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Progress Report

Management of infections in cirrhotic patients: Report of a Consensus Conference☆

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ABSTRACT

The statements produced by the consensus conference on infection in end-stage liver disease promoted by the Italian Association for the Study of the Liver, are here reported.

The topics of epidemiology, risk factors, diagnosis, prophylaxis, and treatment of infections in patient with compensated and decompensated liver cirrhosis were reviewed by a scientific board of experts who proposed 26 statements that were graded according to level of evidence and strength of recommendation, and approved by an independent jury. Each topic was explored focusing on the more relevant clinical questions. By systematic literature search of available evidence, comparison and discussion of expert opinions, pertinent statements answering specific questions were presented and approved. Short comments were added to explain the basis for grading evidence particularly on case of controversial areas.

Introduction

Bacterial infections are a leading cause of acute on chronic liver failure and are associated with high mortality in end-stage liver disease [1]. Dysfunction of the defensive mechanisms against bacterial or fungal infections makes patients with cirrhosis prone to the development of sepsis [2,3].

By reviewing the studies reporting on the clinical course of cirrhosis after infectious episodes, the overall mortality of infected patients is reportedly around 38% with 30.3% of cases occurring at 1 month and 63% at 12 months, with the pooled odds ratio for death of infected versus non infected of 3.75 (95% confidence interval 2.12–4.23) [4].

Spontaneous bacterial peritonitis represents one of the most common infectious complications in patients with cirrhosis. The median mortality in 7062 such patients was 43.7%, with 31.5% of the cases occurring at 1 month and 66.2% at 12 months [5]. Moreover, severe renal failure is common in patients with spontaneous bacterial peritonitis and is associated with a poor outcome.

The goal of this document was to provide clinical guideline for the appropriate management of infections in ESLD and liver

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transplantation. Promoter of this "Consensus Guidelines" was the Italian association for the Study of Liver (AISF).

The methods section is listed in Appendix B. Grading and strength of recommendations were applied according to the Centres for Disease control (CDC) grading system (Table S1).

1. EPIDEMIOLOGY OF INFECTION IN CIRRHOSIS

Question 1.a

What is the prevalence of bacterial infections in cirrhotic patients and which are the risk factors?

Comments. In two studies in patients with liver cirrhosis requiring hospitalization conducted in Italy one in 1995–96 and the other in 2005 bacterial infections occurred respectively in 34 and 38% of hospital admissions [6,7] and an overlapping prevalence was observed in studies performed in other countries [4,8,9]. The occurrence of bacterial infection was associated with higher Child or model for end stage liver disease (MELD) scores. In a retrospective cohort study alcoholic patients with Child–Pugh A/B were more susceptible to infection as compared to non-alcoholics (52/141 vs. 28/122 $p < 0.02$) [8]. Previous infection is a general risk factor for new infection [10]. Bacterial infections occur in about 45% of patients admitted with gastrointestinal bleeding [11].

Statements 1.a

- The prevalence of bacterial infections in hospitalized cirrhotic patients is at least 30% (I).
- The risk of bacterial infection is higher in Child C than in Child A/B cirrhosis or in case with MELD > 15 (I).
- In the setting of Child A/B cirrhosis, alcohol abuse entails a high risk of bacterial infections (II).
- Other risk factors are history of previous infection and gastrointestinal bleeding (II).

Question 1.b

What are the clinical manifestations of bacterial infections and what is the mortality associated with bacterial infections in patients with cirrhosis?

Comments. A variable proportion (from 14 to 25%) of infections are classified as spontaneous bacterial peritonitis due to different proportion of patients with ascites in the examined cohorts. Urinary tract infection, pneumonia and bacteraemia represent 20%, 15% and 12% of infections, respectively, while soft tissue infections had a lower and variable prevalence [6,7,10–12].

A systematic review by meta-analysis showed a pooled odds-ratio for death in infected versus non-infected patients with cirrhosis of 3.75 (95% CI 2.12–4.23) [4]. In the two Italian studies the in-hospital mortality in patients with cirrhosis was 16–19% among those with infections and 7–10% among those without, respectively [6,7].

Statements 1.b

- The most common bacterial infections are spontaneous bacterial peritonitis, urinary tract infections, cellulitis, pneumonia and bacteraemia (II).
- Infections increase mortality by at least 3-fold in cirrhosis; 30% of infected patients will eventually die within 1 month after infection and another 30% by 1 year (I).

Question 1.c

What are the most common bacterial agents responsible for infection in cirrhotic patients?

Comments. Bacteria of intestinal origin, particularly *Escherichia coli* are most often involved in community-acquired infections. Multidrug-resistant (MDR) gram-negative bacilli or MDR gram-positive cocci are increasingly frequent causative organisms in hospital and health care associated infections and in patients receiving quinolone prophylaxis. European epidemiological data show an increasing proportion of resistance to fluoroquinolones and third generation cephalosporins in some species of Enterobacteriaceae, including *E. coli* and *Klebsiella* species. [10–14].

Statements 1.c

- Bacteria of intestinal origin, particularly *E. coli* are most often involved in community-acquired infections.
- Methicillin-resistant Staphylococcus aureus (MRSA) is an increasingly MDR pathogen (II).

Question 1.d

How to detect infection in cirrhotic patients?

Statements 1.d

- Biological fluid cultures are the basic tests for the diagnosis of bacterial infections in cirrhotic patients and should be done in all patients in whom a bacterial infection is suspected.
- Whenever possible, cultures should be carried out before initiation of antibiotic therapy.
- Collection, analytical phases (direct and indirect identification, confirmation and susceptibility test) must be performed according to standard operating procedures (SOP). Results must be reported within predefined timelines [11] (IIIA).

2. EVALUATION OF THE RISK AND THE DIAGNOSIS OF INFECTION IN PATIENTS WITH COMPENSATED AND DECOMPENSATED CIRRHOSIS

Question 2.a

Which are the risk factors for specific pathogen and infectious disease syndromes?

Comment. A high risk of Spontaneous Bacterial Peritonitis (SBP) is observed in cirrhotic patients who have recovered from an episode of SBP and/or with a low (<1.5 g/dl) ascites protein [15]. The incidence of bacterial meningitis in cirrhotic patients is higher than in the general population and has a higher mortality rate [16]. Impaired renal function on admission is associated with increased mortality [16]. Bacteriuria is more common and seems to be associated with female gender and the degree of liver insufficiency (Child class C) [17]. Infectious endocarditis was reported in association with cirrhosis [18]; *Streptococcus bovis* endocarditis was associated with advanced liver disease [19]. Procedures such as tracheal intubation and oesophageal tamponade increase the risk of hospital-acquired pneumonia in cirrhotics [20–23]. Transjugular portosystemic shunts (TIPS) can be complicated by primary infection of the device (endotipsitis) or with TIPS-associated bacteraemia [24].

