

Management of bacterial infection in the liver transplant candidate

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Abstract

Bacterial infection (BI) is a common cause of impairment of liver function in patients with cirrhosis, especially in the liver transplant candidates. These patients share an immunocompromised state and increased susceptibility to develop community and hospital-acquired infections. The changing epidemiology of BI, with an increase of multidrug resistant strains, especially in healthcare-associated settings, represents a critical issue both in the waiting list and in the post-operative management. This review focused on the role played by BI in patients awaiting liver transplantation, evaluating the risk of drop-out from the waiting list, the possibility to undergo liver transplantation after recovery from infection or during a controlled infection.

Key words: Cirrhosis; Portal hypertension; Bacterial infection; Liver transplantation

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Core tip: Bacterial infection (BI) is a common cause of impairment of liver function in patients with cirrhosis, especially in the liver transplant candidates. BI may play a detrimental role in patients awaiting liver transplantation, increasing the risk of drop-out from the waiting list.

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INTRODUCTION

The liver is actively involved in inflammatory response against bacteria, and plays a central role in the regulation of immune defense, bacterial clearance, acute-phase protein, cytokine production and metabolic adaptation to inflammation^[1]. Conversely, sepsis-induced hypoxic hepatitis and cholestasis make hepatic dysfunction an independent predictor of mortality during bacterial infection (BI)^[2,3].

Cirrhosis is *per se* an immunocompromised state which predisposes to the development of BI, and sepsis-related death^[4]. It's characterized by an immunodeficient state due to an impaired response to pathogens at different levels of the immune system, involving innate and adaptive cell dysfunction^[5]; this condition coexists with a persistent stimulation of immune system, with enhanced serum levels of pro-inflammatory cytokines^[6,7]. The severity of this inflammatory state correlates with severity of liver dysfunction^[8,9]. Moreover, other superimposed conditions - such as impaired gut microbiota and intestinal barrier dysfunction - further increase the risk of BI^[10]. In a study by Rasaratnam *et al*^[11], when patients were treated with selective intestinal decontamination, their hepatic venous pressure gradient decreased by a mean of 2.43 mmHg, further strengthening the hypothesis that bacteria contribute to the hyperdynamic circulation and portal hypertension in cirrhosis.

Sepsis-related organ damage in cirrhosis is characterized by both an excessive inflammatory response and a decrease in the hepatic capacity of tolerance^[12]. This further increases circulatory dysfunction, with splanchnic vasodilation and organ hypo-perfusion^[13,14], leading to worsening of portal hypertension (*via* activation of neurohumoral pathways) and fluid retention^[15]. Development of BI is a common trigger of extra-hepatic organ failures, in particular acute kidney injury^[16], hepatic encephalopathy^[17], coagulopathy^[18], adrenal insufficiency^[19] and respiratory failure^[20].

CHANGING EPIDEMIOLOGY OF BACTERIAL INFECTION IN DECOMPENSATED CIRRHOSIS

In the past decades, there have been several improvements in the management of cirrhosis and its complications, such as hepatocellular carcinoma and portal hypertension. However, a significant proportion of patients with decompensated cirrhosis still need liver transplantation (LT), which represents the only effective therapeutic option.

In this setting, development of BI could significantly

impair the natural history of the liver transplant candidate^[21,22]. Preventive and therapeutic strategies for most of the complications of cirrhosis are well-defined; nevertheless, even if risk factors for the onset of BI in decompensated patients awaiting LT are well-known, they remain poor preventable.

The protean epidemiology of BI in cirrhosis depends on several factors, such as site of infection, setting of BI development, and local epidemiology.

Spontaneous bacterial peritonitis (SBP) and urinary tract infections are the most frequent BI in cirrhosis, followed by pneumonia, skin and soft tissue infections, bloodstream infections (BSI)^[12,23]. SBP is mainly due to bacterial translocation - especially gram-negative strains^[24], however epidemiology is rapidly changing. A multicenter study from Portugal^[25], evaluating patients with severe liver dysfunction (median Child-Pugh class C-10; MELD score 19) recently showed an increase in gram-positive bacteria (GPB, 42%) at diagnosis of SBP; notably, one out of three SBP episodes occurred during hospitalization. This has determined the adoption of new antibiotic strategies: Piano *et al*^[26] demonstrated that the combination of broad-spectrum antibiotics, meropenem plus daptomycin, was significantly more effective than conventional therapy (ceftazidime) in the treatment of nosocomial SBP (86.7% vs 25%; $P < 0.001$).

BSI represent another common cause of BI in cirrhosis^[12], mainly due to gram-positive strains^[27], because of the high number of invasive procedures and quinolone prophylaxis. However, there's an increasing prevalence of gram-negative bacteria (GNB) as the cause of BSI; Bartoletti *et al*^[28] showed in a multicenter observational study on 312 cirrhotic patients in Italy, an equal distribution between GNB and GPB (53% vs 47%) at diagnosis of BSI.

In the last decades, clinical practice in Hepatology has dramatically changed as a consequence of the implementation of the liver transplant programs. Cirrhotic patients are nowadays frequently admitted to the ICU and undergo many diagnostic and therapeutic invasive procedures. This is associated with a higher risk of secondary infections caused by nonclassical pathogens. Fernandez *et al*^[29] included 572 BI, 39% of which were nosocomial, reporting an increase in the rate of GPB infections associated with the increasing use of invasive procedures during hospitalization and in the ICU. More recently, Merli *et al*^[30], collected 173 episodes of BI requiring hospitalization or occurred during hospitalization in 424 patients with cirrhosis; BI episodes were further divided into three classes (community acquired, hospital acquired, health-care acquired). GNB were more frequent in community acquired and health-care acquired infections, while GPB in hospital-acquired ones. *Enterobacteriaceae* (44.3%) (particularly *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*) and *Enterococci* (*Enterococcus faecium* and *Enterococcus faecalis*) (19.7%), were the pathogens most frequently responsible for infection.

Table 1 Risk factors of bacterial infection in cirrhosis

Risk factors for bacterial infection in cirrhosis
Impairment of liver function
Child-Pugh score ^[36-38]
MELD score ≥ 15 ^[40]
Low serum albumin ^[39]
Alcohol related disease ^[45,51]
Total ascitic fluid protein concentration < 15 g/L ^[84]
ICU admission ^[39,85]
Variceal bleeding ^[41,86]
Blood transfusion requirements
Mean arterial pressure
Severity of bleeding
Malnutrition ^[40]
Invasive procedures ^[29]
ERCP in PSC patients or with incomplete drainage ^[87]
Hospitalization ^[29,40,43,44]

MELD: Model for end stage liver disease; ICU: Intensive care unit; ERCP: Endoscopic retrograde cholangiopancreatography; PSC: Primary sclerosing cholangitis.

