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Chapter III

Bacterial Infections in Cirrhosis

Zsuzsanna Vitalis and Maria Papp*
Institute of Medicine, Department of Gastroenterology,
University of Debrecen, Medical and Health Science Center,
Debrecen, Hungary

Abstract

Patients with cirrhosis are highly susceptible for bacterial infections and their severe courses. Infections occur more often in advanced stage of liver disease, impair hepatic function, trigger the onset of complications, and are significant factors of mortality as well. Gastrointestinal hemorrhage confers a higher risk for infections and infections play important role in provoking of variceal bleeding episodes and can also be associated with the failure to control bleeding. In the past, the dominant pathogens were Gram-negative bacteria, but nowadays participation of Gram-positive strains has been increasing. Occurrence of opportunistic bacteria is far from rare. Spreading of resistant organisms and appearance of *Clostridium difficile* associated disease related with higher mortality are increasing problem due to the consequence of repeated antibiotic treatment of recurring infections, multiple hospitalizations and use of long-term antibiotic prophylaxis. In cirrhosis, immunodeficiency is multifactorial and progresses with the disease severity. Thus bacteria commonly get into the circulation from the infection ports causing frequent and prolonged bacteremia. Circulating bacteria colonize and proliferate in different organs inducing secondary focal infections. Intestinal tract considered a significant portal of entry. Translocation of the gut microflora mainly related to the development of spontaneous bacterial peritonitis. It is reasonable to assume that spontaneous bacteremia leads to other systemic infections but this is yet to be outlined adequately. Identification of infectious episodes are challenging due to the lack of typical signs and courses up to fifty percent of the cases. Early recognition and effective treatment of infections are essential in decreasing the high mortality.

* Correspondence to: Maria Papp, M.D., Ph.D., 2nd Department of Medicine, Division of Gastroenterology, University of Debrecen, Nagyerdei krt. 98, H-4032 Debrecen, Hungary, Phone/Fax: 36-52-255-152, e-mail: papp.maria@med.unideb.hu.

List of Abbreviations

ACLF: acute-on-chronic liver failure
ARF: acute renal failure
BT: bacterial translocation
CIRCI: critical illness related corticosteroid insufficiency
CRP: C-reactive protein
CDAD: Clostridium difficile associated diseases
ESBL: extended-spectrum beta-lactamase
GNB: Gram-negative bacteria
GPC: Gram-positive cocci
HE: hepatic encephalopathy,
Hp: haptoglobin
HRS: hepatorenal syndrome
IE: infective endocarditis
LBP: lipopolysaccharide-binding protein
MALDI-TOF MS: Matrix Assisted Laser Desorption Ionization – Time of Flight Mass Spectometry
MBL: mannose-binding lectin
MRSA: methicillin-resistant *Staphylococcus aureus*
NSAID: non-steroidal anti-inflammatory drug
NOD2: nucleotid-binding oligomerization domain containing 2
PCT: procalcitonin
PMN: polymorphonuclear leukocyte/ neutrophil
RAI: relative adrenal insufficiency
RES: reticuloendothelial system
SBE: spontaneous bacterial empyema
SBP: spontaneous bacterial peritonitis
TLR: toll-like receptor
UTI: urinary tract infection
WBC: white blood cell

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Introduction

Association between cirrhosis and bacterial infections has been investigated intensively for a long time. Cirrhosis has been characterized as the commonest acquired immunodeficiency syndrome worldwide. Patients with cirrhosis are highly susceptible for bacterial infections and their severe forms. Moreover, infections aggravate the liver failure: impair liver functions and trigger the onset of various complications (coagulopathy,

hepatorenal syndrome, hepatic encephalopathy, variceal bleeding) and important causes of mortality [1]. Bacterial infections have been observed in 32-34% of the hospitalized cirrhotic patients [2]. Independent risk factors for bacterial infections are the advanced disease depicted by Child-Pugh stage [3, 4] presence of gastrointestinal hemorrhage [5] and existence of severe co-morbidity [6]. Approximately 20% of patients with upper gastrointestinal bleeding are already infected at admission, and 50% develop an infection during hospitalization [7]. On the other hand, there are convincing data that during infectious episodes the risk of variceal bleeding is four times higher and these episodes are often associated with the failure to control bleeding, predisposition of early rebleeding and increased mortality as well [8]. Accordingly, bacterial infections cannot only be the consequence, but also – at least partly - the cause of variceal rupture [9, 10]. Once infection develops, it adversely affects the survival. The in-hospital mortality of cirrhotic patients with infection is more than twice that of patients without infection. Infection is directly responsible for 30-50% of death in cirrhosis [2, 4]. During an on-going infection, the advanced cirrhosis, presence of renal failure and the hemodynamic instability are definitely bad prognostic factors.

Among patients with cirrhosis and bacterial infection some have "mere" decompensated cirrhosis while others exhibit decompensated cirrhosis associated with newly developed liver and/or extra-hepatic organ failure(s). Patients with cirrhosis and "acute" organ failure(s) are at high risk of short-term death. These patients are considered to have acute-on-chronic liver failure (ACLF) [11]. Recently published CANONIC study [12] provided a robust definition and grades of ACLF (grade 1-3). Establishment of ACLF grades is based on the numbers of organ failures and associated with increasing risk of short-term death from grade 1 (22%) to grade 3 (77%). Bacterial infections are the most common precipitating event of ACLF (33%). Among patients with bacterial infection, ACLF is more common in spontaneous bacterial peritonitis (SBP) or pneumonia than in those with infections of other sites.

In cirrhosis, during the last decades, dominant pathogens of bacterial infections were Gram-negative bacteria (GNB) of the normal intestinal flora, but recently the participation of Gram-positive cocci (GPC) has grown due to the invasive procedures and administration of the antibiotic prophylaxis. Nowadays, GNB and GPC account for about 50-50% of the infectious episodes [13, 14]. Spread of resistant organisms and the higher prevalence of Clostridium difficile associated diseases (CDAD) [15] is an imminent threat and significant cause of the mortality, especially in patients with multiple hospitalizations, antibiotic treatment for recurring infections or secondary prophylaxis of SBP. Widespread use of proton-pump inhibitors is also a risk factor for CDAD development in this patient population. Monitoring and early detection of CDAD is all the more important. It's worth to note, that opportunistic bacteria can also be isolated higher frequency [16].