Statement 2.a

- An increased incidence of infections caused by several pathogens (see Table S2) have been described in case-control studies in cirrhotics (II).

Question 2.b

Are there specific risk factors for infections based on disease aetiology or treatment of chronic liver disease?

Comments. Patients with hemochromatosis have been reported to be at higher risk of acquiring *V. vulnificus* and of liver abscess in the presence of *Y. enterocolitica* infection [25–28]. Primary sclerosing cholangitis is a risk factor for ascending cholangitis especially after invasive procedures or in the presence of stones, strictures or cholangiocarcinoma [29,30]. Human immunodeficiency virus

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(HIV)-related bacterial and fungal infections are strongly associated with positive hepatitis C virus (HCV) serology and HCV-related cirrhosis; the risk is higher among patients with cirrhosis than among HCV antibody–positive patients without cirrhosis [31]. Treatment with pegylated interferon is associated with a higher risk of infection independently of occurrence of secondary neutropenia and in relationship with older age, diabetes, ribavirin induced lymphocytopenia and impaired liver function [32–36]. Preliminary data from French cohorts suggest that this risk could be increased by concomitant administration of first generation protease inhibitors (Telaprevir and Boceprevir) [37]. Patients with autoimmune hepatitis receiving steroid and/or immunosuppressive treatment seem to have an intermediate-high risk of bacterial and non-bacterial opportunistic infection especially invasive Aspergillosis [38,39]. An increased incidence of fungal infections has been reported in primary biliary cirrhosis [40,41]

Statements 2.b

- Hemochromatosis: higher risk of acquiring *V. vulnificus* and liver abscess from *Y. enterocolitica* infection (III).
- Primary sclerosing cholangitis: risk factor for ascending cholangitis especially after invasive procedures or in the presence of stones, strictures or cholangiocarcinoma (III).
- Autoimmune hepatitis: intermediate-high risk of bacterial and non-bacterial opportunistic infection (III).
- Primary biliary cirrhosis: increased incidence of fungal infections (III).
- HCV infection: HIV-related bacterial and fungal infections are strongly associated with positive HCV serology and HCV-related cirrhosis (II).
- Treatment with pegylated interferon is associated with a higher risk of infection (II); this risk could be increased by concomitant administration of first generation protease inhibitors (Telaprevir and Boceprevir) (III).

Question 2.c

Is gastric acid suppression by proton pump inhibitors (PPI) associated with an increased risk of infection?

Comments. A systematic review with meta-analysis shows an association between the use of PPI and the development of SBP (OR 2.77 95% CI 1.82–4.23) [42]. The association with *Clostridium difficile* (CD) infections seems less evident in a recent meta-analysis (OR 1.65 95% CI 1.47–1.85 with significant heterogeneity and evidence of publication bias) challenging a previous case control study [43,44].

Statements 2.c

- Proton pump inhibitors (PPIs) have been associated with an increased incidence of SBP and CD infection in patients with cirrhosis (II).
- PPIs should be used with caution in patients with cirrhosis and limited to those patients with evidence-based indications for peptic diseases (III B).

Question 2.d

Which signs and symptoms suggest an infection in patients with cirrhosis, especially if decompensated?

Comments. A high level of suspicion of bacterial infection is recommended on the basis of higher incidence and risk of complications and mortality in cirrhotic patients; the definition of systemic inflammatory response syndrome (SIRS) and sepsis are particularly difficult due to the following findings [7,45–47]: reduced baseline polymorphonuclear cell count due to hypersplenism; elevated baseline heart rate due to hyperdynamic circulatory syndrome; hyperventilation due to hepatic encephalopathy; blunted elevation of body temperature is often observed in cirrhotic patients.

Statements 2.d

An infection should be suspected in the presence of the classic general and local symptoms or of one of the following signs (II):

- new onset of porto-systemic encephalopathy without obvious causes;
- worsening of renal function;
- increase of white blood cell (WBC) count; and
- worsening of liver function tests.

Question 2.e

Which is the diagnostic workup in cirrhotic patients with a suspected infection?

Statements 2.e

- Identification of symptoms and signs of SIRS, severe sepsis or septic shock [47] (I A).
- Assessment of organ function.
- Identification of source of infection by blood and urine culture, and chest X-ray.
- Paracentesis is recommended at admission in all hospitalized patients with ascites (I A) as well as ascitic fluid neutrophil count; culture of ascitic fluid (10 mL in a blood culture bottle at bedside) for bacteria [48–50].
- Culture and Gram staining of sputum in the presence of symptoms or positive chest X-ray (III A).
- Ultrasonography in case of abdominal symptoms (III B).
- Stool culture and Clostridium toxin assay in case of gastrointestinal symptoms (III B).
- Wound culture and cerebrospinal fluid (CSF) culture when indicated (III B).
- If fungal infection is suspected, and in all patients assuming steroids or immunosuppressive drugs, galactomannan in sputum or bronchio-alveolar lavage (BAL) and cryptococcal serum antigen should be assayed and chest high-resolution CT (HRCT) should be considered (III B).

Question 2.f

What is the most appropriate approach to the diagnosis of fever of unknown origin (FUO) in cirrhosis?

Comments. FUO is classically defined as fever exceeding 38.3 °C on several occasions of more than 3-week duration which can also be nosocomially acquired and caused by neutropenia. Causes are manifold and include infectious, rheumatic/inflammatory, neoplastic and miscellaneous disorders, including cirrhosis. Fever is often of low-grade, protracted, unaccompanied by focal signs and symptoms, and less likely to be associated with tachycardia and tachypnea than in patients with infections. In small series of patients the origin of fever remained unknown and was attributed to cirrhosis itself in up to 20% of cases [51–54].

Statements 2.f

- An extensive diagnostic approach is recommended to rule out a wide variety of disorders responsible of FUO. A thorough history, physical examination, and standard laboratory testing is the basis of the initial evaluation of FUO (IIIA).
- Empiric therapy for FUO should be discouraged except in critically ill patients (IIIA).
- Cirrhotic patients may have infections without fever (III).

Question 2.g

Which is the value of markers of infections and of prognostic scores in patients with cirrhosis?

Comments. C-reactive protein (CRP) is a reliable marker of bacterial infections in cirrhosis. However, the accuracy of CRP decreases in advanced disease or in the presence of ascites. The

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combination of CRP with pro-calcitonin (PCT) slightly increases the diagnostic accuracy. Elevated CRP level in patients without overt infection, is a useful predictor of clinically significant bacterial infections in the next weeks or months [55–58].