The spreading of multidrug resistant (MDR) bacteria-related infection is alarming worldwide^[31,32]. In the past, patients with cirrhosis remained largely unaffected by this phenomenon because they were rarely admitted to the ICU. Nowadays, frequent hospitalizations, development of LT programs and antibiotic prophylaxis made cirrhosis at high risk of MDR infections^[33]. A multicenter study in Italy^[34] reported a 27% (83/395) prevalence of MDR infections, mainly due to GNB (extended-spectrum β lactamase *E. Coli* and Carbapenems resistant *K. Pneumoniae*). Another study from Greece^[35] reported 19% MDR infection rate amongst patients with SBP, being MDR bacteria associated with healthcare-acquired infections and with patients at higher MELD score (28 vs 19, $P = 0.012$). Also in the above-mentioned study by Merli *et al.*^[30], MDR infections occurred more frequently during hospitalization (56% in hospital acquired/healthcare-associated infections vs 22% in community acquired infections, $P = 0.008$).

RISK FACTORS FOR BACTERIAL INFECTION IN END STAGE LIVER DISEASE

Patients with end stage liver disease, listed for LT, have the highest risk for BI development. This might be due to frequent hospitalizations, severity of liver dysfunction and multiorgan failure (Table 1). Correlation between the development of BI and severity of liver disease has been widely demonstrated^[36]. In a Japanese group of patients with cirrhosis and hepatocellular carcinoma^[37], incidence of BI rose from 2.3% in Child-Pugh class A patients to 25.6% in Child-Pugh class C patients. In a further study^[38], even if patients with cirrhosis were younger and had less cardiopulmonary comorbidities than patients without cirrhosis, they had higher rates of septic shock at hospital admission, and equal mortality. Moreover, bacteremia and mortality increased with the severity of liver disease (5.6%, 20.5%, 33.3% and

0%, 8.5%, 38.9% in Child-Pugh classes A, B, and C, respectively; $P = 0.038$).

Furthermore, low serum albumin, ICU admission, and GI bleeding, are other independent predictors of BI development, according to Deschenes *et al.*^[39]. Merli *et al.*^[40] analyzing 54 BI episodes occurred in 50 patients, showed that, at multivariate analysis, a MELD score ≥ 15 (OR: 2.8, 95%CI: 1.3-6.1), history of previous infection within 12 mo (OR: 4.7, 95%CI: 2.2-10.6), and a diagnosis of malnutrition (OR: 4; 95%CI: 1.5-10) were independent predictors for infections and sepsis.

Variceal bleeding is another predictor of BI onset; Tandon *et al.*^[41], reviewing the available literature on patients admitted for GI bleeding without receiving antibiotic prophylaxis, showed that 242 out of 552 (44%) developed an episode of BI. Severity of GI bleeding, according to blood transfusion requirements (HR: 1.22; 95%CI: 1.01-1.47), mean arterial pressure (HR: 0.96; 95%CI: 0.93-0.99) were independent predictors for BI onset^[42]. In another Spanish study^[29], 126 patients underwent at least one invasive procedure, comprising variceal sclerotherapy or banding, surgical intervention, trans-jugular intrahepatic portosystemic shunt, having a higher probability of developing BI due to GPB.

Sinclair *et al.*^[43] showed that 43% of LT candidates required at least one hospitalization within 1 year; moreover, a significant proportion of hospitalized patients (> 45%) required repetitive hospitalisations. Patients with cirrhosis have 4 to 5-fold higher probability to develop a BI episode during hospitalization than non cirrhotic population^[42,44].

The role of etiology of underlying liver disease as a risk factor for BI development is debated^[45]. Alcohol abuse is associated with increased intestinal permeability, dysbiosis and increased bacterial translocation^[46]. Furthermore, Legionella and Mycobacterium tuberculosis infections are significantly more prevalent in patients with alcohol abuse^[47,48]. In the setting of cirrhosis, several studies reported a higher rate of BI in patients with alcoholic etiology when compared with non-alcoholic^[49,50]. Sargenti *et al.*^[51] evaluating characteristics of 398 BI in 633 cirrhotics (363 alcoholic, 270 nonalcoholic), reported a similar occurrence of BI between groups, but pointed out that alcohol related disease was significantly associated with bacterial pneumonia and GPB.

IMPACT OF BACTERIAL INFECTIONS IN LIVER FUNCTION

Worsening of liver function is frequently observed in patients with infection, especially in those with sepsis, being itself a trigger for multiorgan failure, and development of Acute on Chronic Liver Failure (ACLF)^[52-54].

In the above-mentioned study by Merli *et al.*^[40], Child-Pugh and MELD scores worsened in 62% of patients after infection; moreover, onset of ascites, hepatic encephalopathy, hyponatremia, hepatorenal

syndrome, were more frequent in patients with infection as compared with those who were not infected.

Prognosis of BI significantly correlates with the severity of liver disease and with the severity of extra-hepatic organ involvement^[54,55]. A systematic review^[21] considering 11987 patients with an episode of BI from 178 different studies, reported 1-, 3-, and 12-mo mortality of 30.3%, 44%, and 63%, respectively, and almost half of patients surviving at 1 mo died within a year. Renal failure, stage of cirrhosis (according to Child-Pugh score), age and severe sepsis were the factors independently associated with death. Several studies confirmed the critical role of renal failure in patients with cirrhosis and BI^[56,57]. Mortality increased with the occurrence and severity of acute kidney injury and with the outcome of renal failure (15% 90-d mortality after complete recovery, 40% after partial renal recovery, and 80% in patients without renal recovery or progression). According to the study by Cazzaniga *et al.*^[58], systemic inflammation and fulfillment of SIRS criteria, are other factors significantly associated with mortality, since in-hospital mortality of these decompensated patients with MELD score > 18 rose from 12% to 43%. Dionigi *et al.*^[22] retrospectively evaluated prognosis of patients who were hospitalized in a tertiary center in the United Kingdom; they demonstrated that in-hospital mortality rate was higher in those patients who had infection at admission and/or developed infection during hospitalization (HR: 5.02; 95%CI: 2.75–9.16; $P < 0.001$).