About fifty percent of the infections present atypical clinical appearance [2]. Patients often have no fever; white blood cell (WBC) count alone is not informative because due to hypersplenia the basal WBC count may usually be lower than normal. Thus a WBC count in normal range should be considered as leukocytosis, mainly in otherwise leucopenic patients. In severe bacterial infections, nevertheless, the WBC count can reach extremely high level. Sometimes hepatic encephalopathy (HE) or hepatorenal syndrome (HRS) is the only sign of the infection. In cirrhosis, low blood pressure and elevated heart rate is usual as a result of hyperkinetic circulation, which are further modified by administration of non-selective beta-blockers to vast majority of patients. HE that is also a frequent complication during the

infectious episodes elevates the rate of breath. For these reasons, the application of classic criteria of sepsis has limitations in cirrhosis further delaying the diagnosis of sepsis [17]. To identify an infection in time, physicians should always think of its possible existence and seek for that thoroughly. Even in the absence of typical signs of infection, screening is highly recommended (C-reactive protein [CRP] and/or procalcitonin [PCT] [18], urine sediment, ascitic fluid polymorphonuclear [PMN] count, chest X-ray) in those patients who present a sudden impairment of the liver function, diuretic-resistant ascites, deteriorating renal function, increasing jaundice or encephalopathy. Further thoughtfulness required to localize the infection and to find the causative microbe(s). The occurrence of resistant strains and unexpected pathogens calls for regular taking of cultures (ascites, blood, urine, sputum, wound discharge, etc.) [19].

Compromised Host Defense, Prolonged Bacteremia

The liver is a bacterial filter and the sinusoidal Kupffer cells play an important role in the elimination of intestinal bacteria and endotoxin translocated from the intestine. Patients with cirrhosis have impaired function of the reticuloendothelial system (RES) along with a decrease in the number and function of Kupffer cells [20, 21]. Additionally, because of the formation of collateral circulation, certain part of the blood-volume by-passes the liver, reaching directly the systemic circulation.

Immunodeficiency in cirrhosis is multifactorial deeply affecting both the innate and adaptive immunity and associated to the disease severity. PMN are fully activated potentially through the sustained exposure to bacterial products such endotoxin leading to an energy depleted status of the PMN and therefore inability to function properly (decreased chemotaxis, phagocytosis and bactericidal capacity). It is not only PMNs that appear defective due to the continuous endotoxin exposure. Monocytes show “immune paralysis” as well (decreased Fc mediated clearance of bacteria) [22, 23, 24]. Low opsonic activity and decreased complement levels, mainly C3, deteriorate the bacterial recognition and bactericidal capacity [25]. Fecal IgA content of cirrhotic patients has been reported to be lower as compared to healthy subjects, presumably reflecting the decreased mucosal IgA secretion. There is T cell depletion in advanced disease as well [26] Genetic immune defects (nucleotid-binding oligomerization domain containing 2 [NOD2] variants [27], toll-like receptor [TLR] polymorphisms [28] mannose-binding lectin [MBL] deficiency [29], haptoglobin polymorphism [Hp] could further deteriorate the immune defence mechanisms and could contribute to the high risk of bacterial infections in cirrhosis. Excessive iron stores, which are characteristics for certain types of cirrhosis, may have an adverse effect on immunity. Iron overload seems to exert subtle effect on immune system by altering the proliferation of T and B-lymphocytes [31, 32]. Furthermore, bacteria utilize the iron of the host organism as an important nutrient [33].

Secondary to compromised local and systemic host defense mechanisms, during local infections or often without it, bacteria can easily get into the circulation practically without restraint and cause prolonged bacteraemia. In cirrhosis, the occurrence of bacteraemia is five times more often and long lasting as compared to the subjects with maintained immunity [34,

35]. Gut is a particularly important portal of entry for the bacteria in patients with cirrhosis (chronic bacterial translocation [BT]). Circulating bacteria can colonize and proliferate in different organs inducing SBP or even meningitis, endocarditis, sepsis with high mortality. Prompt diagnosis and early treatment of these secondary infections are crucial. It would be even more important to prevent them. This could happen through the recognition and eradication of primary infections and reduction of intestinal bacterial translocation ("closure of infection ports"). The most common bacterial infections are SBP (25%), urinary tract infections (UTI) (20%), pneumonia (15%), and bacteremia (12%) [8].

Infection Ports

Bacterial Translocation (BT)

BT means the passage of not only viable bacteria but also endotoxins and other bacterial products, such as bacterial DNA itself from the intestinal lumen to the systemic circulation. It is considered a normal physiologic event that occurs in healthy individuals without deleterious consequences [36]. Small amounts of endotoxin, and bacteria probably constitute a physiologically important boost to the RES, especially to the Kupffer cells. Loss of integrity of the gut mucosa – as the consequence of inflammation and circulatory disturbance due to the portal hypertension –, altered gut micobiota (small bowel bacterial overgrowth) and dysmotility, and also the impairment of host defense mechanisms make possible the invasion of bacterial products or bacteria themselves into the systemic circulation in greater amount leading to systemic inflammatory reaction or overt bacterial infection. BT can turn into pathologic event as well. One third of the patients with advanced cirrhosis have small bowel hypomotility, decreased IgA secretion into the intestinal lumen due to dysfunction of the Paneth cells, altered gut microflora (a decrease in the number of anaerobes with an increase of both the GNB and GPC) [26]. Medically induced hypochlorhydria (administration of H2-receptor blockers, proton-pump inhibitors) and decreased bile acid secretion also contribute to the intestinal bacterial overgrowth in the small bowel [37]. Elevated portal pressure deteriorates the mucosal integrity of the intestine including widening of intercellular spaces, increasing permeability of tight junctions and developing of the edema [26]. However, in experimental animals, it has been revealed that the presence of elevated portal pressure is not sufficient for the BT and the process itself fairly associated to the advanced parenchymal disease [38, 39]. Likewise, in cirrhotic patients subjected to abdominal surgery, growing of enteric organism of mesenteric lymph nodes were found in those with the most severe liver disease (stage Child C) [40]. Impairment of intestinal wall integrity comprises one of the most important portals of entry for the bacteria. In cirrhosis, GNB of the gut microflora are the microbes that often translocate from the gut to the systemic circulation. BT becomes clinically significant when bacteremia or SBP develops [41]. However, without these overt infectious complications sustained exposures to endotoxin has also significant role in the further derangement of the previously altered circulatory state and aggravate the preexisting portal hypertension in cirrhosis [42, 43]. BT is mainly acknowledged to be an important process in the development of SBP. It is reasonable that BT may also possess a pathogenetic role in the development of other infections in cirrhotic patients: spontaneous bacteremia may