Statements 2.g

- Elevated CRP level in patients without overt infection, is a useful predictor of clinically significant bacterial infections (II B).
- General models for assessing outcome in critically ill cirrhotic patients (i.e. Acute Physiology and Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA), organ failure score (OFS)) are superior to Child–Pugh score of liver function and comparable to MELD score for prediction of infection outcome (II A).

3. PROPHYLAXIS OF INFECTIONS IN PATIENTS WITH CIRRHOSIS

Question 3.a

Antibiotic prophylaxis: when and for whom is it appropriate?

Comments. Trials on long-term antibiotic prophylaxis are hampered by potential publication bias, poor methodology, small sample size and limited follow-up periods [9,59–61]. More importantly, these studies are often older than 20 years, and therefore performed in a setting whose microbiological and antibiotic-resistance patterns may be different from the current clinical scenario, making these results scarcely applicable nowadays.

Statement 3.a

Given the inevitable risk of developing resistant organisms, the use of prophylactic antibiotics must be rigorously restricted to those patients at highest risk of developing SBP or other bacterial infections (III A).

Question 3.b.

Should antibiotic prophylaxis be adopted in case of upper gastrointestinal bleeding?

Comments. The incidence of bacterial infections, including SBP, ranges between 25% and 65% in patients with gastrointestinal bleeding [62–66] being higher in patients with advanced cirrhosis and/or severe haemorrhage [64,65]. In addition, the presence of bacterial infection in patients with variceal haemorrhage is associated with an increased rate of failure to control bleeding [63,64,67,68] and hospital mortality [65,68–70]. A meta-analysis [65] of five studies performed in patients with gastrointestinal bleeding has shown that antibiotic prophylaxis significantly decreased both the incidence of severe infections (SBP and/or septicaemia) and mortality. A study comparing oral norfloxacin to intravenous ceftriaxone for the prophylaxis of bacterial infection in patients with gastrointestinal bleeding and advanced cirrhosis (as defined by at least 2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin >3 mg/dl) showed that ceftriaxone was more effective than norfloxacin in preventing infections [71].

Statements 3.b

- Short-term antibiotic prophylaxis is standard of care for patients with cirrhosis presenting with upper gastrointestinal bleeding and should be instituted immediately at admission (I A).
- Available data does not allow to establish the best regimen for antibiotic prophylaxis (IA).
- The choice of the antibiotic regimen should be based according to the patient clinical characteristics and the local pattern of antibiotic resistances (I A).
- However, i.v. third-generation cephalosporins may be preferentially used in patients with advanced cirrhosis, in hospital settings with high prevalence of quinolone-resistant bacterial infections and in patients on quinolone prophylaxis (II B).

Question 3.c

Should antibiotic prophylaxis be adopted in patients with prior spontaneous bacterial peritonitis (secondary prophylaxis)?

Comments. Norfloxacin has been shown to reduce the probability of recurrence of SBP from 68% to 20% and the probability of SBP due to Gram negative bacteria (GNB) from 60% to 3%. Survival benefits could not be determined by the study as prophylaxis therapy was discontinued at 6 months.

Three other randomized trials of inferior quality have shown a significant decrease in the incidence SBP with antibiotic prophylaxis conducted with norfloxacin, ciprofloxacin and trimethoprim-cotrimoxazole. It is not clear whether prophylaxis should be continued until transplantation or resolution of ascites.

Statements 3.c

- Long-term antibiotic prophylaxis is recommended in patients with prior SBP (I A).
- Prophylaxis should be instituted after completion of antibiotic therapy for acute SBP, but its duration is unknown (I A).
- Norfloxacin (400 mg/day) is the first-choice regimen (I A). Ciprofloxacin (750 mg once week) and trimethoprim-cotrimoxazole (1 g/day for 5 days/week) may represent an alternative to norfloxacin, but these antimicrobials present a pattern of resistance very similar to that of norfloxacin (I B).
- The efficacy of prophylaxis with oral quinolones in patients with a documented episode of SBP caused by Gram-positive bacteria or by quinolone-resistant Gram-negative bacteria is questionable (III B). At present, no data support the use of other regimens.

Question 3.d

When should primary antibiotic prophylaxis against SBP be adopted?

Comments. Cirrhotic patients with low ascitic fluid protein concentration (<10 g/L) and/or high serum bilirubin levels are at risk of developing a first episode of SBP [2,72].

Of four trials aimed at assessing the beneficial effect of norfloxacin prophylaxis in patients at risk of a first episode of SBP, all demonstrated a reduced incidence of infections due to Gram negative bacteria, three demonstrated a lower incidence of SBP and two demonstrated a favourable impact on survival and/or occurrence of hepatorenal syndrome. Nevertheless in one study prophylaxis induced a higher resistance of the intestinal flora to norfloxacin [73–76].

Statements 3.d

Antibiotic prophylaxis in patients with no prior history of SBP is indicated when ascitic fluid protein content is <15 g/L and at least one of the following negative prognostic factors is present (I A):

a) severe liver failure (Child–Pugh ≥ 9 with bilirubin ≥ 3 mg/dL);
b) renal failure (creatinine ≥ 1.2 mg/dL and Blood Urea Nitrogen (BUN) ≥ 25 mg/dL);
c) moderate hyponatremia (serum sodium ≤ 130 mEq/L); and
d) Norfloxacin 400 mg/day is the suggested regimen (IA).

- The duration of prophylaxis is unknown (III).
- The efficacy of primary prophylaxis in reducing SBP and improving survival, in patients with ascitic fluid protein content < 15 g/L and none of the negative prognostic factors listed above, is less clear. Oral quinolones (norfloxacin 400 mg/day or ciprofloxacin 500 mg/day) are the preferred regimes (IB).
- Trimethoprim/cotrimoxazole (1 g/day for 5 days/week) may represent an alternative regimen (IIB).

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Question 3.e

Which vaccinations should be recommended in patients with cirrhosis?

Comments. Acute hepatitis A is associated with increased mortality and morbidity in patients with cirrhosis [77,78]. The safety and tolerability of hepatitis A virus (HAV) vaccination appear to be similar to those of the general population [78–82].

Hepatitis B is associated with increased morbidity and mortality compared with patients with cirrhosis of other aetiologies [83,84]. The safety and tolerability of hepatitis B virus (HBV) vaccination appear to be similar to those of the general population [85–91].

Influenza is associated with an increased morbidity and mortality in patients with cirrhosis [27,82,92–95]. The safety and tolerability of vaccination against influenza appear to be similar to those of the general population [96–99].

Infections related to *Streptococcus pneumoniae* are associated with greater morbidity and mortality in patients with cirrhosis and antibiotic resistance to Pneumococcus is increasing. The safety and tolerability of vaccination against Pneumococcus appear to be similar to those of the general population. A novel conjugated 13-valent vaccine is now available on the market. Future strategies of vaccination will include a sequential schedule of vaccination consisting in the administration of a dose of the 13-valent conjugated vaccine followed by the 23-valent vaccine given three months apart [82,100–104].