IMPACT OF BACTERIAL INFECTION IN THE LIVER TRANSPLANT CANDIDATE

The onset of BI usually determines a further worsening of liver function and multiorgan failure, with high probability of death or drop-out from the WL^[59,60]. Reddy *et al.*^[61] prospectively evaluated the outcome of 136 patients after an episode of BI developed while awaiting LT: 42% were delisted or died, 35% underwent transplantation, and only 24% achieved transplant-free survival within 6 mo. As expected, those who remained in the waiting list had a lower MELD score compared to those who either received a transplant or died/delisted; furthermore, those patients who underwent LT after BI recovery had a significant higher survival than those without LT (95% vs 5%; $P < 0.001$). At univariate analysis, the number of organ failures was the main factor that predicted death or delisting, whereas MELD score did not differentiate between those who were ultimately transplanted vs those who were delisted. Mounzer *et al.*^[62] showed that, 38% of patients who had experienced an episode of SBP before waiting list admission, were subsequently removed from the list or died.

Regarding patients who fully recovered from an episode of BI, the study by Sun *et al.*^[63] showed that recipients with pre-transplant BI ($n = 32$) within 12 mo before LT had a higher MELD score (median 25 vs 22, $P < 0.05$) at transplant, higher time of post-LT intubation

(3 d vs 2 d, $P = 0.05$), and longer post-transplant hospitalization (29 d vs 20 d, $P = 0.05$). However, post-transplant mortality was not different between groups (9.4% vs 2.9%) and was not associated with pre-LT infection. Lin *et al.*^[64] retrospectively analyzed the outcome of 34 living donor LT candidates who had experienced an episode of BI within 4 wk prior surgery, which was effectively treated (*e.g.*, disappearance of symptoms and signs suggestive of sepsis, normalization or improvement of laboratory and/or imaging findings after antibiotic therapy). The post-operative outcome was compared with 20 patients with pre-LT ACLF without infection. The only difference between groups was the longer total hospital stay (89.0 d vs 65.5 d, $P = 0.024$), whereas post-LT ICU stay, one-year survival, and post-LT infection rates were similar between groups. Few data are available on the possibility to offer a standardized MELD exception after recovery from infection^[65-67]. A possible scenario is the onset of recurrent episodes of cholangitis in PSC candidates; in a study by Goldberg *et al.*^[68], 300 patients who received MELD exception points for an increased risk of waitlist mortality, had a lower proportion of death/drop out (20.0% vs 1.3% $P < 0.001$); however, this non-standardized exception has not been further confirmed.

Several studies recently investigated the outcome of patients who underwent LT under “controlled” infection. In an Italian study^[69], 84 patients were considered eligible for LT after disappearance of symptoms and signs suggestive of severe sepsis/septic shock. The overall post-LT 90-d mortality, septic shock, and sepsis as cause of death were not significantly different between infected and not-infected LT recipients; however, patients with previous infection had in the post-operative course higher rates of infections (40% vs 36%, $P = 0.003$) and post-transplant MDR strains (26% vs 13%, $P = 0.005$). Artru *et al.*^[70] recently demonstrated that ACLF grade 3 patients were transplanted in France after they had recovered from an episode of BI according to a subjective criterion of “controlled sepsis” for at least 24 h within transplant; the authors demonstrated an excellent 1-year post-LT survival (83.8%), not different than that observed in patients with no ACLF or with lower stages of ALCF.

MDR bacteria colonization represents another important issue in the setting of WL, because of the risk of spreading of BI in the post-operative course and/or after the introduction of immunosuppression. Giannella *et al.*^[71] prospectively evaluate the role of carbapenems resistant *K. pneumoniae* (CR-KP) colonization (*e.g.*, presence of MDR bacteria in the rectal swab in absence of symptoms and signs of active infection) in 237 patients awaiting LT, of whom 11 (4.6%) were positive at the time of LT. Hospital admission, higher MELD at LT, prior antibiotic exposure, post-operative complications, and ICU length of stay were the factors associated with the CR-KP active infection after LT. In addition, the same group, performing a multicenter prospective

study on CR-KP carriers^[72], not only in the setting of LT, demonstrated that the number of additional colonization sites was an independent risk factor for invasive infection.

In conclusion, BI significantly modify the natural history of patients with cirrhosis listed for LT. Severe BI in a sick and frail patient can produce a multiorgan failure comprising further deterioration of liver function. Even if this can increase priority in the WL, this gain in priority should be used only after adequate control of infection. To date, standardized definition of "controlled infection" is lacking. As for other patients with severe ACLF in the WL^[73,74], prioritization rules in the respect of distributive justice, definition of the ideal timing for LT and definition of delisting criteria have to be refined in the next future.

MEDICAL PROPHYLAXIS OF BACTERIAL INFECTION

Antibiotic prophylaxis in patients with decompensated cirrhosis is standard of care in patients with recent gastrointestinal bleeding^[75], and in those with high risk of SBP (e.g., Child-Pugh > 9, serum bilirubin > 3 mg/dL and impaired renal function), or in secondary prophylaxis for SBP^[24].

Antibiotic prophylaxis after upper GI bleeding reduces the incidence of in-hospital infections, re-bleeding rate within 7 d (7% vs 34%), and 28-d mortality (13% vs 35%, $P = 0.04$).

However, some concerns about long-term prophylaxis has been recently raised, since it's been associated with high prevalence of MDR BI, before and after LT. Tandon *et al*^[76] evaluating 110 episodes of BI (30% hospital acquired), reported 47% of antibiotic resistance and a significant association between previous exposure to systemic antibiotics and antibiotic-resistance. Infections due to MDR bacteria are associated with an increased risk of septic shock, acute kidney injury, and death, in the post-transplant setting^[44]. Furthermore, antibiotic use has been identified as the strongest predictor of invasive post-transplant fungal infection, associated with a 60% mortality^[77].

Even if several studies suggested the need to stratify patients who need antibiotic prophylaxis, both after variceal bleeding and after an episode of SBP, no robust data are available to date^[12,23,78,79].

Patients with cirrhosis admitted to ICU could be at higher risk of BI. Recently, a meta-analysis on prognosis of cirrhotics admitted to ICU showed that acute kidney injury and sepsis as indications to ICU admission were the only factors significantly associated with mortality^[80]. Another retrospective study^[81] on 42 patients who underwent LT from the ICU, showed that pre-LT intubation was a factor significantly associated with post-LT pneumonia ($P = 0.02$).

On the contrary, patients who recover liver function while in the WL (e.g., after viral eradication/suppress-

sion), history of BI would not be a sufficient factor for administering long-term antibiotic prophylaxis. In addition, the spreading of MDR bacteria will reduce the potential role of antibiotic mono-prophylaxis with quinolones or cephalosporines.