lead to hematogenous spread and secondary focal infections, yet this remains only a theory that has not been outlined, or studied adequately at least, in clinical practice [41]. This hypothesis is supported by the fact, that patients with increased serum lipopolysaccharide-binding protein (LBP) level were four times more likely to have severe bacterial infection during follow-up than patients with normal LBP [44]. Increased serum LBP level in the lack of overt infection is considered as a BT marker. Our group has recently reported, that the presence of IgA type anti-microbial antibodies was independently associated with not only SBP but also other clinically significant bacterial infections [6, 45]. Marked increase in the proportion of IgA2 type antibodies with the presence of secretory component supports the involvement of gut mucosal immune system and sustained exposure to bacterial constituents as a trigger of antibody formation and development of clinically significant bacterial infections as well in cirrhosis.

Dental Foci

Any bacterial foci hidden anywhere over the body, can serve a source for the bacterial spreading. Systemic infections or even sepsis can start from these loci in immunocompromised state. Though majority of cirrhotic patients have poor dental hygiene and untreated dental diseases, dental foci are rarely taken into account. Up to 67% of the patients suffer from caries due to their lifestyles [46]. Many of them are smokers. Smoking itself increases susceptibility to the accumulation of dental plaques, which are the precursors for the development of dental caries and periodontal disease. Many drugs administered to cirrhotic patients (i.e., mood modifiers with anticholinergic activity, diuretics, and antihypertensive agents) may decrease saliva production, causing oral mucosal dryness and so that they enhance the occurrence of dental diseases [47]. Dental foci might be the source of systemic infection. These infections often caused by unusual bacteria such as *Micrococcus*, *Fusobacterium*, *Peptostreptococcus* belongs to the normal oral microflora [46].

Skin and Soft Tissue Infections

Skin and soft tissue infection often develops in cirrhotic patients with edema or ascites especially in those suffering from diabetes mellitus concurrently. Cellulitis is found in 2-11% of the cases. GPC, *Staphylococci* and *Streptococci* are the most prevalent pathogens, but *Enterobacteriaceae* and anaerob bacteria can also be the causes of these infections [41]. GNB (*Escherichia [E.] coli*, *Klebsiella [K.] pneumoniae*) should also be considered as potential etiologic agents. In these latter cases, supposedly, the source of the bacteria is the gut itself. As a result of BT, enteric bacteria reach the systemic circulation, cause bacteremia and seed the tissues of the extremities [48]. Early recognition is important because the course of the disease is usually rapid and fatal. Progression to septic shock is common [49]. Inefficiency of empirical antibiotics against GPB or appearance of bullous cellulitis and gas formation highly suggest GNB infection. Culture of the bullous fluid may facilitate diagnosis and management. Antibiotics that are effective against both GBC and GNB should be preferred (amoxicillin/clavulanic acid (3x 1.2 g) or moxifloxacin (1x 0.4 g). Zoonosis (*Bergeyella*

zoohelcum [50], *Pasturella multocida [51]*) can also cause serious cellulitis even without injures caused by animal bite.

Airways Infections

Airways are the most common entrance for the bacteria. Infections of upper airways can easily spread downward to the lung due to the immunocompromised state. In cirrhosis, pneumonia is the third most frequent infection (15%). However, the mortality rate of pneumonia is much higher than in any non-cirrhotic population [8]. The defect in early bactericidal activity of alveolar lining components (reduced levels of lysosim and complement C3) explains the extreme sensibility for *Pneumococcus* pneumonia and the high mortality [52].

The pathogen spectrum of *community acquired pneumonia* is similar to general population [53]. The higher occurrence and particularly severe course of *Pneumococcus* infection may be worth considering. *Pneumococci* produce a virulence factor with cytotoxic activity called pneumolysin. Pneumolysin activating the complement system and further reduces the complement level of cirrhotic patient and attenuate the opsonophagocytic activity [52]. Other prevalent pathogens are *Klebsiella pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella species*. As in other localizations, opportunistic infection can occur in the lung.

Treatment strategy of community-acquired pneumonias in cirrhotic patients does not differ from the scheme used either in general population [53] likewise other immunodeficient states associated with pneumonia [54]. Nonetheless antibiotics should be administered intravenously in all cases and except for fluoroquinolones single-drug administration is generally not sufficient [53]. Macrolids (e.g., clarithromycin 2x500 mg, azithromycin 1x250 mg) + third-generation cephalosporins (ceftriaxone with a single dose of 2 g followed by a 2x1 g, or cefotaxime 3x2 g) could be adequate. An alternative regimen includes macrolid + amoxicillin/clavulanic acid (3x1.2 g). The duration of treatment should be 10 days at least; antibiotics can be omitted after concomitant resolution of clinical symptoms and normalization of CRP level [53]. Newer generation "respiratory fluoroquinolones" (levofloxacin, moxifloxacin) having antibacterial activity against GPC as well, can be effectively used in monotherapy for either community-acquired typical or atypical pneumonias [8]. They are also suitable for early oral administration, which increases the cost effectivity of the treatment. The dose of levofloxacin is 2x0.5 g and moxifloxacin is 1x0.4 g. Recently, moxifloxacin is considered the most advanced anti-*Pneumococcus* drug [55].

