Infections related morbidity and mortality in the cirrhosis of the liver

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ABBREVIATIONS:

- ACLF – Acute- on- chronic liver failure
- AI – Adrenal insufficiency
- AKI – Acute kidney injury
- AMP – Antimicrobial peptide
- APC – Antigen presenting cell
- ARDS – Acute respiratory distress syndrome
- BT – Bacterial translocation
- CA – Community - acquired
- CAID – Cirrhosis- associated immune dysfunction
- CLIF-SOFA score – Chronic Liver failure- Sequential Assessment of Organ Failure score
- CRP – C- reactive protein
- DAMP – Damage associated molecular pattern
- DCs – Dendritic cells
- DST – Direct susceptibility tests
- ESBL – Extended- spectrum beta- lactamase producing Enterobacteriaceae
- HCA – Health care-associated
- HRS – Hepatorenal syndrome
- ICA – International Club of Ascites
- KC – Kupfer cell
- LPS – Lipopolysaccharides
- LSEC – Liver sinusoidal endothelial cell
- MDR – Multi- drug resistant
- MELD – Model for end-stage liver disease
- MHC – Major histocompatibility complex
- MRSA – Methicillin- resistant staphylococcus aureus
- NSBB – Nonselective β blockers
- PAMP – Pathogen associated molecular pattern
- PCT – Procalcitonin
- PD-L1 – Programmed death-ligand 1
- PMC – Polymorphonuclear cells
- PPI – Proton pump inhibitor
- PRR – Pattern recognition receptor
- RAI – Relative adrenal insufficiency
- SBP – Spontaneous bacterial peritonitis
- SIBO – Small intestinal bacterial overgrowth

- SIRS – Systemic inflammatory response syndrome
- TJ – Tight junction
- TLR – Toll like receptor
- UTI – Urinary tract infection
- VRE – Vancomycin- resistant enterococci

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ABSTRACT

Title: Infections related morbidity and mortality in the cirrhosis of the liver

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Bacterial infection is a common complication of liver cirrhosis and accounts for major morbidity and mortality. Cirrhosis associated immune dysfunction and bacterial translocation are the key pathophysiologic mechanisms favoring this increased susceptibility. The most common types of bacterial infections in liver cirrhosis are spontaneous bacterial peritonitis (SBP), urinary tract infection and pneumonia. Usually these infections are caused by gram negative bacteria. However, in clinical settings, gram positive microbes predominate and more than half of them are multi drug resistant.

Due to the altered immune response commonly encountered in liver cirrhosis, presentation of the disease might be atypical. Because of this, diagnosis is often difficult and clinical suspicion should be kept high. The presence of SIRS, increased CRP and procalcitonin are current markers used to facilitate diagnosis and microbiological culture methods are the standard to identify causative agents. Current research is working on newer technologies, that can identify pathogens earlier and hence allow early targeted therapy.

Once infection in patients with cirrhosis is suspected, it is crucial to initiate antibiotic treatment immediately, since a delay is associated with increased incidence of complications and death. Antibiotics should be chosen according to type, severity and origin of infection and one should be familiar with the local epidemiological patterns of antibiotic resistance.

Prophylactic antibiotic treatment has proven to be efficient, but must be strictly reserved for patients, who are at risk for bacterial infections, in order to prevent emergence of antibiotic resistance. Belonging to this category are patients with upper gastrointestinal bleeding, advanced cirrhosis and previous history of SPB.

Despite improvements in prophylaxis and treatment, unfortunately prognosis of infections in liver cirrhosis remains poor. Out of the infected cirrhotic patients approximately 29% die within the first month, 44% within the first three months and 63% within the first year.

Key words: cirrhosis, bacterial infection, immune dysfunction, antibiotic treatment, mortality

SAŽETAK

Naslov: Pobol i ishod akutnih infekcija u cirozi jetre

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Bakterijske infekcije česta su komplikacija ciroze jetre i odgovorne su za veliki dio mortaliteta i morbiditeta. Disfunkcija imunološkog sustava i translokacija bakterija ključni su patofiziološki mehanizmi koji utječu na veću učestalost bakterijskih infekcija u bolesnika sa cirozom jetre. Najčešći tipovi bakterijskih infekcija u cirozi jetre su: spontani bakterijski peritonitis (SBP), urinarne infekcije i upala pluća. Najčešći uzročnici navedenih infekcija su Gram negativne bakterije, dok u nozokomijalnim infekcijama dominiraju Gram pozitivni (G+) koki. Više od polovice G+ uzročnika je multirezistentno na antibiotike.