Given the crucial role played by dysbiosis in BI in patients with cirrhosis, several studies assessed the role of intestinal decontamination. Grat *et al*^[82] evaluated the fecal microflora in 40 LT candidates, showing that abundance of several species (e.g., *Bifidobacterium* and *Enterococcus*) significantly correlated with the severity of liver disease. In systematic review and meta-analysis, Safdar *et al*^[83] compared parenteral (e.g., cephalosporins/quinolones), topically applied or non-absorbable antibiotic strategies (polymyxin, gentamicin, and nystatin) for intestinal decontamination. The Authors found an association between selective decontamination and reduction of GNB infections ($P = 0.001$), however studies were underpowered and heterogeneous.

CONCLUSION

BI represent a turning point in the natural history of cirrhosis, being the first cause of development of ACLF, and significantly affecting the outcome of patients listed for LT. These patients are at the highest risk of infection, because of frequent hospitalizations and contacts with healthcare facilities, immune dysregulation, end-stage liver disease. SBP, pneumonia and bloodstream infection represent the commonest sites of BI. In such cases, early institution of empirical antibiotic therapy is mandatory, to reduce infection-related mortality. However, empirical antibiotic therapy should take into account the changing epidemiology of infections, related both to an increase of gram positive strains and to MDR bacteria.

In the setting of LT, patients should be considered suitable for transplant after resolution of infection. However, according to recent studies, selected patients with "controlled infection" should be considered for transplant, since this condition does not impair the post-transplant outcome^[69,70]. Antibiotic prophylaxis is the standard of care in cirrhotic patients with gastrointestinal bleeding or with previous episodes of SBP. However, it should be considered also in other settings with a high prevalence of BI, as in patients listed for LT, admitted to ICU and requiring intubation, because of a higher risk of post-LT pneumonia.

REFERENCES

- 1 **Strnad P**, Tacke F, Koch A, Trautwein C. Liver - guardian, modifier and target of sepsis. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 55-66 [PMID: 27924081 DOI: 10.1038/nrgastro.2016.168]
- 2 **Koch A**, Horn A, Dücker H, Yagmur E, Sanson E, Bruensing J, Buendgens L, Voigt S, Trautwein C, Tacke F. Increased liver stiffness denotes hepatic dysfunction and mortality risk in critically ill non-cirrhotic patients at a medical ICU. *Crit Care* 2011; **15**: R266 [PMID: 22082207 DOI: 10.1186/cc10543]