Majority of the *nosocomial pneumonias* are caused by GNB and *Staphylococci* species. In cirrhosis, certain interventions – e.g., intratracheal intubation, esophageal balloon tamponade - and the presence of hepatic encephalopathy significantly increase the risk of pneumonia. Identification of the pathogen bacteria is very important. In GNB induced pneumonias, the treatment of choice could be the third (ceftazidime 3x2 g) or fourth generation cephalosporins (cefepime 2-3x2 g), piperacillin/tazobactam (3x4.5 g), imipenem/ cilastatin (3-4x0.5-1 g) or meropenem (3x1 g). In *Staphylococcus aureus* caused pneumonias oxacillin/flucloxacillin (4x 2 g-6x1-2 g), high-dose amoxicillin/clavulanic acid (3x2.4 g), or moxifloxacin (1x0.4 g) can be used [56]. When methicillin-resistant *Staphylococcus aureus* (MRSA) infection is suspected, the antibiotic regimen should be supplemented with

vancomycin (2x1 g). However, linezolid (2x600 mg) yielded a higher rate of both microbiological and clinical success than vancomycin [57]. In case of extended-spectrum beta-lactamase (ESBL)-producing strains, the effective treatment is imipenem/ cilastatin (4x0.5 g) or meropenem (3x1 g) (cefepime or piperacillin/tazobactam could also be used). After ruling out *Pseudomonas* of the causative agents on the basis of the culture result, ertapenem (1 g/day) should be the treatment choice. Against carbapenem-resistant strains, colisitin (3x1-3 ME/nap) could be effective [58, 59]. New antibiotic strategies tailored according to the local epidemiological patterns are needed for the empirical treatment of nosocomial infections in cirrhosis not only in pneumonias but also the other type of infections [60].

When pulmonary aspiration cannot be ruled out, clindamycin (3x600 mg) should be added to the treatment regimen, or indicated antibiotics having antibacterial activity against anaerobes as well. Ampicillin/sulbactam (4x 1.5 g), amoxicillin/clavulanic acid (3x1.2 g), piperacillin/tazobactam (3x4.5 g) or moxifloxacin could equally be suitable in these cases [55, 61].

Patients with cirrhosis – especially those with alcoholic etiology – are more susceptible to acquire tuberculosis due to their impaired cellular immune response. During the disease course, higher mortality rate and more frequent side effect to anti-tuberculosis drug are expected. Because of the preexisting liver dysfunction, application of multi-drug combination regimen warrants strict surveillance [62, 63].

Urinary Tract Infections (UTIs)

UTIs are frequent complications in hospitalized cirrhotic patients (20%), however they are often asymptomatic. The occurrences of UTIs were found about 5% among non-hospitalized patients with advanced diseases and on waiting list for liver transplantation [64] UTIs are important and often solely precipitating factors of HE [65] and can be the source of bacteremia as well. For these reasons, screening of UTIs is important in cirrhotic patients. Risk factors of UTIs are urinary catheters dwelling, female gender and concomitant diabetes mellitus. The typical pathogens are GNBs (*E. coli, K. pneumonia*). Recommended empiric antibiotic treatment regimes comprise newer quinolone-derivatives (ciprofloxacin 2x500 mg) or the traditional trimethoprim/sulfamethoxazole (2x800/160 mg) in uncomplicated infections. This latter antibiotic still has a strong anti-GNB activity and reaches high concentrations in the urine. Fosfomycin (3 g single dose) or nitrofurantoin (2x100 mg) is also recommended as first-line agent [66]. Other antibiotic regimens, mainly in cases of systemic UTI, include intravenous amoxicillin/clavulanic acid (3-4x 1.2 g) or cephalosporins (cefotaxime 2x2 g or ceftriaxone 1-2x1 g) [19]. One should always consider the history of preceding antibiotic treatment when choose empiric antibiotic therapy. The on-going empiric antibiotic treatment should be adjusted according to microbiologic results of urine culture. In recurrent UTIs, high resistance rate is expected for the previously used antibiotics. Unfortunately ESBL producing strains have emerged as significant pathogens in community-onset infections [67].

Lesser is known about the frequencies and courses of other localized infections. During bacteremia with unknown origin, it is highly suggested to check maxillary sinus region or look for aviator ear, especially in patients with HE and poor cooperation. Following a

minimal cranial trauma, in an alcoholic cirrhotic patient with maxillary sinusitis, an extensive arborisation of abscess was developed in the tissues of facial and cranial skin (our non-published case).

Secondary Infections

As a consequence of immunocompromised state of cirrhotic patients pathogens can get easily into the bloodstream across primary portal of entry, and cause bacteremia. However, the occurrence and duration of bacteremia is five times increased as compared to immunocompetent subjects [34, 35], which explain the higher incidence of bacterial spreading.

Spontaneous Bacterial Peritonitis (SBP)

In the presence of ascites, bacteria often colonize ascitic fluid in the peritoneal cavity and cause SBP. The low opsonic activity of the ascites – lower than in serum – serves suitable environment for bacterial growing [34]. SBP defined as the infection of ascitic fluid in the absence of any intraabdominal, surgically treatable source of infection (e.g., perforation or abscess). SBP occurs in 10-30% of hospitalized cirrhotic patients with ascites [67, 68]. The prevalence is even higher when severe hepatic insufficiency is present indicated by high serum bilirubin concentration (>3.2 mg/dl) and low platelet count (< 98 000/mm^3) or in the presence of gastrointestinal bleeding [69]. The low level of total protein (< 1 g/dL) or high concentration of LBP in ascitic fluid – the latter is considered an indirect marker of BT – significantly increase the risk of SBP [70]. Severe liver dysfunction results in fairly decreased protein synthesis. Concomitantly, low ascitic protein level is associated to the impairment of opsonic and antibacterial activity in the peritoneal cavity [34]. Gastrointestinal bleeding is accompanied by sustained bacteremia [71].