Overall, the immunological response is reduced, especially in advanced cirrhotic disease, but it is still sufficient to induce protection in the majority of cases.

Statements 3.e

- Screening and vaccination are recommended in susceptible cirrhotic patients for:
  a) Hepatitis A virus (IIIA)
  b) Hepatitis B virus (IIIA)
- Patients should be preferably vaccinated in the initial stage of cirrhosis and the antibody sero-conversion should be verified after vaccination (IIIB). In case of failure of response to anti-HBV vaccination an additional dose of vaccine may be administered (IIIB).
- Vaccinations are also indicated in cirrhotic patients for:
  a) Seasonal Influenza virus regardless of age (III A). Vaccination should be extended to household contacts and to healthcare workers (III B)
  b) Pneumococcus (III B). Vaccination currently consists of a single administration of a 23-valent vaccine, with a suggested recall every 5 years (III B).

4. FIRST LINE TREATMENT OF BACTERIAL INFECTIONS IN CIRRHOTIC PATIENTS AND MANAGEMENT OF TREATMENT FAILURES

Question 4.a

What are the best empirical therapeutic approaches to SBP?

Statements 4.a

- SBP is mainly caused by Enterobacteriaceae in cirrhotic patients. Empirical therapy is based on 3rd generation cephalolosporins. Cefotaxime 2 g bid for 5 days is as effective as higher dosages and longer treatments but is not superior to other cephalosporins (II A).
- Orally or intravenously administered quinolones have shown the same efficacy as cephalosporins, even though in studies characterized by a low statistical power (II A).
- Quinolones should be avoided if previous prophylaxis with norfloxacin had been instituted (II A).
- Aminoglycosides should be avoided for risk of renal toxicity (II A).

Question 4.b

In case of infection other than spontaneous bacterial peritonitis what is the recommended empirical treatment?

Comments. SBP either community or nosocomially acquired, is among the most common bacterial infections in cirrhotic patients and, therefore, empirical treatment should be oriented towards treatment of SBP. It must be differentiated from secondary peritonitis, which should be treated surgically. Diagnosis is based on polymorph nuclear leucocyte (PMN) count in ascitic fluid (>250 mm^{-3}) and/or positive cultures. The principal pathogens involved are Enterobacteriaceae followed by Streptococcus and Staphylococcus spp. It should be emphasized that no meta-analysis of published clinical trials on SBP treatment could be performed because too many different drugs were used, with different comparators, at different doses and duration of treatment. Epidemiological data on quinolone-resistant and extended-spectrum β-lactamase (ESBL)-producer strains of Enterobacteriaceae in SBP are missing in cirrhotic patients. The use of cephalosporins in severe infections, especially as mono-therapy, is not supported by large prospective studies and should be discouraged. In case of ESBL-producing enterobacteria carbapenem or tigecycline may be used, although the latter reaches lower serum concentrations than in the ascitic fluid, making it less effective in treating bacteraemia. Whenever possible, the extensive use of carbapenems in hospitals should be discouraged to avoid the emergence of resistant strains. Combinations of drugs still active against ESBL – or class C (Beta lactamase) (AmpC)-producing enterobacteria - should be used.

Statement 4.b

Patients with bacterial infections other than SBP should be treated according to specific guidelines for single infections (e.g., pneumonia, Surgical Site tract infections (SSTI), Urinary Tract Infection (UTI), etc. and local epidemiology of bacterial resistance (III A).

Question 4.c

When should antimicrobial treatment failure be suspected and what are the most frequent causes?

Comments. The most common scenario for antimicrobial treatment failure (ATF) is empirical antimicrobial treatment, although it may also develop under targeted therapy. Empirical ATF is usually associated with narrow antimicrobial coverage. Inappropriate pathogen coverage is probably the major cause of ATF. The true incidence of ATF in cirrhosis is extremely difficult to estimate because no consensus definition is available. Causes include altered pharmacokinetics due to chronic liver failure and portal hypertension which may alter absorption and distribution of orally administered drugs, expansion of the extracellular fluid compartment due to low serum albumin and ascites which may increase the volume of distribution of hydrophilic antimicrobials, whereas reduced first-pass metabolism and/or total hepatic biotransformation may increase exposure to and decrease clearance of lipophilic antimicrobials [6,105–109].

Statement 4.c

- Failure of antibiotic therapy should be suspected if there is worsening of clinical signs or no improvement in clinical symptoms and signs and/or no marked reduction or increase in ascitic fluid neutrophil count compared to levels at diagnosis. Failure of antibiotic therapy is usually due to resistant microorganism(s) and/or secondary peritonitis (I A).

Question 4.d

How should treatment be adjusted in case of suspected antimicrobial treatment failure?

Comments. In case of ESBL or AmpC producers, carbapenems or tigecycline (except if bacteraemia is suspected or defined) may

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be used, alternatively piperacillin/tazobactam at higher doses and prolonged infusion, alone or in association may be used, especially if minimal inhibitory concentration (MIC) is ≤4 mg/L.

Statements 4.d

- In case of failure of the initial treatment with cephalolosporins, combination therapy with carbapenems plus glycopeptide or tigecycline, may be recommended (III B).
- Glycopeptides or tigecycline or linezolid may be used in case of isolation of MRSA *Staphylococcus aureus* or resistant enterococci (III C).
- In cirrhotic patients the loading dose of hydrophilic antimicrobials should be increased, whereas the maintenance dose of highly extracted lipophilic agents should be reduced, according to Child–Pugh score (III B). In addition, switch from intravenous to oral treatment in patients with hypertensive gastropathy should be considered with caution [110–115] (III B).

5. INFECTIONS ASSOCIATED WITH INVASIVE PROCEDURES

Question 5.a

Is there evidence of higher risk of Surgical Site Infections in cirrhotic patients?

Comments. Based on the high prevalence of infections and related mortality rate in cirrhotic patients undergoing abdominal (as well extra-abdominal) surgery, particular attention should be paid to the clinical management of these patients. Literature data of risk of SSI in cirrhosis is limited to a single report showing no evidence of higher risk compared to the general patient population [116].

Statement 5.a

- At present there is no evidence supporting a need for a different schedule of perioperative prophylaxis in cirrhotic patients. It is recommended to adhere to current Italian (PNLG 2008) guidelines for perioperative prophylaxis. Further scientific efforts in this setting are required in the near future (III B).

Question 5.b

What is the risk of infection in patients with End-Stage Liver Disease (ESLD) undergoing Endoscopic Retrograde Cholangio-Pancreatography (ERCP)? What are the indications to antibiotic prophylaxis in this setting?