- 3 **Dizier S**, Forel JM, Ayzac L, Richard JC, Hraiech S, Lehingue S, Loundou A, Roch A, Guerin C, Papazian L; ACURASYS study investigators; PROSEVA Study Group. Early Hepatic Dysfunction Is Associated with a Worse Outcome in Patients Presenting with Acute Respiratory Distress Syndrome: A Post-Hoc Analysis of the ACURASYS and PROSEVA Studies. *PLoS One* 2015; **10**: e0144278 [PMID: 26636318 DOI: 10.1371/journal.pone.0144278]
- 4 **Foreman MG**, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. *Chest* 2003; **124**: 1016-1020 [PMID: 12970032 DOI: 10.1378/chest.124.3.1016]
- 5 **Albillos A**, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 2014; **61**: 1385-1396 [PMID: 25135860 DOI: 10.1016/j.jhep.2014.08.010]
- 6 **Tazi KA**, Quioc JJ, Saada V, Bezeaud A, Lebrec D, Moreau R. Upregulation of TNF- α production signaling pathways in monocytes from patients with advanced cirrhosis: possible role of Akt and IRAK-M. *J Hepatol* 2006; **45**: 280-289 [PMID: 16635535 DOI: 10.1016/j.jhep.2006.02.013]
- 7 **Úbeda M**, Muñoz L, Borrero MJ, Díaz D, Francés R, Monserrat J, Lario M, Lledó L, Such J, Álvarez-Mon M, Albillos A. Critical role of the liver in the induction of systemic inflammation in rats with preascitic cirrhosis. *Hepatology* 2010; **52**: 2086-2095 [PMID: 21105108 DOI: 10.1002/hep.23961]
- 8 **Lee FY**, Lu RH, Tsai YT, Lin HC, Hou MC, Li CP, Liao TM, Lin LF, Wang SS, Lee SD. Plasma interleukin-6 levels in patients with cirrhosis. Relationship to endotoxemia, tumor necrosis factor- α , and hyperdynamic circulation. *Scand J Gastroenterol* 1996; **31**: 500-505 [PMID: 8734349 DOI: 10.3109/00365529609006772]
- 9 **Tilg H**, Wilmer A, Vogel W, Herold M, Nölchen B, Judmaier G, Huber C. Serum levels of cytokines in chronic liver diseases. *Gastroenterology* 1992; **103**: 264-274 [PMID: 1612333]
- 10 **Wiest R**, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol* 2014; **60**: 197-209 [PMID: 23993913 DOI: 10.1016/j.jhep.2013.07.044]
- 11 **Rasaratnam B**, Kaye D, Jennings G, Dudley F, Chin-Dusting J. The effect of selective intestinal decontamination on the hyperdynamic circulatory state in cirrhosis. A randomized trial. *Ann Intern Med* 2003; **139**: 186-193 [PMID: 12899586 DOI: 10.7326/0003-4819-139-3-200308050-00008]
- 12 **Jalan R**, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, Stadlbauer V, Gustot T, Bernardi M, Canton R, Albillos A, Lammert F, Wilmer A, Mookerjee R, Vila J, Garcia-Martinez R, Wendon J, Such J, Cordoba J, Sanyal A, Garcia-Tsao G, Arroyo V, Burroughs A, Ginès P. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol* 2014; **60**: 1310-1324 [PMID: 24530646 DOI: 10.1016/j.jhep.2014.01.024]
- 13 **Moreau R**, Soubrane O, Sogni P, Hadengue A, Gaudin C, Lin HC, Pussard E, Nahoul K, Lebrec D. Hemodynamic, neurohumoral, and metabolic responses to amino acid infusion in patients with cirrhosis. *Gastroenterology* 1992; **103**: 601-608 [PMID: 1386049]
- 14 **Moreau R**, Hadengue A, Soupison T, Kirstetter P, Mamzer MF, Vanjak D, Vauquelin P, Assous M, Scot C. Septic shock in patients with cirrhosis: hemodynamic and metabolic characteristics and intensive care unit outcome. *Crit Care Med* 1992; **20**: 746-750 [PMID: 1597026 DOI: 10.1097/00003246-199206000-00008]
- 15 **Thalheimer U**, Triantos CK, Samonakis DN, Patch D, Burroughs AK. Infection, coagulation, and variceal bleeding in cirrhosis. *Gut* 2005; **54**: 556-563 [PMID: 15753544 DOI: 10.1136/gut.2004.048181]
- 16 **Sort P**, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Ginès P, Rodés J. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; **341**: 403-409 [PMID: 10432325 DOI: 10.1056/NEJM199908053410603]
- 17 **Merli M**, Lucidi C, Pentassuglio I, Giannelli V, Giusto M, Di Gregorio V, Pasquale C, Nardelli S, Lattanzi B, Venditti M, Riggio O. Increased risk of cognitive impairment in cirrhotic patients with bacterial infections. *J Hepatol* 2013; **59**: 243-250 [PMID: 23523580 DOI: 10.1016/j.jhep.2013.03.012]
- 18 **Plessier A**, Denninger MH, Consigny Y, Pessione F, Francoz C, Durand F, Franque S, Bezeaud A, Chauvelot-Moachon L, Lebrec D, Valla DC, Moreau R. Coagulation disorders in patients with cirrhosis and severe sepsis. *Liver Int* 2003; **23**: 440-448 [PMID: 15002397 DOI: 10.1111/j.1478-3231.2003.00870.x]
- 19 **Fede G**, Spadaro L, Tomaselli T, Privitera G, Germani G, Tsochatzis E, Thomas M, Bouloux PM, Burroughs AK, Purrello F. Adrenocortical dysfunction in liver disease: a systematic review. *Hepatology* 2012; **55**: 1282-1291 [PMID: 22234976 DOI: 10.1002/hep.25573]
- 20 **Doyle RL**, Szaflarski N, Modin GW, Wiener-Kronish JP, Matthay MA. Identification of patients with acute lung injury. Predictors of mortality. *Am J Respir Crit Care Med* 1995; **152**: 1818-1824 [PMID: 8520742 DOI: 10.1164/ajrccm.152.6.8520742]
- 21 **Arvaniti V**, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, Burroughs AK. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010; **139**: 1246-1256, 1256.e1-5 [PMID: 20558165 DOI: 10.1053/j.gastro.2010.06.019]
- 22 **Dionigi E**, Garcovich M, Borzio M, Leandro G, Majumdar A, Tsami A, Arvaniti V, Roccarina D, Pinzani M, Burroughs AK, O'Beirne J, Tsochatzis EA. Bacterial Infections Change Natural History of Cirrhosis Irrespective of Liver Disease Severity. *Am J Gastroenterol* 2017; **112**: 588-596 [PMID: 28220780 DOI: 10.1038/ajg.2017.19]
- 23 **Fagioli S**, Colli A, Bruno R, Craxi A, Gaeta GB, Grossi P, Mondelli MU, Puoti M, Sagnelli E, Stefani S, Toniutto P, Burra P; 2011 AISF Single Topic Group. Management of infections pre- and post-liver transplantation: report of an AISF consensus conference. *J Hepatol* 2014; **60**: 1075-1089 [PMID: 24384327 DOI: 10.1016/j.jhep.2013.12.021]
- 24 **European Association for the Study of the Liver**. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946 DOI: 10.1016/j.jhep.2010.05.004]
- 25 **Oliveira AM**, Branco JC, Barosa R, Rodrigues JA, Ramos L, Martins A, Karvellas CJ, Cardoso FS. Clinical and microbiological characteristics associated with mortality in spontaneous bacterial peritonitis: a multicenter cohort study. *Eur J Gastroenterol Hepatol* 2016; **28**: 1216-1222 [PMID: 27391170 DOI: 10.1097/MEG.0000000000000700]
- 26 **Piano S**, Fasolato S, Salinas F, Romano A, Tonon M, Morando F, Cavallin M, Gola E, Sticca A, Loregian A, Palù G, Zanùs G, Senzolo M, Burra P, Cillo U, Angeli P. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: Results of a randomized, controlled clinical trial. *Hepatology* 2016; **63**: 1299-1309 [PMID: 26084406 DOI: 10.1002/hep.27941]
- 27 **Campillo B**, Richardet JP, Kheo T, Dupeyron C. Nosocomial spontaneous bacterial peritonitis and bacteremia in cirrhotic patients: impact of isolate type on prognosis and characteristics of infection. *Clin Infect Dis* 2002; **35**: 1-10 [PMID: 12060868 DOI: 10.1086/340617]
- 28 **Bartoletti M**, Giannella M, Lewis R, Caraceni P, Tedeschi S, Paul M, Schramm C, Bruns T, Merli M, Cobos-Trigueros N, Seminari E, Retamar P, Mu-oz P, Tumbarello M, Burra P, Torrani Cerenzia M, Barsic B, Calbo E, Maraolo AE, Petrosillo N, Galan-Ladero MA, D'Offizi G, Bar Sinai N, Rodríguez-Ba-o J, Verucchi G, Bernardi M, Viale P; ESGBIS/BICHRROME Study Group. A prospective multicentre study of the epidemiology and outcomes of bloodstream infection in cirrhotic patients. *Clin Microbiol Infect* 2017; pii: S1198-743X(17)30426-3 [PMID: 28818628 DOI: 10.1016/j.cmi.2017.08.001]
- 29 **Fernández J**, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, Rodés J. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002; **35**: 140-148 [PMID: 11786970 DOI: 10.1053/