The underlying mechanisms of SBP have not been fully revealed. SBP is usually monomicrobial (in 92% of the cases) and the most common types of pathogens are the constituents of intestinal microflora (*Enterobacteriaceae*) highly suggesting that BT is the principal mechanism in its development. Other facts support this notion as well. Pharmacological prevention of BT (e.g., by the reduction of portal pressure) diminishes the incidence of SBP [72]. Similarly, intestinal decontamination by oral non-absorbable antibiotics reduces the occurrence of SBP [73]. Besides BT, SBP could also be a consequence of bacteremia associated to primary infections (airway, skin and soft tissue or UTIs) or invasive procedures (e.g., endoscopic interventions) through the colonization of the ascitic fluid. In these cases, the pathogens are GPC, primarily *Streptococcus species*. In nosocomial SBP, the proportion of GPC is around 59% [74].

The clinical signs and symptoms of SBP are aspecific. In early stage, the infection is usually asymptomatic, while during the progression signs of peritonitis appear: fever, abdominal pain, and tenderness. In almost half of the cases, SBP presents as deterioration of consciousness, while one third of the patients complain of diarrhea or ileus. Hypotension or hypothermia could also be present, but in less than 20%. Due to scarcity of typical signs and

symptoms, diagnostic paracentesis should be performed in all newly discovered cases of ascites, including those with Budd-Chiari syndrome or cardiac insufficiency as well. Diagnostic paracentesis should also be performed in any cirrhotic patients with ascites admitted to hospital due to sudden deterioration of liver function, HE, gastrointestinal bleeding or renal impairment [7]. The diagnosis of SBP is based on ascitic fluid analysis obtained by paracentesis. An ascitic fluid PMN count ≥ 250 cells/mm^3 independently of culture result is considered diagnostic for SBP and comprises an indication to initiate an empirical antibiotic treatment immediately [75]. Ascitic PMN cell counts can be determined either by a traditional haematological method using a light microscope and a manual counting chamber or by automated cell counters [76]. Advantages of automated cell counter are that they are easily accessible in emergencies and provide results within short time [69]. Use of reagent test strips to assess leukocyte esterase activity of activated PMNs for the diagnosis of SBP cannot be recommended owing to low sensitivity and an unacceptable high rates of false negative results [77]. Determination in ascitic fluid of lactoferrin, an iron-binding protein contained by PMNs and released on degranulation, might be suitable for bedside diagnosis of SBP, however further studies are needed [78]. Besides establishment of the diagnosis, it is also important to identify the pathogens causing the SBP episode. Inoculation of ascitic fluid into blood culture bottle at bedside increases the sensitivity, even though the culture results are negative in 25-50 % of the samples. Collection of separate and simultaneous blood culture also yields an increase in the sensitivity. 30-58% of SBP cases are associated with bacteremia [69]. Early and more efficient identification of bacteria and their antimicrobial susceptibility in ascitic fluid could result in more timely treatment of SBP. Recently, the application of the Matrix Assisted Laser Desorption Ionization – Time of Flight Mass Spectometry (MALDI-TOF MS) to identify bacteria directly from ascitic fluid or from positive blood culture proposed for early identification of the causal agent of the infection. Moreover, MALDI-TOF MS allows detecting the mechanism of resistance to different antimicrobial agents rapidly [79].

Secondary peritonitis constitutes the main differential diagnosis of SBP. Its mortality is much higher than that of SBP (66% vs. 10%) [80]. Diagnosis of secondary peritonitis is based on Runyon's criteria [81]. A secondary peritonitis is very likely when at least two of the following criteria are present in ascitic fluid: glucose levels <50 mg/dl, protein concentration >1.0 g/dL, LDH concentration >normal serum levels.

In *community-acquired SBP*, the suggested empiric antibiotics are the third-generation *cephalosporins*, which are proved to be effective in 90% of the cases. *Cefotaxime* should be administered intravenously in dose of 3x2 g/ day at least 5 days. However the length of the antibiotic treatment should be adjusted individually according to improvement of clinical symptoms, and normalization of CRP and ascitic fluid PMN count. The other therapeutic options are c*efriaxon* (1x2 g) or *cefonicid* (2x2 g) that should be used for 1-2 weeks [43]. Two recent studies confirmed the safety and efficacy of intravenously administered *amoxicillin/clavulanic acid* (3-4x1.2 g) in the treatment of SBP [82, 83]. In uncomplicated SBP (absence of the followings: ileus, gastrointestinal bleeding, septic shock, HE with grade 2-4 or serum creatinin > 3 mg/dL) oral, highly bioavailable quinolones (ofloxacin 2x400 mg, ciprofloxacin 2x500 mg) have been found as effective as the intravenous third-generation cephalosporins [84, 85]. However, quinolons are not recommended in patients receiving norfloxacin prophylaxis or in geographic areas with a high prevalence of quinolone-resistant bacteria. Resistance to third-generation cephalosporins and quinolons increases continuously.

Moreover, *Enterococci*, which are intrinsically resistant to cephalosporins, should be considered as one of the causes of treatment failure. The prognosis of enterococcal SBP is poor. Adding vancomycin (iv. 2x1 g) to the baseline therapy is effective due to the low incidence of vancomycin-resistant strains [86]. Aminoglycosides are also effective against *Enterococci*, however their administration should be avoided due to their increased nephrotoxicity in patients with cirrhosis. Regardless of the severity of hepatic insufficiency aminoglycoside administration carries a significant risk for development of renal failure and should only be used when no other options are available [87].

The response to antibiotic therapy should be assessed by follow-up paracentesis and monitoring of PMN count in the ascitic fluid. Reduction of the baseline PMN count lesser than 25% after 2 days antibiotic therapy suggest treatment failure and warrant adjustment [43].

In *nosocomial SBP*, the above-mentioned antibiotic regimens lead to unacceptably low rates of resolution due to the increasing incidence of ESBL-producing bacteria and multiresistant GPBs such as *Enterococcus faecium* or MRSA [69]. Largely in patients with high risk: previous hospitalization (particularly within 3 months and intensive care treatment) and prior antibiotic treatment (within 30 days).