Radi promijenjenog imunološkog odgovora koji je čest u cirozi jetre, prezentacija bolesti može biti atipična. Posljedično tome, postavljanje točne dijagnoze često je otežano. Prisutnost SIRS-a, povišenog CRP-a i prokalcitonina pokazatelji su prisutnosti infekcije, dok su mikrobiološke kulture standard utvrđivanja uzročnika. Trenutna istraživanja baziraju se na novim tehnologijama koje omogućuju raniju identifikaciju uzročnika i shodno tome raniji početak ciljane antimikrobne terapije.

Čim se posumnja na infekciju u bolesnika sa cirozom jetre, od iznimne je važnosti što raniji početak antibiotske terapije jer odlaganje dovodi do povećane incidencije komplikacija i smrti. Izbor antibiotika mora biti određen na temelju tipa, intenziteta i sijela infekcije uz razmatranje lokalnih epidemioloških podataka o rezistenciji na antibiotike.

Profilaktička primjena antibiotika dokazano je učinkovita, mora biti strogo rezervirana za bolesnike koji su u povećanom riziku od bakterijskih infekcija da bi se spriječila pojava rezistencije na antibiotike. Bolesnici koji spadaju u tu kategoriju su oni s krvarenjem iz gornjeg dijela probavnog sustava, uznapredovalom cirozom jetre i sa SBP u anamnezi.

Unatoč poboljšanjima u profilaksi i liječenju, prognoza akutne infekcije u bolesnika sa cirozom jetre je loša. Smrtnost bolesnika sa cirozom jetre i infekcijom je 29% u roku od mjesec dana, 44% u roku od tri mjeseca, i 63% u roku od godinu dana.

Ključne riječi: ciroza, bakterijska infekcija, disfunkcija imunološkog sustava, antibiotsko liječenje, mortalitet

1. Introduction

Liver cirrhosis is considered to be the 10th most common cause of death worldwide and many times this is connected to complicated infections (1). Indeed, bacterial infection is present in 25 to 35% of patients and is associated with increased morbidity and mortality (2,3). The development of this susceptibility is still not fully understood, but mechanisms like bacterial translocation and altered immune function play an important role. Once an overt infection is present, it can rapidly progress to complications like sepsis, renal failure, etc., collectively known as multiple organ failure. Hence, prophylaxis, early recognition and rapid management are key for improving survival.

In the following review pathophysiological mechanisms, etiology and types of infections will be extensively discussed. The aim is to provide an overview about diagnostic methods, prophylaxis and treatment options and to give a perspective on current and future research.

2. Pathophysiology

2.1. Cirrhosis associated immune dysfunction

When it comes to immunology the liver plays a critical role. Its distinct cellular structure and anatomical positioning downstream of the gut makes it one of the first line organs in defending blood - born infections. Diverse in vivo research on animals has illustrated this importance (4,5). For instance, infection in mice with *Borrelia burgdorferi* is normally not lethal, but in Kupfer cell- depleted mice it resulted in increased bacterial load and mortality (5).

In order to fulfill this task, the liver is composed of various resident immune cells and has the capacity for rapid recruitment of other immune cells, i.e. peripheral leukocytes and platelets (6–8).

Kupfer cells (KC) are found in the liver and make up 80-90% of all tissue macrophages (9). Due to expression of scavenger, Toll like (TLRs), complement and antibody receptors, they are able to detect, capture and internalize pathogens and their associated molecular patterns (10). In contrast to other macrophages, KCs possess the unique ability to pick up pathogens under shear, non-static conditions (11). Together with liver sinusoidal endothelial cells (LSECs) and dendritic cells they belong to the class of antigen presenting cells (APCs), expressing major histocompatibility complex (MHC) class I, MHC class II and costimulatory receptors (12).