- jhep.2002.30082]
- 30 **Merli M**, Lucidi C, Di Gregorio V, Falcone M, Giannelli V, Lattanzi B, Giusto M, Ceccarelli G, Farcomeni A, Riggio O, Venditti M. The spread of multi drug resistant infections is leading to an increase in the empirical antibiotic treatment failure in cirrhosis: a prospective survey. *PLoS One* 2015; **10**: e0127448 [PMID: 25996499 DOI: 10.1371/journal.pone.0127448]
 - 31 **Boyle DP**, Zembower TR. Epidemiology and Management of Emerging Drug-Resistant Gram-Negative Bacteria: Extended-Spectrum β -Lactamases and Beyond. *Urol Clin North Am* 2015; **42**: 493-505 [PMID: 26475946 DOI: 10.1016/j.ucl.2015.05.005]
 - 32 **Dheda K**, Gumbo T, Maartens G, Dooley KE, McNerney R, Murray M, Furin J, Nardell EA, London L, Lessem E, Theron G, van Helden P, Niemann S, Merker M, Dowdy D, Van Rie A, Siu GK, Pasipanodya JG, Rodrigues C, Clark TG, Sirgel FA, Esmail A, Lin HH, Atre SR, Schaaf HS, Chang KC, Lange C, Nahid P, Udawadia ZF, Horsburgh CR Jr, Churchyard GJ, Menzies D, Hesselting AC, Nuernberger E, McIlleron H, Fennelly KP, Goemaere E, Jaramillo E, Low M, Jara CM, Padayatchi N, Warren RM. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir Med* 2017; pii: S2213-2600(17)30079-6 [PMID: 28344011 DOI: 10.1016/S2213-2600(17)30079-6]
 - 33 **Fernández J**, Bert F, Nicolas-Chanoine MH. The challenges of multi-drug-resistance in hepatology. *J Hepatol* 2016; **65**: 1043-1054 [PMID: 27544545 DOI: 10.1016/j.jhep.2016.08.006]
 - 34 **Salerno F**, Borzio M, Pedicino C, Simonetti R, Rossini A, Boccia S, Cacciola I, Burroughs AK, Manini MA, La Mura V, Angeli P, Bernardi M, Dalla Gasperina D, Dionigi E, Dibenedetto C, Arghittu M; AISF Investigators. The impact of infection by multidrug-resistant agents in patients with cirrhosis. A multicenter prospective study. *Liver Int* 2017; **37**: 71-79 [PMID: 27364035 DOI: 10.1111/liv.13195]
 - 35 **Alexopoulou A**, Papadopoulos N, Eliopoulos DG, Alexaki A, Tsiriga A, Toutouza M, Pectasides D. Increasing frequency of gram-positive cocci and gram-negative multidrug-resistant bacteria in spontaneous bacterial peritonitis. *Liver Int* 2013; **33**: 975-981 [PMID: 23522099 DOI: 10.1111/liv.12152]
 - 36 **Caly WR**, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. *J Hepatol* 1993; **18**: 353-358 [DOI: 10.1016/S0168-8278(05)80280-6]
 - 37 **Yoshida H**, Hamada T, Inuzuka S, Ueno T, Sata M, Tanikawa K. Bacterial infection in cirrhosis, with and without hepatocellular carcinoma. *Am J Gastroenterol* 1993; **88**: 2067-2071 [PMID: 8249975]
 - 38 **Viasus D**, Garcia-Vidal C, Castellote J, Adamuz J, Verdaguer R, Dorca J, Manresa F, Gudiol F, Carratalà J. Community-acquired pneumonia in patients with liver cirrhosis: clinical features, outcomes, and usefulness of severity scores. *Medicine (Baltimore)* 2011; **90**: 110-118 [PMID: 21358441 DOI: 10.1097/MD.0b013e318210504c]
 - 39 **Deschênes M**, Villeneuve JP. Risk factors for the development of bacterial infections in hospitalized patients with cirrhosis. *Am J Gastroenterol* 1999; **94**: 2193-2197 [PMID: 10445549 DOI: 10.1111/j.1572-0241.1999.01293.x]
 - 40 **Merli M**, Lucidi C, Giannelli V, Giusto M, Riggio O, Falcone M, Ridola L, Attili AF, Venditti M. Cirrhotic patients are at risk for health care-associated bacterial infections. *Clin Gastroenterol Hepatol* 2010; **8**: 979-985 [PMID: 20621200 DOI: 10.1016/j.cgh.2010.06.024]
 - 41 **Tandon P**, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. *Semin Liver Dis* 2008; **28**: 26-42 [PMID: 18293275 DOI: 10.1055/s-2008-1040319]
 - 42 **Fernández J**, Ruiz del Arbol L, Gómez C, Durandez R, Serradilla R, Guarner C, Planas R, Arroyo V, Navasa M. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology* 2006; **131**: 1049-1056; quiz 1285 [PMID: 17030175 DOI: 10.1053/j.gastro.2006.07.010]
 - 43 **Sinclair M**, Poltavskiy E, Dodge JL, Lai JC. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. *World J Gastroenterol* 2017; **23**: 899-905 [PMID: 28223735 DOI: 10.3748/wjg.v23.i5.899]
 - 44 **Fernandez J**, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol* 2012; **56** Suppl 1: S1-S12 [DOI: 10.1016/S0168-8278(12)60002-6]
 - 45 **Gustot T**, Fernandez J, Szabo G, Albillos A, Louvet A, Jalan R, Moreau R, Moreno C. Sepsis in alcohol-related liver disease. *J Hepatol* 2017; **67**: 1031-1050 [PMID: 28647569 DOI: 10.1016/j.jhep.2017.06.013]
 - 46 **Cirera I**, Bauer TM, Navasa M, Vila J, Grande L, Taurá P, Fuster J, Garcia-Valdecasas JC, Lacy A, Suárez MJ, Rimola A, Rodés J. Bacterial translocation of enteric organisms in patients with cirrhosis. *J Hepatol* 2001; **34**: 32-37 [DOI: 10.1016/S0168-8278(00)00013-1]
 - 47 **Happel KI**, Nelson S. Alcohol, immunosuppression, and the lung. *Proc Am Thorac Soc* 2005; **2**: 428-432 [PMID: 16322595 DOI: 10.1513/pats.200507-065JS]
 - 48 **Lönnroth K**, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. *BMC Public Health* 2008; **8**: 289 [PMID: 18702821 DOI: 10.1186/1471-2458-8-289]
 - 49 **Conejo I**, Augustin S, Pons M, Ventura-Cots M, González A, Esteban R, Genescà J. Alcohol consumption and risk of infection after a variceal bleeding in low-risk patients. *Liver Int* 2016; **36**: 994-1001 [PMID: 26643867 DOI: 10.1111/liv.13038]
 - 50 **Rosa H**, Silvério AO, Perini RF, Arruda CB. Bacterial infection in cirrhotic patients and its relationship with alcohol. *Am J Gastroenterol* 2000; **95**: 1290-1293 [PMID: 10811341 DOI: 10.1111/j.1572-0241.2000.02026.x]
 - 51 **Sargenti K**, Prytz H, Nilsson E, Bertilsson S, Kalaitzakis E. Bacterial infections in alcoholic and nonalcoholic liver cirrhosis. *Eur J Gastroenterol Hepatol* 2015; **27**: 1080-1086 [PMID: 26011234 DOI: 10.1097/MEG.0000000000000396]
 - 52 **Mücke MM**, Rummyantseva T, Mücke VT, Schwarzkopf K, Joshi S, Kempf VAJ, Welsch C, Zeuzem S, Lange CM. Bacterial infection-triggered acute-on-chronic liver failure is associated with increased mortality. *Liver Int* 2017; Epub ahead of print [PMID: 28853199 DOI: 10.1111/liv.13568]
 - 53 **Sargenti K**, Prytz H, Nilsson E, Kalaitzakis E. Predictors of mortality among patients with compensated and decompensated liver cirrhosis: the role of bacterial infections and infection-related acute-on-chronic liver failure. *Scand J Gastroenterol* 2015; **50**: 875-883 [PMID: 25697824 DOI: 10.3109/00365521.2015.1017834]
 - 54 **Moreau R**, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL-CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; **144**: 1426-1437, 1437.e1-1437.e9 [PMID: 23474284 DOI: 10.1053/j.gastro.2013.02.042]
 - 55 **Brunns T**, Zimmermann HW, Stallmach A. Risk factors and outcome of bacterial infections in cirrhosis. *World J Gastroenterol* 2014; **20**: 2542-2554 [PMID: 24627590 DOI: 10.3748/wjg.v20.i10.2542]
 - 56 **Martín-Llahí M**, Guevara M, Torre A, Fagundes C, Restuccia T, Gilabert R, Solá E, Pereira G, Marinelli M, Pavesi M, Fernández J, Rodés J, Arroyo V, Ginès P. Prognostic importance of the cause of renal failure in patients with cirrhosis. *Gastroenterology* 2011; **140**: 488-496.e4 [PMID: 20682324 DOI: 10.1053/j.gastro.2010.07.043]
 - 57 **Wong F**, O'Leary JG, Reddy KR, Patton H, Kamath PS, Fallon MB, Garcia-Tsao G, Subramanian RM, Malik R, Maliakkal B, Thacker LR, Bajaj JS; North American Consortium for Study of End-Stage Liver Disease. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. *Gastroenterology* 2013; **145**: 1280-1288.e1