In these cases antibiotic escalation therapy should be avoided due to it has been found to be associated with poor survival [88, 89]. Therefore in patients with cirrhosis who develop nosocomial SBP and present with such risk factors, *carbapenem* should be the first-line empirical therapy. This regimen should be de-escalated if microbiological results indicate non-resistant easily treatable causative microorganisms [69]. Delay in effective therapy significantly increases mortality [90].

The most dreadful complication of SBP and concurrently the important predictor of mortality is the development of acute renal failure (ARF). Repeated large-volume paracentesis and intensive diuretic treatment can trigger the onset of ARF so that they should be avoided in this case. Likewise, all other drugs that may impair renal function – nephrotoxic antibiotics or non-steroidal anti-inflammatory drugs (NSAID) should also be avoided until full recovery from SBP [17].

Fluid resuscitation and albumin replacement can improve prognosis. Intravenous albumin administration, 1.5 g/kg on the first day, and 1 g/kg on the third day, were found to be associated with decreased incidence of renal failure (33% with cefotaxime+albumin vs. 10% with cefotaxime alone) and decreased mortality (29% vs. 10%, respectively) [91]. Patients in the study who were most likely to benefit from albumin had serum bilirubin levels above 4 mg/dL and/ or serum creatinine above 1 mg/dL. This observation was confirmed in a subsequent study [92]. Consequently, albumin should be reserved for this subgroup of patients with SBP [19].

Spontaneous bacterial empyema (SBE) is a complication of cirrhotic patients in which a pre-existing pleural effusion becomes infected. The mechanism of its development is presumably very similar to SBP. The incidence was found 2.4% in cirrhotic patients and 16% in patients with cirrhosis with hydrothorax. Predominant pathogens in SBE are GNB, and *E. coli* is the most frequently isolated sole pathogen, similarly to SBP. Approximately half of the patients have concomitant SBP as well [93]. The treatment strategy of SBE is in agreement with the regimes used in the management of SBP.

Meningitis

Though meningitis is a relatively infrequent complication of bacteremia in cirrhosis, the susceptibility rate is ten times higher than in general population and these infectious episodes are associated with high mortality rate (more than 50%) [94]. Similarly to other infections in cirrhosis, establishment of the diagnosis is difficult. Clinical characteristics and signs are rarely typical and cirrhosis itself could display central nervous system symptoms as well. One third of the patients have no nuchal rigidity. Headache and vomiting is often absent. Coma is more common and caused by meningitis and HE together. In the absence of typical clinical signs, one rarely thinks of meningeal involvement but more rather HE episode [95]. Besides common pathogens like *Neisseria meningitidis* and *Streptococcus pneumoniae*, GNB should always be considered, mainly in advanced liver disease. Causative agents follow geographic distribution patterns: in Taiwan, for example, *Kl. pneumoniae* was the most frequent pathogen mainly in cases with concomitant diabetes mellitus [96], while in France *Listeria monocytogenes* occurred more often [19]. *E. coli* and *Yersinia enterocolitica* was also reported to cause meningitis [97]. Prognosis of the disease very depends on the early diagnosis and proper antibiotic therapy. Taking both cerebrospinal fluid and blood culture is very important. Cirrhotic patients often have low platelet count or some other hemostatic impairment, so that indication of lumbar puncture is not easy. Though no studies could confirm complications related to the procedure up till now [95]. If atypical clinical signs develop, one should consider the possibility of brain abscess. In this case lumbar puncture can be dangerous (pons herniation) and brain CT is recommended as a first choice for the diagnosis establishment [98]. Empirical treatment of the meningitis in cirrhosis should be started with a combination of ampicillin and third generation cephalosporin. This regime should be modified according to microbiological results. Administration of steroids in meningitis is questionable [99]. Recovery from the meningitis is often long with frequent relapses. Sustained antibiotic treatment may decrease the prevalence of relapses. Apart from immunodeficiency, high mortality rates are also associated to complications (further impairment of liver function or HRS). Sometimes the patient recovers from meningitis but dies in liver failure.

Brain abscess develops as a consequence of hematogenous spreading. The most common pathogen is *Staphylococcus aureus*, especially following trauma or brain surgery. *Streptococcus, Proteus* and *Serratia* species can also be identified. Treatment should be started with vancomycin if the suspected bacterium is *Staphylococcus*, in other cases the suggested empiric therapy is a combination of some beta-lactam antibiotic with chloramphenicol or metronidasol until the availability of microbiological result. Surgical removal of the abscess is not always possible, and very hazardous considering the severe comorbidities. The decision is difficult and should always be individual. Postoperative mortality rate was 24%, while it turned out to be 45% if no surgery could be performed [100].

Endocarditis

Infective endocarditis (IE) in cirrhotic patients is rarely reported but is a serious hazard for hospitalized cirrhotic patients with a 26-80% mortality rate that much higher than non-cirrhotic population. The most advanced the liver disease is, the higher the mortality rate is.

[101]. Operative mortality during valve replacement was extremely high in patients at stages B and C [102]. *Snyder and coworkers* [103] reported a three times higher incidence rate in patients with cirrhosis as compared to non-cirrhotic subjects (0.34% vs. 0.1%). Guerro et al. found that thirty-one (9.8%) patients among 316 cases of IE had hepatic cirrhosis [102]. Thus, cirrhotic patients are apparently more susceptible to the development of IE, although the overall risk is still fairly low. *Staphylococcus aureus* was the most common causative microorganism in different studies [101, 102], however, in cirrhosis, β-hemolytic *Streptococci* (*S. pyogenes*, S. *agalactiae*) were frequently isolated as well. *E. coli and Pseudomonas aeruginosa* were isolated from nosocomial endocarditis. In another study, *Enterococcus faecalis* was also amongst bacterial organisms [101]. In cirrhosis, females are more frequently affected and endocarditis typically involves the mitral valve. Risk factors for nosocomial endocarditis are dwelling of central venous or urinary catheter, and endoscopic interventions during gastrointestinal bleeding or liver biopsy. Endocarditis was also reported to associate to pneumonia, SBP or hip replacement surgery [101]. Data shows that endocarditis in cirrhosis could also develop without a known valvular heart disease. Only in the 62% of the cases had previously known valvular heart disease [104, 105].