LSCEs, the most abundant non-parenchymal liver cells, have similar functions to KCs, i.e. pathogen detection and antigen presentation (10). Under non- pathological conditions, gut - and blood - derived antigen presentation to T-cells leads to the expression of specific immunosuppressive molecules, like programmed death-ligand 1 (PD-L1). Even though T cell proliferate upon contact with LSCEs, they remain unlicensed for cytotoxic effects under the presence of PD-L1. This mechanism is essential for developing tolerance for antigens derived from food and commensal gut bacteria, which are continuously found in the portal circulation (13).

Hepatocytes themselves exhibit an immunological function, as well. They are responsible for the production of complement components, pattern recognition receptors (PRRs) and acute phase proteins (10).

Despite the liver's capacity of immune system activation, under basal conditions it persists in a state of immune hypo-responsiveness or tolerance. In contrast, viral or bacterial infections shift this towards a rapid inflammatory response. This finely tuned homeostasis between immune tolerance and immune activation, is highly important to differentiate threats, e.g. pathogens, from nonthreats, e.g. food or commensal bacteria (14).

The term cirrhosis-associated immune disfunction (CAID) refers to a range of immunological disturbances that develop in liver cirrhosis. It is characterized by two patterns, systemic inflammation and immunodeficiency. The type of immune response depends on the disease stage (compensated, decompensated, acute- on- chronic liver failure (ACLF)) (Fig. 1), extent of liver injury and presence of environmental stimulation, e.g. pathogen and damage associated molecular patterns (PAMPs, DAMPs) from bacterial translocation (BT) (12).

In compensated cirrhosis and still in the absence of BT, activation of the immune system is mainly due to DAMPs released by necrotic hepatocytes. As the disease progresses, intestinal permeability increases, subsequently leading to bacterial translocation. As a result, increased exposure to gut microbes and microbial products (PAMPs) further stimulates the immune system (15). This is characterized by rising serum levels of pro inflammatory cytokines, e.g. TNFα, IL-17, IFN-γ, and enhanced synthesis of immunoreceptors and their costimulatory molecules, chemokines and adhesion molecules. Further hallmarks are recruitment and activation of leukocytes to the liver, increased phagocytic activity, vascular endothelial injury and hepatic synthesis of acute (12,15).

Additionally, the extent of systemic inflammation in liver cirrhosis might be linked to certain genetic polymorphisms. Specific variations in the genes coding for PRR, e.g. TLR2, showed a correlation with higher systemic immune responses and infection susceptibilities (16–18).

Systemic inflammation is also thought to play a pathophysiological role in several clinical manifestations of cirrhosis. For example, excessive nitric oxide production due to cytokine stimulation worsens splanchnic and systemic vasodilation (19). Moreover, inflammatory cytokines in the brain may contribute to the development of encephalopathy and fatigue by direct activation of resident macrophages, endothelial and astrocytic cell function modulation, etc. (20,21).

In the late decompensated stage of cirrhosis, e.g. ACLF, BT reaches its peak and excessively exposes the liver to PAMPs, leading to an immune response reprogramming. Meanwhile the decompensated structure of the liver causes exhauster of the immunological and synthetic capacities of the liver. This results in a switch from the proinflammatory phenotype of early cirrhosis to a predominant immunodeficient phenotype (15). Experimentally it is demonstrated by the fact, that rats with decompensated cirrhosis and high BT, show decreased cytokine production and phagocytosis by dendritic cells. Whereas bowel decontamination induces partial normalization (22).

Immunologically, the state of immunodeficiency in CAIDs is characterized by the inability of monocytes to produce TNFα in response to LPS, reduced T lymphocyte IFN-γ production and extensive release of anti-inflammatory cytokines, e.g. IL-10. Clinically, this is expressed by a poor response to vaccination, increased susceptibility to bacterial infections and higher mortality rates due to infections (12).