- [PMID: 23999172 DOI: 10.1053/j.gastro.2013.08.051]
- 58 **Cazzaniga M**, Dionigi E, Gobbo G, Fioretti A, Monti V, Salerno F. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. *J Hepatol* 2009; **51**: 475-482 [PMID: 19560225 DOI: 10.1016/j.jhep.2009.04.017]
- 59 **Bajaj JS**, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, Fallon MB, Garcia-Tsao G, Maliakkal B, Malik R, Subramanian RM, Thacker LR, Kamath PS; North American Consortium For The Study Of End-Stage Liver Disease (NACSELD). Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology* 2014; **60**: 250-256 [PMID: 24677131 DOI: 10.1002/hep.27077]
- 60 **Kim WR**, Lake JR, Smith JM, Skeans MA, Schladt DP, Edwards EB, Harper AM, Wainright JL, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2015 Annual Data Report: Liver. *Am J Transplant* 2017; **17** Suppl 1: 174-251 [PMID: 28052604 DOI: 10.1111/ajt.14126]
- 61 **Reddy KR**, O'Leary JG, Kamath PS, Fallon MB, Biggins SW, Wong F, Patton HM, Garcia-Tsao G, Subramanian RM, Thacker LR, Bajaj JS; North American Consortium for the Study of End-Stage Liver Disease. High risk of delisting or death in liver transplant candidates following infections: Results from the North American Consortium for the Study of End-Stage Liver Disease. *Liver Transpl* 2015; **21**: 881-888 [PMID: 25845966 DOI: 10.1002/lt.24139]
- 62 **Mounzer R**, Malik SM, Nasr J, Madani B, Devera ME, Ahmad J. Spontaneous bacterial peritonitis before liver transplantation does not affect patient survival. *Clin Gastroenterol Hepatol* 2010; **8**: 623-628.e1 [PMID: 20417723 DOI: 10.1016/j.cgh.2010.04.013]
- 63 **Sun HY**, Cacciarelli TV, Singh N. Impact of pretransplant infections on clinical outcomes of liver transplant recipients. *Liver Transpl* 2010; **16**: 222-228 [PMID: 20104499 DOI: 10.1002/lt.21982]
- 64 **Lin KH**, Liu JW, Chen CL, Wang SH, Lin CC, Liu YW, Yong CC, Lin TL, Li WF, Hu TH, Wang CC. Impacts of pretransplant infections on clinical outcomes of patients with acute-on-chronic liver failure who received living-donor liver transplantation. *PLoS One* 2013; **8**: e72893 [PMID: 24023787 DOI: 10.1371/journal.pone.0072893]
- 65 **Cholongitas E**, Germani G, Burroughs AK. Prioritization for liver transplantation. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 659-668 [PMID: 21045793 DOI: 10.1038/nrgastro.2010.169]
- 66 **Cillo U**, Burra P, Mazzaferro V, Belli L, Pinna AD, Spada M, Nanni Costa A, Toniutto P; I-BELT (Italian Board of Experts in the Field of Liver Transplantation). A Multistep, Consensus-Based Approach to Organ Allocation in Liver Transplantation: Toward a "Blended Principle Model". *Am J Transplant* 2015; **15**: 2552-2561 [PMID: 26274338 DOI: 10.1111/ajt.13408]
- 67 **Goldberg DS**, Olthoff KM. Standardizing MELD exceptions: Current challenges and future directions. *Curr Transplant Rep* 2014; **1**: 232-237 [PMID: 25530936 DOI: 10.1007/s40472-014-0027-4]
- 68 **Goldberg D**, Bittermann T, Makar G. Lack of standardization in exception points for patients with primary sclerosing cholangitis and bacterial cholangitis. *Am J Transplant* 2012; **12**: 1603-1609 [PMID: 22335632 DOI: 10.1111/j.1600-6143.2011.03969.x]
- 69 **Bertuzzo VR**, Giannella M, Cucchetti A, Pinna AD, Grossi A, Ravaioli M, Del Gaudio M, Cristini F, Viale P, Cescon M. Impact of preoperative infection on outcome after liver transplantation. *Br J Surg* 2017; **104**: e172-e181 [PMID: 28121031 DOI: 10.1002/bjs.10449]
- 70 **Artru F**, Louvet A, Ruiz I, Levesque E, Labreuche J, Ursic-Bedoya J, Lassailly G, Dharancy S, Boleslawski E, Lebuffe G, Kipnis E, Ichai P, Coilly A, De Martin E, Antonini TM, Vibert E, Jaber S, Herrero A, Samuel D, Duhamel A, Pageaux GP, Mathurin P, Saliba F. Liver transplantation in the most severely ill cirrhotic patients: A multicenter study in acute-on-chronic liver failure grade 3. *J Hepatol* 2017; **67**: 708-715 [PMID: 28645736 DOI: 10.1016/j.jhep.2017.06.009]
- 71 **Giannella M**, Bartoletti M, Morelli MC, Tedeschi S, Cristini F, Tumietto F, Pasqualini E, Danese I, Campoli C, Lauria ND, Faenza S, Ercolani G, Lewis R, Pinna AD, Viale P. Risk factors for infection with carbapenem-resistant *Klebsiella pneumoniae* after liver transplantation: the importance of pre- and posttransplant colonization. *Am J Transplant* 2015; **15**: 1708-1715 [PMID: 25754742 DOI: 10.1111/ajt.13136]