Comments. In a meta-analysis the benefit of antibiotic prophylaxis in case of resolution of biliary obstruction at the first procedure is imprecisely estimated and not demonstrated as statistically significant (RR 0.98, 95% CI 0.35–2.69) [117]. Assessing infective risk for invasive diagnostic and therapeutic procedures in ESLD is important. The most frequently involved procedures are: central venous catheter access, hepatic venous pressure gradient measurement, trans jugular liver biopsy, trans jugular intrahepatic porto-systemic shunt, pleural drainage, trans arterial chemoembolization (TACE), loco-regional percutaneous ablative procedures (radio frequency thermal ablation (RFTA), PEI).

Statements 5.b

- ERCP is a procedure carrying a high risk of infectious cholangitis, bacteraemia and pancreatitis in the general population; however there are no studies in the literature addressing the risk of infection in patients with ESLD. Antibiotic prophylaxis for patients undergoing elective ERCP prevents cholangitis, septicaemia, bacteraemia and pancreatitis but has no impact on overall reduction in mortality [27,118] (I).
- The beneficial effect of antibiotic prophylaxis on prevention of cholangitis was not demonstrated in patients in whom ERCP resolved the biliary obstruction at the first procedure (I).
- Cefotaxime, piperacillin, cefonicid, cefuroxime, minocycline show similar results and should be administered 30–60 min as a single dose prior to the procedure [117] (I A).

Question 5.c

Are patients with cirrhosis at major risk of Catheter-Related Blood Stream Infections (CR-BSI)? Which prevention measures should be adopted?

Comments. No specific epidemiological data are available from cohorts of patients with end stage liver disease. Central venous catheters medicated with anti-infective agents have shown a significant advantage in preventing CR-BSI (IA) but there is no evidence supporting their use in cirrhotic patients [119].

Statements 5.c

- Patients who are more susceptible to infections are more prone to develop severe CR-BSI.
- For insertion and management of central vein catheter (CVC) it is recommended to adhere to the Infectious diseases society of America (IDSA) guidelines [120] (I A).

Question 5.d

Should antibiotic prophylaxis be adopted for infections associated with positioning a Transjugular Intrahepatic Porto-systemic Shunt (TIPS)?

Statements 5.d

- The use of prophylactic antibiotics during the initial TIPS procedure is controversial; however, despite the lack of beneficial evidence, prophylaxis is the common practice to reduce procedural infection (III).
- Endotipsitis develops a median of 100 day following the procedure but there is no evidence supporting prophylaxis in prevention of infectious complications in this setting (III B).
- Ceftriaxone 1 g. should be given i.v. before the procedure. Alternatively, ampicillin/sulbactam 1.5–3 g. i.v. may be used (III B).
- Removal of central venous catheter after TIPS insertion must be considered if not strictly necessary [121,122] (III B).

Question 5.e

Should antibiotic prophylaxis be adopted prior to loco-regional treatments of liver tumours?

Comments. Previous radiological, endoscopic or surgical procedures on the biliary tree have been shown to increase the risk of abscess formation [123].

Statements 5.e

In high risk patients antibiotic prophylaxis together with bowel decontamination should be used [124,125] (II B).

Optimal schedule is not yet defined. In case of percutaneous ethanol injection (PEI) or radiofrequency thermal ablation (RFA), the risk of abscess formation is extremely low [123,126,127] (I) and no prophylaxis is recommended (III C).

6. LIVER TRANSPLANTATION

Question 6.a

Is there a role for prophylaxis of fungal and viral infections (excluding HBV) in liver transplant candidates?

Comments. Invasive fungal infections (IFIs) are important causes of morbidity and mortality in solid organ transplant recipients. A meta-analysis of 10 randomized trials of antifungal prophylaxis

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in 1106 liver transplant (LT) recipients revealed that antifungal prophylaxis did not reduce mortality, although fluconazole prophylaxis decreased invasive fungal infections by 75% [128,129].

Statement 6.a

- Based on current available data prophylaxis of fungal and viral infections is not recommended in liver transplant candidates (III C).

Question 6.b

Should a surveillance of infections in liver transplant candidates be performed while in the waiting list?

Statement 6.b

- During wait-listing periodical surveillance for infectious risk may be advisable (III C).

Question 6.c

Which is the proper infectious management in patients while in the waiting list?

Statements 6.c

- Any clinical sign of an infectious disease in liver transplant candidates on the waiting list should be investigated (III B).
- Any infectious event must be notified to the Liver Transplant centre and the patient might be temporarily suspended from the list until complete resolution is achieved, according to the multidisciplinary transplant team decision (III B).
- In case of MDR bacteria colonization/infection, eligibility to LT should be reconsidered by the team, on a case-by-case basis (III B).

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2013.07.015.

References [2]