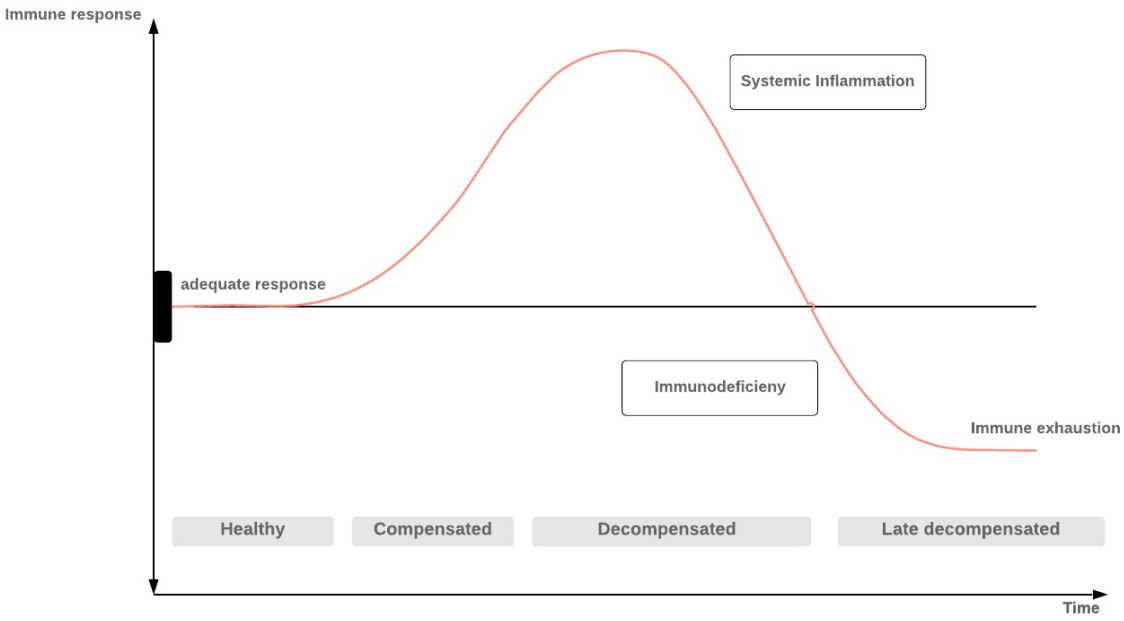

Figure 1: Schematic representation of cirrhosis associated immune dysfunction
Adapted from Albillos A, et al., Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance. Journal of Hepatology. 2014.

Lastly, clinical factors, such as frequent hospitalizations, immunosuppressive therapy (in autoimmune hepatitis, post- transplantation), and interferon therapy (in viral hepatitis), further promote the development of CAID.
Also, the long-term use of proton pump inhibitors has been associated with intestinal bacterial overgrowth and the development of bacterial translocation. Invasive diagnostic and therapeutic procedures additionally increase the risk for nosocomial infections (12,15).

2.2. Pathological bacterial translocation

Bacterial translocation is defined as the migration of microorganisms or PAMPs from the intestinal lumen to extra- intestinal tissue. Even though it can occur in healthy individuals to a limited extent, it is highly pronounced in cirrhotic patients and thus considered pathological. BT related exposure to microorganisms and PAMPs builds the pathogenic basis of CAID (see Chapter 2.1 Cirrhosis associated immune dysfunction) and subsequent susceptibility to infection (23). According to clinical studies pathological bacterial translocation occurs in 25-50% of cirrhotic patients and increases in prevalence with worsening of the disease (24). It can be caused by both viable bacteria and bacterial fragments, causing bacterial infection or increased inflammatory response, respectively.
There are three main mechanisms underlying pathological BT: small intestinal bacterial overgrowth (SIBO), intestinal barrier dysfunction, and immunological impairment (23).

2.2.1. Small intestinal bacterial overgrowth

The proximal small intestine (duodenum, jejunum) is sparsely colonized by commensal bacteria. However, from the ileum on there is a sharp increase in bacterial density, forming from 10^5 colony forming units (CFU)/ ml in the proximal jejunum to 10^8 in the distal jejunum (25). SIBO has been defined by most as > 10^5 CFU/ml in proximal jejunal aspirate and its prevalence in cirrhotic patients is estimated to range from 48% to 73% (26). Nevertheless, the exact number of affected patients is difficult to obtain, since diagnosis by upper jejunal aspiration is limitedly performed.