Selecting the best treatment strategy is troublesome: heart surgery is very hazardous in this patient population and associated with high postoperative mortality (60-80% in the first month) [103]. Furthermore, the anticoagulant therapy may also be challenging due to the common occurrence of concomitant hemostatic impairment. Antibiotic selection is also problematic. Due to the probable occurrence of *Enterococcus faecalis*, the foremost-recommended empiric antibiotics are beta-lactams with gentamycin. This combination seems to be the only effective regimen. This combination is also the suggested initial therapy for *Staphylococci, GNB and Pseudomonas ssp.* Administration of aminoglycosids in cirrhosis is especially hazardous due to their nephrotoxic properties [87]. However, the risk of nephrotoxicity versus the possible harmful effects of omitting an effective treatment option should always be carefully considered individually. After receiving microbiologic result, if the pathogen is not *Enterococcus faecalis* and the patient doesn't have artificial valve, gentamycin can be stopped or replaced. During aminoglycosid therapy the patient requires sufficient fluid resuscitation, and close monitoring of renal function and gentamycin serum level. Ampicillin (6x 2 g) or ceftriaxone (3x2 g) could be the choices of beta-lactam antibiotics. The dose of gentamycin is 2x1 mg/ bwt. In MRSA endocarditis, the antibiotic regimen should be supplemented with vancomycin (2x1 g) [106].

Sepsis

Any severe infection could progress into sepsis accompanied by exaggerated inflammatory response and multiple organ failure. Unfortunately, in cirrhotic patients the classic signs and symptoms of sepsis can be absent or ambiguous, often mistaken with general signs of cirrhosis, thus leading to delay in the diagnosis establishment. Hypothermia is characteristic for cirrhosis; therefore, temperatures above 37.8 °C should always be taken seriously. For a proper evaluation of the actual WBC count considering the previous baseline WBC level is very important. Not only absolute but also relative leukocytosis is important. This latter category regards to previously leucopenic patients due to hypersplenism. In these cases, normal WBC count should be considered "leukocytosis", relative raise in WBC.

Hyperkinetic circulation causes higher pulse rate, and hypotension is also not uncommon state in cirrhosis. Encephalopathy itself may cause mental disturbances and elevated respiratory rates without sepsis. Similarly, increased prothrombin time and elevated liver enzymes can be seen in non-septic cirrhosis. Declining renal function is not surely a sign of the multiorgan failure in cirrhosis, because of HRS without sepsis can cause impairment of kidney function [107]. Sometimes it is very difficult to spot the difference. High serum level of CRP and/or PCT, absolute or relative leukocytosis with 'left shift', together with the aforementioned symptoms, and rapidly worsening condition of the patient are highly suggestive for sepsis. When in doubt, one should always consider the possibility of a septic condition. Prognosis of severe sepsis or septic shock is poor with hospital mortality rate from 30% to 70% [1, 108]. The treatment of sepsis requires integrated strategy in an intensive care unit [109, 110] early diagnosis, antibiotic treatment, fluid resustitation, vasoactive drugs and other supportive measures (mechanical ventilation, renal replacement therapy, sedation, glucose control protocol and prophylactic strategies) if required.

Regarding antibiotic treatment, broad-spectrum antibiotics covering all likely pathogens should be administered as early as possible, always within the first hour if the diagnosis is established. De-escalation to the most appropriate single antibiotic should be done once susceptibility profile of the responsible bacteria is known [111].

In the last ten years it has just been revealed, that adrenal insufficiency in critically ill patients with sepsis is far from rare condition. *Annane* et al. [112] reported an incidence of 60% in patients with severe sepsis and septic shock. Pathogenesis of adrenal insufficiency is complex and poorly understood. In 2008 a consensus statement [113] proposed the term critical illness related corticosteroid insufficiency (CIRCI) instead of relative adrenal insufficiency (RAI) and defined it as an inadequate peripheral corticosteroid activity for the severity of the patients illness. Despite of these facts the effect of low-dose hydrocortisone therapy in septic shock patients remains controversial. Randomized controlled trials and meta-analyses still show conflicting results. Furthermore, classic diagnostic tools to assess adrenal insufficiency used by endocrinologist are not useful in the critically ill patient population. At this moment there is no good diagnostic tool that is sensitive and specific enough to guide treatment and better definition of adrenal insufficiency is also warranted [114]. According to currently published guideline, a continuous infusion of 200 mg hydrocortisone per day should only be started if hemodynamic stability is not restored with adequate fluid resuscitation and vasopressor therapy. ACTH stimulation test should not be used to identify adult septic shock patient that requires hydrocortisone treatment [115]. Adrenal insufficiency was found to be a common cause of hemodynamic instability in patients with cirrhosis and concomitant sepsis (52–77%) as well. This condition was associated with hypotension, which was refractory to volume administration and vasopressor drugs, and leaded to mortality rate 81% *vs.* 37% in patients without adrenal dysfunction [116]. Despite of it the efficacy of stress dose steroids on the outcome of cirrhotic patients with septic shock is unclear and gastrointestinal bleedings may develop more frequently. At this moment, only date of one small, prospective, randomised controlled trial is available. This study showed that hydrocortisone, given until shock resolution, was associated with a significant reduction in vasopressor doses and a higher rate of shock reversal, but it did not reduce 28-day mortality [117]. Assessment of adrenal function and treatment with stress doses of hydrocortisone, therefore, is not recommended for the management of severe sepsis

in cirrhotic patients for the present. Larger interventional trials are needed to address this issue in critically ill cirrhotic patients [19].

Antibiotic Prophylaxis

Antibiotic prophylaxis comprises two distinct approaches. Short-term prophylaxis aims to protect against development of a presumed bacteremia, usually following an invasive procedure. It should be administrated right before the intervention or short-term thereafter. In contrast, long-term antibiotic prophylaxis is used to protect patients with increased susceptibility either temporarily or permanently against pathogens invading through any portal of entry. This second type of prophylaxis is rather controversial. In cirrhosis both types of prophylaxis may play a certain role.