[1] Bajaj JS, O'Leary JG, Wong F, et al. Bacterial infections in end-stage liver disease: current challenges and future directions. Gut 2012;61:1219–25.
[2] Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Gastroenterology 2001;120:726–48.
[3] Navasa M, Rodes J. Bacterial infections in cirrhosis. Liver International 2004;24:277–80.
[4] Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010;139:1246–56, e1–5.
[5] Perdomo Coral G, Alves de Mattos A. Renal impairment after spontaneous bacterial peritonitis: incidence and prognosis. Canadian Journal of Gastroenterology 2003;17:187–90.
[6] Borzio M, Salerno F, Piantoni L, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. Digestive and Liver Disease 2001;33:41–8.
[7] Fasolato S, Angeli P, Dallagnese L, et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. Hepatology 2007;45:223–9.
[8] Rosa H, Silverio AO, Perini RF, et al. Bacterial infection in cirrhotic patients and its relationship with alcohol. American Journal of Gastroenterology 2000;95:1290–3.
[9] Fernandez J, Navasa M, Gomez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology 2002;35:140–8.
[10] Merli M, Lucidi C, Giannelli V, et al. Cirrhotic patients are at risk for health care-associated bacterial infections. Clinical Gastroenterology and Hepatology 2010;8:979–85.
[11] Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Seminars in Liver Disease 2008;28:26–42.
[12] Fernandez J, Acevedo J, Castro M, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012;55:1551–61.
[13] Gustot T, Durand F, Lebrec D, et al. Severe sepsis in cirrhosis. Hepatology 2009;50:2022–33.
[14] Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. Journal of Hepatology 2000;32:142–53.
[15] Guarner C, Sola R, Soriano G, et al. Risk of a first community-acquired spontaneous bacterial peritonitis in cirrhotics with low ascitic fluid protein levels. Gastroenterology 1999;117:414–9.
[16] Barahona-Garrido J, Hernandez-Calleros J, Tellez-Avila FI, et al. Bacterial meningitis in cirrhotic patients: case series and description of the prognostic role of acute renal failure. Journal of Clinical Gastroenterology 2010;44:e218–23.
[17] Cadranel JF, Denis J, Pauwels A, et al. Prevalence and risk factors of bacteriuria in cirrhotic patients: a prospective case–control multicenter study in 244 patients. Journal of Hepatology 1999;31:464–8.
[18] Snyder N, Atterbury CE, Pinto Correia J, et al. Increased concurrence of cirrhosis and bacterial endocarditis. A clinical and postmortem study. Gastroenterology 1977;73:1107–13.
[19] Tripodi MF, Adinolfi LE, Ragone E, et al. *Streptococcus bovis* endocarditis and its association with chronic liver disease: an underestimated risk factor. Clinical Infectious Diseases 2004;38:1394–400.
[20] Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. American Journal of Respiratory and Critical Care Medicine 2001;163:1730–54.
[21] Falguera M, Trujillano J, Caro S, et al. A prediction rule for estimating the risk of bacteremia in patients with community-acquired pneumonia. Clinical Infectious Diseases 2009;49:409–16.
[22] Yang YY, Lin HC. Bacterial infections in patients with cirrhosis. Journal of the Chinese Medical Association 2005;68:447–51.
[23] Mehta G, Rothstein KD. Health maintenance issues in cirrhosis. Medical Clinics of North America 2009;93:901–15, viii–ix.
[24] Passeron A, Mihaila-Amrouche L, Perreira Rocha E, et al. Recurrent enterococcal bacteremia associated with a transjugular intrahepatic protosystemic shunt. Gastroentérologie Clinique et Biologique 2004;28:1284–6.
[25] Khan FA, Fisher MA, Khakoo RA. Association of hemochromatosis with infectious diseases: expanding spectrum. International Journal of Infectious Diseases 2007;11:482–7.
[26] Ashrafian H. Hepcidin: the missing link between hemochromatosis and infections. Infection and Immunity 2003;71:6693–700.
[27] Brann OS. Infectious complications of cirrhosis. Current Gastroenterology Reports 2001;3:285–92.
[28] Mennecier D, Lapprand M, Hernandez E, et al. Liver abscesses due to Yersinia pseudotuberculosis discloses a genetic hemochromatosis. Gastroentérologie Clinique et Biologique 2001;25:1113–5.
[29] Melzer M, Toner R, Lacey S, et al. Biliary tract infection and bacteraemia: presentation, structural abnormalities, causative organisms and clinical outcomes. Postgraduate Medical Journal 2007;83:773–6.
[30] Pohl J, Ring A, Stremmel W, et al. The role of dominant stenoses in bacterial infections of bile ducts in primary sclerosing cholangitis. European Journal of Gastroenterology & Hepatology 2006;18:69–74.
[31] d'Arminio Monforte A, Cozzi-Lepri A, Castagna A, et al. Risk of developing specific AIDS-defining illnesses in patients coinfected with HIV and hepatitis C virus with or without liver cirrhosis. Clinical Infectious Diseases 2009;49:612–22.
[32] Antonini MG, Babudieri S, Maida I, et al. Incidence of neutropenia and infections during combination treatment of chronic hepatitis C with pegylated interferon alfa-2a or alfa-2b plus ribavirin. Infection 2008;36:250–5.
[33] Roomer R, Hansen BE, Janssen HL, et al. Risk factors for infection during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. Hepatology 2010;52:1225–31.
[34] Roche B, Samuel D. Antiviral therapy in HCV-infected cirrhotics awaiting liver transplantation: a costly strategy for mixed virological results. Journal of Hepatology 2009;50:652–4.
[35] Carrion JA, Martinez-Bauer E, Crespo G, et al. Antiviral therapy increases the risk of bacterial infections in HCV-infected cirrhotic patients awaiting liver transplantation: a retrospective study. Journal of Hepatology 2009;50:719–28.
[36] Iacobellis A, Siciliano M, Annicchiarico BE, et al. Sustained virological responses following standard anti-viral therapy in decompensated HCV-infected cirrhotic patients. Alimentary Pharmacology & Therapeutics 2009;30:146–53.
[37] Hezode C, Dorival C, Zoulim F, et al. Safety of Telaprevir or Boceprevir in Combination with Peginterferon alfa/Ribavirin, in Cirrhotic Non Responders. First Results of the French Early Access Program (ANRS CO20-CUPIC). In: 47th Annual Meeting of the European Association for the Study of the Liver (EASL). Volume 56: Journal of Hepatology: S4. 2012.

[2] Additional references are supplied as supplemental material (see Appendix C).