The development of SIBO is multifactorial, with the main factors being impaired intestinal motility, low gastric acid secretion, decreased pancreato-biliary secretion and modified intestinal immunological factors (19).

SIBOs is highly interconnected with the development of BT and this is experimentally illustrated by the fact, that the absence of SIBO is associated with a low rate of BT (0-11%). However, half of the cirrhotic animals with SIBO do not show BT, which suggests, that there might be other factors involved in the pathogenesis of BT (24).

In addition to the quantitative changes also qualitative changes of the microbiota have been observed in liver cirrhosis. Pyro- sequencing techniques have shown reductions in microbial diversity and depletion of beneficial bacteria, e.g. *Lachnospiraceae* (25). It is suggested, that these microorganisms outnumber other bacteria under normal conditions and by doing so limit overgrowth and subsequent translocation of pathological bacteria. Nevertheless, the exact role of qualitative microbiota changes in the development of BT remains unclear and needs to be further evaluated (27).

2.2.2. Intestinal barrier dysfunction

The function of the intestinal barrier is regulated by two main components, the mechanical and the secretory. The mechanical component consists of a single layer of columnar epithelial cells and acts as a physical barrier for intruding bacteria and molecules. Furthermore, epithelial cells deliver critical secretory compounds to the intestinal lumen, such as IgA, mucus proteins and antimicrobial peptides (AMPs) and thus form the secretory component. Alterations on both levels have been observed in liver cirrhosis, creating another field of investigation in the pathogenesis of the disease (26).

Under normal conditions tight junctions (TJs) maintain a permeability seal, restricting paracellular movement of very small molecules, including bacteria and macromolecules such as LPS. In duodenal biopsies of cirrhotic patients though, a reduced number of TJs has been observed, possibly leading to increased intestinal permeability for bacteria and PAMPs (28).

However, most of the bacteria critical for BT are transported via the transcellular route. Experimental studies have shown, that BT occurs in 87% of rats with increased intestinal permeability and SIBO and not at all in animals with only increased intestinal permeability. This raises the suspicion, that loosening of TJs is not the determining factor in the development of BT, but it is rather a multifactorial process (19).

The secretory compartment is formed by AMPs, Mucins, Bile and IgA antibodies. Important parts of AMPs are α- and β- defensins, since they provide crucial bactericidal activity by disrupting the structure and function of microbial membranes. Experimentally, a decreased production of α-defensins by Paneth cells has been demonstrated in cirrhotic rats with BT but not in those without BT. In contrast, a reduction in β- defensins, which are secreted by epithelial rather than Paneth cells, has not been proven. Hence, intestinal BT might be related to compromised Paneth cell function (29).

The intestinal mucus can be subdivided into a "firm" inner layer and "loose" outer layer. Mucins of the inner part form a glycoprotein layer, which inhibits direct microbial contact with the epithelium. In contrast, the outer layer acts as a habitat for commensal bacteria and provides specific binding sites for bacterial adhesins. Recent studies have shown, that the overall mucus thickness in the duodenum of cirrhotic patients is increased, presenting as mucous congestion. Weather these changes are the cause, or the result of BT still remains unclear and further research is required (26).

Furthermore, intraluminal bile acid concentrations are markedly reduced in liver cirrhosis. This has been attributed to decreased overall secretion and increased deconjugation by bacteria. Normally bile inhibits bacterial overgrowth, exerts a trophic effect on the intestinal mucosa and neutralizes endotoxins. Hence, its diminished production further contributes to the development of BT. Indeed, experimental studies on cirrhotic mice models have shown, that administration of oral bile acids reduces bacterial overgrowth, BT, and endotoxemia in cirrhotic rats (30).

2.2.3. Immunological impairment

Despite the CAID originating in the liver, the intestinal mucosal immune function may be compromised as well. Under normal conditions BT induces the release of chemokines by gut epithelial cells in order to recruit Dendritic Cells (DCs) to the mucosa. Once activated, DCs have the ability to signal mucosal B and T cell activation, hence forming the adaptive intestinal immune response against invading commensals (26). On the contrary, in cirrhotic patients a reduction in these memory B cells has been observed (31).

