CYP a Lijekovi koji su jaki induktori P glikoproteina (P gp) ili jaki induktori citokroma P450 (CYP) (rifampicin, rifabutin, gospina trava [Hypericum perforatum], karbamazepin, fenobarbital i fenitoin). Istodobna primjena značajno će smanjiti koncentraciju sofosbuvira ili velpatasvira u plazmi i tako može dovesti do gubitka djelotvornosti lijeka Epclusa. **Posebna upozorenja i mjere opreza pri uporabi:** Epclusa se ne smije primjenjivati istodobno s drugim lijekovima koji sadrže sofosbuvir. Teška bradikardija i srčani blok Slučajevi teške bradikardije i srčanog bloka uočeni su kada se sofosbuvir primijenjen u kombinaciji s drugim antivirotičima koji djeluju direktno primjenjivao istodobno s amiodaronom sa ili bez drugih lijekova koji snižavaju srčanu frekvenciju. Mehanizam nije ustanovljen. Istodobna primjena amiodarona bila je ograničena tijekom kliničkog razvoja sofobuvira uz antivirotike koji djeluju direktno. Slučajevi su potencijalno opasni po život, stoga se amiodaron smije primjenjivati samo u pacijenata koji primaju lijek Epclusa u slučajevima kada se drugi alternativni antiaritmici ne podnose ili su kontraindicirani. Bolesnici u kojih je prethodna terapija režimom koji sadrži inhibtor NS5A bila neuspješna Nema kliničkih podataka koji bi poduprli djelotvornost sofosbuvira/velpatasvira za liječenje bolesnika u kojih je liječenje režimom koji sadrži drugi inhibitor NS5A bilo neuspješno. Oštećenje bubrega Nije potrebna prilagodba doze lijeka Epclusa u pacijenata s blagim ili umjerenim oštećenjem bubrega. Sigurnost lijeka Epclusa nije procijenjena u bolesnika s teškim oštećenjem bubrega (eGFR < 30 ml/min/1,73 m2) ili završnim stadijem bolesti bubrega koji zahtijeva hemodijalizu. Primjena s umjerenim induktorima P gp a ili umjerenim induktorima CYP a

Lijekovi koji su umjereni induktori P gp a ili umjereni induktori CYP a (npr. okskarbazepin, modafinil ili efavirenz) mogu smanjiti koncentracije sofosbuvira ili velpatasvira u plazmi što dovodi do smanjenog terapijskog učinka lijeka Epclusa.Upotreba s određenim antiretrovirusnim režimima za HIV Pokazalo se da Epclusa povećava izloženost tenofoviru, naročito kada se koristi zajedno s režimom za HIV koji sadrži tenofovirdizoproksilfumarat i farmakokinetički pojačivač (ritonavir ili kobicistat). Primjena u bolesnika s dijabetesom Nakon uvođenja liječenja HCV infekcije direktno djelujućim antivirotikom, bolesnici s dijabetesom mogu imati bolju kontrolu glukoze u krvi, što može dovesti do simptomatske hipoglikemije. Koinfekcija HCV-om/HBV-om (virusom hepatitisa B) Tijekom ili nakon liječenja antiviroticima koji djeluju izravno, zabilježeni su slučajevi reaktivacije virusa hepatitisa B (HBV), neki od njih sa smrtnim ishodom. Probir na HBV mora se provesti u svih bolesnika prije početka liječenja. Bolesnici istodobno zaraženi HBV-om/HCV-om izloženi su riziku od reaktivacije HBV-a te ih stoga treba pratiti i liječiti sukladno važećim kliničkim smjernicama. Ciroza jetre CPT stadija C Sigurnost i djelotvornost lijeka Epclusa nije procijenjena u bolensika s cirozom jetre CPT stadija C (vidjeti dijelove 4.8 i 5.1).

Bolesnici s transplantiranom jetrom Sigurnost i djelotvornost lijeka Epclusa u liječenju infekcije HCV-om u bolesnika u kojih je transplantirana jetra nisu procijenjene. **ZA DODATNE INFORMACIJE POGLEDATI ODOBRENI SAŽETAK OPISA SVOJSTAVA LIJEKA. Nuspojave:** Sažetak sigurnosnog profila

Procjena sigurnosti primjene lijeka Epclusa temeljila se na objedinjenim podacima iz kliničkog ispitivanja faze 3 bolesnika s infekcijom HCV-a genotipa 1, 2, 3, 4, 5 ili 6 (sa ili bez kompenzirane ciroze) uključujući 1035 bolesnika koji su primali lijek Epclusa tijekom 12 tjedana.Bolesnici s dekompenziranom cirozom Sigurnosni profil lijeka Epclusa procijenjen je u otvorenom ispitivanju u kojem su bolesnici s cirozom CPT stadija B primali lijek Epclusa tijekom 12 tjedana (n = 90), lijek Epclusa + RBV tijekom 12 tjedana (n = 87) ili lijek Epclusa tijekom 24 tjedna (n = 90). Opaženi štetni događaji bili su konzistentni s očekivanim kliničkim posljedicama bolesti dekompenzirane jetre ili poznatim profilom toksičnosti ribavirina za bolesnike koji su primali lijek Epclusa u kombinaciji s ribavirinom. Opis odabranih nuspojava *Srčane aritmije* Slučajevi teške bradikardije i srčanog bloka uočeni su kada se sofosbuvir u kombinaciji s drugim antivirotikom koji djeluje direktno primjenjivao istodobno s amiodaronom i/ili lijekovima koji snižavaju srčanu frekvenciju (vidjeti dijelove 4.4 i 4.5).

**ZA DODATNE INFORMACIJE POGLEDATI ODOBRENI SAŽETAK OPISA SVOJSTAVA LIJEKA. Doziranje i način primjene:** Liječenje lijekom Epclusa treba započeti i nadzirati liječnik iskusan u liječenju bolesnika s infekcijom HCV a. Preporučena doza lijeka Epclusa je jedna tableta, peroralno, jedanput na dan s hranom ili bez nje (vidjeti dio 5.2). **ZA DODATNE INFORMACIJE POGLEDATI ODOBRENI SAŽETAK OPISA SVOJSTAVA LIJEKA. Prijavljivanje sumnji na nuspojavu:** Nakon dobivanja odobrenja lijeka važno je prijavljivanje sumnji na njegove nuspojave. Time se omogućuje kontinuirano praćenje omjera koristi i rizika lijeka. Od zdravstvenih radnika se traži da prijave svaku sumnju na nuspojavu lijeka putem nacionalnog sustava prijave nuspojava:

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**SAMO ZA ZDRAVSTVENE RADNIKE. ZA DODATNE INFORMACIJE POGLEDATI ODOBRENI SAŽETAK OPISA SVOJSTAVA LIJEKA. Datum revizije teksta:** Detaljnije informacije o ovom lijeku dostupne su na internetskoj stranici Europske agencije za lijekove http://www.ema.europa.eu.

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**Nositelj odobrenja za stavljanje lijeka u promet:** Gilead Sciences Ireland UC, Carrigtohill, County Cork, T45 DP77, Irska

**Predstavnik nositelja odobrenja u Hrvatskoj:** Medicopharmacia d.o.o., Ulica Pere Budmanija 5, 10 000 Zagreb

**REFERENCE**

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EASL = European Association for the Study of the Liver; GT = genotip; HCV = hepatitis C virus; RBV = ribavirin; SVR = održani virološki odgovor.

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## VENUE

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