[38] Russo A, Falcone M, Vena A, et al. Invasive pulmonary aspergillosis in non-neutropenic patients: analysis of a 14-month prospective clinical experience. Journal of Chemotherapy 2011;23:290–4.
[39] Falcone M, Massetti AP, Russo A, et al. Invasive aspergillosis in patients with liver disease. Medical Mycology 2011;49:406–13.
[40] Melero JL, Bastida G, Yago M, et al. Fungal liver abscesses in a patient with primary sclerosing cholangitis and Crohn's disease. Gastroenterology and Hepatology 2008;31:576–9.
[41] Kulaksiz H, Rudolph G, Kloeters-Plachky P, et al. Biliary candida infections in primary sclerosing cholangitis. Journal of Hepatology 2006;45:711–6.
[42] Trikudanathan G, Israel J, Cappa J, et al. Association between proton pump inhibitors and spontaneous bacterial peritonitis in cirrhotic patients – a systematic review and meta-analysis. International Journal of Clinical Practice 2011;65:674–8.
[43] Bajaj JS, Ananthakrishnan AN, Hafeezullah M, et al. Clostridium difficile is associated with poor outcomes in patients with cirrhosis: A national and tertiary center perspective. American Journal of Gastroenterology 2010;105:106–13.
[44] Tleyjeh IM, Bin Abdulhak AA, Riaz M, et al. Association between proton pump inhibitor therapy and clostridium difficile infection: a contemporary systematic review and meta-analysis. PLoS ONE 2012;7:e50836.
[45] Cazzaniga M, Dionigi E, Gobbo G, et al. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. Journal of Hepatology 2009;51:475–82.
[46] Wong F, Bernardi M, Balk R, et al. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. Gut 2005;54:718–25.
[47] Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Critical Care Medicine 2008;36:296–327.
[48] Runyon BA, Canawati HN, Akriviadis EA. Optimization of ascitic fluid culture technique. Gastroenterology 1988;95:1351–5.
[49] Nguyen-Khac E, Cadranel JF, Thevenot T, et al. Review article: the utility of reagent strips in the diagnosis of infected ascites in cirrhotic patients. Alimentary Pharmacology & Therapeutics 2008;28:282–8.
[50] Mendler MH, Agarwal A, Trimzi M, et al. A new highly sensitive point of care screen for spontaneous bacterial peritonitis using the leukocyte esterase method. Journal of Hepatology 2010;53:477–83.
[51] Cunha BA. Fever of unknown origin: clinical overview of classic and current concepts. Infectious Disease Clinics of North America 2007;21: 867–915, vii.
[52] Roth AR, Basello GM. Approach to the adult patient with fever of unknown origin. American Family Physician 2003;68:2223–8.
[53] Lorenzen J, Buchert R, Bohuslavizki KH. Value of FDG PET in patients with fever of unknown origin. Nuclear Medicine Communications 2001;22:779–83.
[54] Mandell G, Bennett J, Dolin R. Principles and practice of infectious diseases. 5th ed. New York: Churchill Livingstone; 2000. p. 622–31.
[55] Papp M, Vitalis Z, Altorjay I, et al. Acute phase proteins in the diagnosis and prediction of cirrhosis associated bacterial infections. Liver International 2012;32:603–11.
[56] Li CH, Yang RB, Pang JH, et al. Procalcitonin as a biomarker for bacterial infections in patients with liver cirrhosis in the emergency department. Academic Emergency Medicine 2011;18:121–6.
[57] Elefsiniotis IS, Skounakis M, Vezali E, et al. Clinical significance of serum procalcitonin levels in patients with acute or chronic liver disease. European Journal of Gastroenterology & Hepatology 2006;18:525–30.
[58] Bota DP, Van Nuffelen M, Zakariah AN, et al. Serum levels of C-reactive protein and procalcitonin in critically ill patients with cirrhosis of the liver. Journal of Laboratory and Clinical Medicine 2005;146:347–51.
[59] Soriano G, Guarner C, Teixido M, et al. Selective intestinal decontamination prevents spontaneous bacterial peritonitis. Gastroenterology 1991;100:477–81.
[60] Singh N, Gayowski T, Yu VL, et al. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. Annals of Internal Medicine 1995;122:595–8.
[61] Campillo B, Dupeyron C, Richardet JP, et al. Epidemiology of severe hospital-acquired infections in patients with liver cirrhosis: effect of long-term administration of norfloxacin. Clinical Infectious Diseases 1998;26: 1066–70.
[62] Soriano G, Guarner C, Tomas A, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. Gastroenterology 1992;103:1267–72.
[63] Pauwels A, Mostefa-Kara N, Debenes B, et al. Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk of infection. Hepatology 1996;24:802–6.
[64] Deschenes M, Villeneuve JP. Risk factors for the development of bacterial infections in hospitalized patients with cirrhosis. American Journal of Gastroenterology 1999;94:2193–7.
[65] Bernard B, Grange JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology 1999;29:1655–61.
[66] Hou MC, Lin HC, Liu TT, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. Hepatology 2004;39:746–53.
[67] Goulis J, Armonis A, Patch D, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. Hepatology 1998;27:1207–12.
[68] Vivas S, Rodriguez M, Palacio MA, et al. Presence of bacterial infection in bleeding cirrhotic patients is independently associated with early mortality and failure to control bleeding. Digestive Diseases and Sciences 2001;46:2752–7.
[69] Soares-Weiser K, Brezis M, Tur-Kaspa R, et al. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. Cochrane Database of Systematic Reviews 2002. CD002907.
[70] Carbonell N, Pauwels A, Serfaty L, et al. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology 2004;40:652–9.
[71] Fernandez J, Ruiz del Arbol L, Gomez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology 2006;131:1049–56 [quiz 1285].
[72] Runyon BA. Low-protein-concentration ascitic fluid is predisposed to spontaneous bacterial peritonitis. Gastroenterology 1986;91:1343–6.
[73] Novella M, Sola R, Soriano G, et al. Continuous versus inpatient prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. Hepatology 1997;25:532–6.
[74] Grange JD, Roulot D, Pelletier G, et al. Norfloxacin primary prophylaxis of bacterial infections in cirrhotic patients with ascites: a double-blind randomized trial. Journal of Hepatology 1998;29:430–6.
[75] Fernandez J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818–24.
[76] Terg R, Fassio E, Guevara M, et al. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. Journal of Hepatology 2008;48:774–9.
[77] Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. New England Journal of Medicine 1998;338:286–90.
[78] Pramoolsinsap C, Poovorawan Y, Hirsch P, et al. Acute, hepatitis-A superinfection in HBV carriers, or chronic liver disease related to HBV or HCV. Annals of Tropical Medicine and Parasitology 1999;93:745–51.
[79] Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR – Recommendations and Reports 2006;55:1–23.
[80] Keeffe EB, Iwarson S, McMahon BJ, et al. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. Hepatology 1998;27:881–6.
[81] Lee SD, Chan CY, Yu MI, et al. Safety and immunogenicity of inactivated hepatitis A vaccine in patients with chronic liver disease. Journal of Medical Virology 1997;52:215–8.
[82] Loulergue P, Pol S, Mallet V, et al. Why actively promote vaccination in patients with cirrhosis? Journal of Clinical Virology 2009;46:206–9.
[83] Koff RS. Risks associated with hepatitis A and hepatitis B in patients with hepatitis C. Journal of Clinical Gastroenterology 2001;33:20–6.
[84] Yoneyama K, Miyagishi K, Kiuchi Y, et al. Risk factors for infections in cirrhotic patients with and without hepatocellular carcinoma. Journal of Gastroenterology 2002;37:1028–34.
[85] Wiedmann M, Liebert UG, Oesen U, et al. Decreased immunogenicity of recombinant hepatitis B vaccine in chronic hepatitis C. Hepatology 2000;31:230–4.
[86] Arslan M, Wiesner RH, Sievers C, et al. Double-dose accelerated hepatitis B vaccine in patients with end-stage liver disease. Liver Transplantation 2001;7:314–20.
[87] De Maria N, Idilman R, Colantoni A, et al. Increased effective immunogenicity to high-dose and short-interval hepatitis B virus vaccination in individuals with chronic hepatitis without cirrhosis. Journal of Viral Hepatitis 2001;8:372–6.
[88] Idilman R, De MN, Colantoni A, et al. The effect of high dose and short interval HBV vaccination in individuals with chronic hepatitis C. American Journal of Gastroenterology 2002;97:435–9.
[89] Aziz A, Aziz S, Li DS, et al. Efficacy of repeated high-dose hepatitis B vaccine (80 microg) in patients with chronic liver disease. Journal of Viral Hepatitis 2006;13:217–21.
[90] Pascasio JM, Aoufi S, Gash A, et al. Response to a vaccination schedule with 4 doses of 40 microg against hepatitis B virus in cirrhotic patients evaluated for liver transplantation. Transplantation Proceedings 2008;40:2943–5.
[91] Dhillon S, Moore C, Li SD, et al. Efficacy of high-dose intra-dermal hepatitis B virus vaccine in previous vaccination non-responders with chronic liver disease. Digestive Diseases and Sciences 2012;57:215–20.
[92] Rizzo C, Bella A, Viboud C, et al. Trends for influenza-related deaths during pandemic and epidemic seasons, Italy, 1969–2001. Emerging Infectious Diseases 2007;13:694–9.
[93] Duchini A, Hendry RM, Redfield DC, et al. Influenza infection in patients before and after liver transplantation. Liver Transplantation 2000;6:531–42.
[94] Song JY, Cheong HJ, Ha SH, et al. Clinical impact of influenza immunization in patients with liver cirrhosis. Journal of Clinical Virology 2007;39:159–63.
[95] Christou L, Pappas G, Falagas ME. Bacterial infection-related morbidity and mortality in cirrhosis. American Journal of Gastroenterology 2007;102:1510–7.
[96] Cheong HJ, Song JY, Park JW, et al. Humoral and cellular immune responses to influenza vaccine in patients with advanced cirrhosis. Vaccine 2006;24:2417–22.
[97] Soesman NM, Rimmelzwaan GF, Nieuwkoop NJ, et al. Efficacy of influenza vaccination in adult liver transplant recipients. Journal of Medical Virology 2000;61:85–93.