Furthermore, due to the inflammatory response induced by BT, increased synthesis of cytokines, specifically TNF- α, interleukins and NO causes oxidative damage to the intestinal mucosa. This in turn further increases intestinal permeability, promoting more BT and finally leading into a vicious cycle (19).

Generally, until now there is only a sparse number of studies on local immunological alterations on the intestinal barrier in liver cirrhosis, so its exact pathophysiological impact on developing infections remains unclear. It is also uncertain, how important these immunological alterations are in causing BT or if they are rather the result of BT (32).

3. Epidemiology and Types of Pathogens

In about 30- 50 % of cirrhotic patients death is caused by bacterial infections (33,34). Infections occur in 32- 34 % of hospitalized patients with cirrhosis and even more often in the presence of gastrointestinal bleeding (45 – 60 %). On the other side, in hospitalized patients, who do not have cirrhosis, infections are present in 5-7%. This means, that there is a 4-5 times higher prevalence of infections in cirrhotic compared to noncirrhotic hospitalized patients (35).

Risk factors for acquiring infections are advanced stages of liver cirrhosis, variceal bleeding, prior spontaneous bacterial peritonitis (SPB), low ascitic fluid protein levels and hospitalization (30,32).

The most common types of bacterial infections in liver cirrhosis are SBP (25-31%), urinary tract infection (UTI) (20-25%), pneumonia (15-21%), bacteremia (12%), and soft tissue infections (11%) (36,37).

The majority of cirrhosis associated infections are community acquired (CA) (60%), whereas 40 % are nosocomial or health care associated (1).

Infections are culture positive in 50-70 % of cases. Most of the causative organisms are gram negative bacteria (~75%), whereas gram positives compromise 20% and anaerobes only 3% (32).

In SBP and UTIs Escherichia coli is the main causative organism, in pneumonia very often Streptococcus pneumoniae is detected, and in procedure- associated bacteremia Staphylococcus aureus is frequently the cause. In up to 15% of severe cases of sepsis fungal infections (especially Candida species) are involved (38).

However, in nosocomial infections this distribution pattern is slightly changed, so that gram positive are more frequently isolated (38-70%) (37,39,40). Out of these, more than half (64%) appear to be resistant to antibiotics and are associated with poor outcomes (see chapter 8.3. Antibiotic prophylaxis and emergence of resistance) (40). Recent hospitalizations, health care support, and previous antibiotics increase the risk of acquiring infections with multi-drug resistant (MDR) bacteria (41).The most frequently encountered MDR bacteria are extended spectrum beta- lactamase (ESBL) producing *Enterobacteriaceae*, non- fermentable Gram-negative bacilli (e.g. *Pseudomonas aeruginosa*), methicillin- resistant *Staphylococcus aureus* (MRSA), and vancomycin- resistant *Enterococci* (VRE) (41). Unless antibiotic administration policy and mentality does not change, the number of these infections is expected to rise in the future.

4. Types of Infections

4.1. Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is defined as the infection of ascitic fluid in the absence of any intra-abdominal source of infection and it is considered to be the most common type of infection in liver cirrhosis (see Chapter 3. Epidemiology and types of pathogens), occurring in about 20% of cirrhotic patients hospitalized with Ascites (38,42). There is an approximately 10% chance to develop the first SPB within one year of ascites development and it is increased with deteriorating liver function, presence of gastrointestinal bleeding and/or low ascitic fluid protein levels (<1g/dL) (42).

Overall mortality of SPB is around 40% (43) and hence clinical suspicion should be high. This means, that every patient with ascites has potentially SPB until proven otherwise (44).

All patients with ascites or gastrointestinal bleeding on admission and all hospitalized patients, who additionally develop signs of sepsis, hepatic encephalopathy or renal impairment, should undergo immediate diagnostic paracentesis. SPB is diagnosed, if the ascitic polymorphonuclear cell count (PMC) is $\geq 250/mm^3$. Positivity of microbiological ascitic fluid culture is not required for the diagnosis and it occurs that more than 50% of microbiological investigations are anyways culture negative (45) (see Figure 2).