- 72 **Giannella M**, Trecarichi EM, De Rosa FG, Del Bono V, Bassetti M, Lewis RE, Losito AR, Corcione S, Saffioti C, Bartoletti M, Maiuro G, Cardellino CS, Tedeschi S, Cauda R, Viscoli C, Viale P, Tumbarello M. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study. *Clin Microbiol Infect* 2014; **20**: 1357-1362 [PMID: 24980276 DOI: 10.1111/1469-0691.12747]
- 73 **Gustot T**, Agarwal B. Selected patients with acute-on-chronic liver failure grade 3 are not too sick to be considered for liver transplantation. *J Hepatol* 2017; **67**: 667-668 [PMID: 28923205 DOI: 10.1016/j.jhep.2017.07.017]
- 74 **Putignano A**, Gustot T. New concepts in acute-on-chronic liver failure: Implications for liver transplantation. *Liver Transpl* 2017; **23**: 234-243 [PMID: 27750389 DOI: 10.1002/lt.24654]
- 75 **de Franchis R**; Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**: 743-752 [PMID: 26047908 DOI: 10.1016/j.jhep.2015.05.022]
- 76 **Tandon P**, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. *Clin Gastroenterol Hepatol* 2012; **10**: 1291-1298 [PMID: 22902776 DOI: 10.1016/j.cgh.2012.08.017]
- 77 **Fernandez J**, Tandon P, Mensa J, Garcia-Tsao G. Antibiotic prophylaxis in cirrhosis: Good and bad. *Hepatology* 2016; **63**: 2019-2031 [PMID: 26528864 DOI: 10.1002/hep.28330]
- 78 **Nadim MK**, Durand F, Kellum JA, Levitsky J, O'Leary JG, Karvellas CJ, Bajaj JS, Davenport A, Jalan R, Angeli P, Caldwell SH, Fernández J, Francoz C, Garcia-Tsao G, Ginès P, Ison MG, Kramer DJ, Mehta RL, Moreau R, Mulligan D, Olson JC, Pomfret EA, Senzolo M, Steadman RH, Subramanian RM, Vincent JL, Genyk YS. Management of the critically ill patient with cirrhosis: A multidisciplinary perspective. *J Hepatol* 2016; **64**: 717-735 [PMID: 26519602 DOI: 10.1016/j.jhep.2015.10.019]
- 79 **Tandon P**, Abralades JG, Keough A, Bastiampillai R, Jayakumar S, Carbonneau M, Wong E, Kao D, Bain VG, Ma M. Risk of Bacterial Infection in Patients With Cirrhosis and Acute Variceal Hemorrhage, Based on Child-Pugh Class, and Effects of Antibiotics. *Clin Gastroenterol Hepatol* 2015; **13**: 1189-1196.e2 [PMID: 25460564 DOI: 10.1016/j.cgh.2014.11.019]
- 80 **Weil D**, Levesque E, McPhail M, Cavallazzi R, Theodoridou E, Cholongitas E, Galbois A, Pan HC, Karvellas CJ, Sauneuf B, Robert R, Fichet J, Piton G, Thevenot T, Capellier G, Di Martino V; METAREACIR Group. Prognosis of cirrhotic patients admitted to intensive care unit: A meta-analysis. *Ann Intensive Care* 2017; **7**: 33 [PMID: 28321803 DOI: 10.1186/s13613-017-0249-6]
- 81 **Knaak J**, McVey M, Bazerbachi F, Goldaracena N, Spetzler V, Selzner N, Cattral M, Greig P, Lilly L, McGilvray I, Levy G, Ghanekar A, Renner E, Grant D, Hawryluk L, Selzner M. Liver transplantation in patients with end-stage liver disease requiring intensive care unit admission and intubation. *Liver Transpl* 2015; **21**: 761-767 [PMID: 25865305 DOI: 10.1002/lt.24115]
- 82 **Grąt M**, Hołówko W, Wronka KM, Grąt K, Lewandowski Z, Kosińska I, Krasnodębski M, Wasilewicz M, Gałęcka M, Szachta P, Zborowska H, Patkowski W, Krawczyk M. The relevance of intestinal dysbiosis in liver transplant candidates. *Transpl Infect Dis* 2015; **17**: 174-184 [PMID: 25728703 DOI: 10.1111/tid.12352]
- 83 **Safdar N**, Said A, Lucey MR. The role of selective digestive decontamination for reducing infection in patients undergoing liver transplantation: a systematic review and meta-analysis. *Liver Transpl* 2004; **10**: 817-827 [PMID: 15237363 DOI: 10.1002/lt.20108]
- 84 **Rimola A**, Garcia-Tsao G, Navasa M, Piddock LJ, Planas R,

- Bernard B, Inadomi JM. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol* 2000; **32**: 142-153 [PMID: 10673079]
- 85 **Galbois A**, Aegerter P, Martel-Samb P, Housset C, Thabut D, Offenstadt G, Ait-Oufella H, Maury E, Guidet B; Collège des Utilisateurs des Bases des données en Réanimation (CUB-Réa) Group. Improved prognosis of septic shock in patients with cirrhosis: a multicenter study. *Crit Care Med* 2014; **42**: 1666-1675 [PMID: 24732239 DOI: 10.1097/CCM.0000000000000321]
- 86 **Chavez-Tapia NC**, Barrientos-Gutierrez T, Tellez-Avila F, Soares-Weiser K, Mendez-Sanchez N, Glud C, Uribe M. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated Cochrane review. *Aliment Pharmacol Ther* 2011; **34**: 509-518 [PMID: 21707680 DOI: 10.1111/j.1365-2036.2011.04746.x]
- 87 **European Society of Gastrointestinal Endoscopy**, European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline. *J Hepatol* 2017; **66**: 1265-1281 [PMID: 28427764 DOI: 10.1016/j.jhep.2017.02.013]

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