Short-Term Prophylaxis

Recent years saw an increasing awareness of endoscopy-related infectious complications. Short (< 30 minutes) asymptomatic bacteremia develops in less than 8% after these procedures, which rate seems to be unaffected by biopsy taking [118]. The risk is higher when performing sclerotherapy (31%), band ligation (1-25%) or esophageal dilatation (45%) [119]. Bacteria from the oral flora usually get into the circulation; the most common pathogen is *Streptococcus viridans*. In cirrhosis, however, the risk of infectious complications due to bacteremia is significantly higher. Data shows that short-term administration of antibiotics following gastrointestinal bleeding and endoscopic intervention improves survival rates and decreases the frequency of complications; thus, it is highly recommended [120]. A daily dose of 2x 400 mg norfloxacin for 7 days is suitable for the prevention of infectious complications followed by gastrointestinal bleeding. The efficacy of amoxicillin (+ clavulanic acid) or non-absorbable antibiotics is still under investigation. In advanced liver disease (ascites, severe malnutrition, HE or icterus), however, 1x1 g of intravenous ceftriaxon proved to be superior to oral norfloxacin [121]. In the case of severe vomiting, intravenous antibiotic treatment is the only effective way.

Long-Term Prophylaxis

The risk of SBP recurrence within one year is up to 70% [122]. Several studies confirmed that prolonged intestinal decontamination with nonabsorbable or poorly absorbed oral antibiotics is highly effective in preventing SBP recurrence. The recurrence rate decreased from 70% to 20-30%. It is established unequivocally, that *secondary prophylaxis* is recommended after resolution of SBP with the strongest evidence supporting use of norfloxacin [7]. Prophylactic treatment with trimethoprim/sulfamethoxazole would be much cheaper but the efficacy of this combination is yet to be confirmed. Administration of 400 mg norfloxacin daily is suggested until the disappearance of ascites, or until liver transplantation or death. A recent meta-analysis of Saab et al. [123] showed further advantages of antibiotic

prophylaxis in secondary prevention. An improved short-term survival and reduced overall risk of infections beyond SBP were also reported in treated patients when compared with untreated control groups.

The role of antibiotic prophylaxis in the primary prevention is uncertain and has to be carefully considered. In early studies [124, 125], long-term *primary prophylaxis* proved to be undeniably beneficial in the prevention of GNB caused SBP in patients with low ascitic fluid total protein levels (≤ 1 g/dL), however the incidence of extraperitoneal infections or actuarial probability of survival did not improved. Recently, Fernandez et al. [126] aimed to investigate the efficacy of norfloxacin in the primary prophylaxis of SBP in a very-high risk group of patients (low protein ascitic levels [< 1.5 g/dL] with advanced liver failure [Child-Pugh score ≥ 9 points with serum bilirubin level ≥ 3 mg/dL] or impaired renal function). In this randomized placebo-controlled study, primary prophylaxis with norfloxacin had a great impact in the clinical course of patients with advanced cirrhosis reducing the incidence of SBP, delaying the development of HRS, and improving survival. The most probable explanation for these findings is the decreased BT due to the intestinal decontamination. This presumption is supported by the laboratory findings of the study. Norfloxacin administration diminished the serum levels of LBP, cytokines and nitric-oxide metabolites. Not only the translocation of the bacteria themselves, but also their antigens or products may play a role in the circulatory derangement characteristic to cirrhotic patients, which is one of the most important factors in the development of HRS. HRS, on the other hand, is among the leading causes of mortality.

The trial of Fernandez et al. was considered to fulfill the highest quality criteria and represents a well-defined group of patients. Primary prophylaxis can be justified in patients with low ascitic protein level (< 1.5 g/dL) and should be used in the presence of advanced liver diseases or renal impairment [69]. Wiest et al. also propose that use of norfloxacin for primary prophylaxis should also be considered in unselected patients with low ascitic protein level if liver transplantation is a realistic option within a few months. In a short-term, the risk for selection of resistant strains is low.

The long-term use of prophylactic antibiotics in cirrhosis has led a selection of quinolone resistant bacteria. In early studies [127, 128] development of quinolone-resistant strains in the stool of patients on prophylaxis was not associated with an increased incidence of quinolone-resistant bacteria. However, subsequent studies reported emergence of UTI and SBP caused by GNB resistant to quinolones with continuously increasing prevalence in patients receiving this prophylaxis [125, 129, 130].

It is becoming increasingly important to develop non-antibiotic strategies to decrease BT and to reduce the incidence of infection in patients with cirrhosis. These non-antibiotic strategies include the use of probiotics, prokinetic agents and supplementation with oral bile acids and areas of future research [131].

Conclusion

Infections became a central problem in the management of cirrhosis. They affect the course of the disease by impairing liver function, increasing the risk of complications and thus the mortality rate. Early detection, prompt an adequate antibiotic treatment is of utmost

importance. Diagnosis establishment of bacterial infection in cirrhosis is often challenging since signs and symptoms could be a specific, often mistaken with other signs of cirrhosis. For the chance of an early detection, one most always think of the possibility of bacterial infection. New tools for the diagnosis of bacterial infections are also clearly needed. Microbiologic results are vital for the diagnosis due to the recent spreading of uncommon, multi-resistant or opportunistic pathogens. Third-generation cephalosporins continue to be the gold-standard antibiotic treatment of many of the community-acquired infections. For the empirical treatment of nosocomial and possibly health-care associated infections data of local antimicrobial resistance surveillance should always be considered. Long-term antibiotic prophylaxis can decrease BT and the incidence of infections in cirrhosis, but also carries the risk of selecting resistant bacteria and CDAD. Unfortunately no single biomarker exists to predict the risk of infection in cirrhosis. However, this information is of outstanding clinical value. Further research is needed to identify potential biomarkers for immune dysfunction to be able to identify the group of patients who benefit most from antibiotic prophylaxis. In the future, effective non-antibiotic prophylactic measures should also be sought intensively to minimize the risk for the development of bacterial resistance.

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