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[98] Gaeta GB, Stornaiuolo G, Precone DF, et al. Immunogenicity and safety of an adjuvanted influenza vaccine in patients with decompensated cirrhosis. Vaccine 2002;20(Suppl. 5):B33–5.
[99] Gaeta GB, Pariani E, Amendola A, et al. Influenza vaccination in patients with cirrhosis and in liver transplant recipients. Vaccine 2009;27:3373–5.
[100] Yu VL, Chiou CC, Feldman C, et al. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. Clinical Infectious Diseases 2003;37:230–7.
[101] Kyaw MH, Rose Jr CE, Fry AM, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. Journal of Infectious Diseases 2005;192:377–86.
[102] Bouza E, Pintado V, Rivera S, et al. Nosocomial bloodstream infections caused by Streptococcus pneumoniae. Clinical Microbiology and Infection 2005;11:919–24.
[103] McCashland TM, Preheim LC, Gentry MJ. Pneumococcal vaccine response in cirrhosis and liver transplantation. Journal of Infectious Diseases 2000;181:757–60.
[104] Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR – Recommendations and Reports 1997;46:1–24.
[105] Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila FI, et al. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. Cochrane Database of Systematic Reviews 2010. CD002907.
[106] EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. Journal of Hepatology 2010;53:397–417.
[107] Koulaouzidis A, Bhat S, Saeed AA. Spontaneous bacterial peritonitis. World Journal of Gastroenterology 2009;15:1042–9.
[108] Sheer TA, Runyon BA. Spontaneous bacterial peritonitis. Digestive Disease 2005;23:39–46.
[109] Delco F, Tchambaz L, Schlienger R, et al. Dose adjustment in patients with liver disease. Drug Safety 2005;28:529–45.
[110] Elbekai RH, Korashy HM, El-Kadi AO. The effect of liver cirrhosis on the regulation and expression of drug metabolizing enzymes. Current Drug Metabolism 2004;5:157–67.
[111] Frye RF, Zgheib NK, Matzke GR, et al. Liver disease selectively modulates cytochrome P450–mediated metabolism. Clinical Pharmacology & Therapeutics 2006;80:235–45.
[112] Edginton AN, Willmann S. Physiology-based simulations of a pathological condition: prediction of pharmacokinetics in patients with liver cirrhosis. Clinical Pharmacokinetics 2008;47:743–52.
[113] McConn 2nd DJ, Lin YS, Mathisen TL, et al. Reduced duodenal cytochrome P450 3A protein expression and catalytic activity in patients with cirrhosis. Clinical Pharmacology & Therapeutics 2009;85:387–93.
[114] Nguyen HM, Cutie AJ, Pham DQ. How to manage medications in the setting of liver disease with the application of six questions. International Journal of Clinical Practice 2010;64:858–67.
[115] Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. European Journal of Clinical Pharmacology 2008;64:1147–61.
[116] Millwala F, Nguyen GC, Thuluvath PJ. Outcomes of patients with cirrhosis undergoing non-hepatic surgery: risk assessment and management. World Journal of Gastroenterology 2007;13:4056–63.
[117] Brand M, Bizos D, O'Farrell Jr P. Antibiotic prophylaxis for patients undergoing elective endoscopic retrograde cholangiopancreatography. Cochrane Database of Systematic Reviews 2010. CD007345.
[118] Banerjee S, Shen B, Baron TH, et al. Antibiotic prophylaxis for GI endoscopy. Gastrointestinal Endoscopy 2008;67:791–8.
[119] Hockenhull JC, Dwan K, Boland A, et al. The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. Health Technology Assessment 2008;12, iii–iv, xi–xii, 1–154.
[120] O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR – Recommendations and Reports 2002;51:1–29.
[121] DeSimone JA, Beavis KG, Eschelman DJ, et al. Sustained bacteremia associated with transjugular intrahepatic portosystemic shunt (TIPS). Clinical Infectious Diseases 2000;30:384–6.
[122] Mizrahi M, Adar T, Shouval D, et al. Endotipsitis-persistent infection of transjugular intrahepatic portosystemic shunt: pathogenesis, clinical features and management. Liver International 2010;30:175–83.
[123] de Baere T, Risse O, Kuoch V, et al. Adverse events during radiofrequency treatment of 582 hepatic tumors. AJR American Journal of Roentgenology 2003;181:695–700.
[124] Geschwind JF, Kaushik S, Ramsey DE, et al. Influence of a new prophylactic antibiotic therapy on the incidence of liver abscesses after chemoembolization treatment of liver tumors. Journal of Vascular and Interventional Radiology 2002;13:1163–6.
[125] Patel S, Tuite CM, Mondschein JI, et al. Effectiveness of an aggressive antibiotic regimen for chemoembolization in patients with previous biliary intervention. Journal of Vascular and Interventional Radiology 2006;17:1931–4.
[126] Curley SA, Marra P, Beaty K, et al. Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients. Annals of Surgery 2004;239:450–8.
[127] Bouza C, Lopez-Cuadrado T, Alcazar R, et al. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. BMC Gastroenterology 2009;9:31.
[128] Playford EG, Webster AC, Sorrell TC, et al. Systematic review and meta-analysis of antifungal agents for preventing fungal infections in liver transplant recipients. European Journal of Clinical Microbiology & Infectious Diseases 2006;25:549–61.
[129] Playford EG, Webster AC, Sorell TC, et al. Antifungal agents for preventing fungal infections in solid organ transplant recipients. Cochrane Database of Systematic Reviews 2004. CD004291.

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