Sometimes patients may have positive ascitic fluid cultures, but a PMC count of less than $250/mm^3$. This state is called bacterascites and can either resolve spontaneously or it can be the initial presentation of SPB. It is crucial to recognize potential SPB and guidelines state the following: If the patient presents with signs of inflammation, he should be treated as if he had SBP. In the case of asymptomatic bacterascites, paracentesis should be repeated after 48 hours. If the PMC count of the second paracentesis is more than $250/mm^3$, antibiotic treatment has to be initiated as well. Otherwise, in case of a repeated PMC count of less than $250/mm^3$ follow up is recommended (46) (see Figure 2).

Since there might be some delay until the results of paracentesis are obtained, the use of reagent strips has been proposed for a rapid bedside diagnosis. These tests were designed to detect high leukocyte esterase activity in urine, demonstrated by a color change on the strip. However, review of different studies has led to the conclusion, that reagent strips have low sensitivity and especially a low specificity for SPB and its use is not recommended anymore (47).

Clinically SBP may present with the classical signs of peritonitis, i.e. localized abdominal pain, tenderness, vomiting, diarrhea or ileus and/or systemic signs of inflammation, such as hyper- or hypothermia, chills, tachycardia and tachypnea. Worsening of liver function, hepatic encephalopathy, shock and renal failure are other possible manifestations. However it is important to keep in mind, that in over half of the cases SPB is asymptomatic (46).

An important differential diagnosis of SBP is secondary bacterial peritonitis. It develops with inflammation or perforation of intraabdominal organs and has to be differentiated from SBP. Clinical suspicion should be high in the presence of the following: localized symptoms, very high ascitic PMC and protein counts (> 1g/dl), polymicrobial ascitic fluid cultures or inadequate response to therapy. In this case prompt CT evaluation should be ordered. Since a delay in surgical treatment can tremendously increase mortality, the possibility of secondary bacterial peritonitis should be always kept in mind (48).

Figure 2: Diagnosis of spontaneous bacterial peritonitis

4.2. Urinary tract infection

Urinary tract infections form the second largest group of infections in liver cirrhosis (see Chapter 3. Epidemiology and types of pathogens) and occur twice as frequent in cirrhotic as in non- cirrhotic patients (38). Patients are usually asymptomatic, presenting only with bacteriuria (49). Urine cultures are most of the time positive for gram negatives, such as *E. coli* and *Klebsiella spp*. and risk factors for acquiring these infections are usually advanced liver disease, female sex and catheters (38,50). The exact mechanism for the development of UTIs in cirrhosis remains unclear, but researchers have been observing an increased post-voiding volume in the ascitic compared to the non- or post- ascitic stage (51).

In case of asymptomatic bacteriuria treatment is not required, but in case of symptomatic UTIs or pyelonephritis empiric antibiotic treatment should be initiated and tapered down after receiving culture results (52).

4.3. Pneumonia

Pneumonia is the third most common infection in liver cirrhosis (see Chapter 3. Epidemiology and types of pathogens) and is considered to have one of the highest overall mortality from all the infections, reaching 37-41% (53,54). It is usually community acquired, but factors like tracheal intubation, esophageal tamponade, or hepatic encephalopathy increase the risk for acquiring pneumonia in the hospital (38). The most common isolated pathogens are like in non- cirrhotic patients *Streptococcus pneumonia*, *Haemophilus inluenzae* or *Klebsiella pneumoniae*. In hospital acquired infections gram negatives, e.g. *Pseudomonas aeruginosa* and *Staphylococci* are more likely the cause (55).

4.4. Skin and soft tissue infections

Skin and soft tissue infections, such as cellulitis and lymphangitis, compromise another frequent group of infections in liver cirrhosis. Most common isolated bacteria in these infections are gram-positives, specifically, *Staphylococcus Aureus* or *Streptococcus Pyogenes*, but also gram-negative bacteria (*E. coli, Klebsiella spp.*, *Pseudomonas aeruginosa*, *Aeromonas spp.*, *Vibrio spp.*) are more often being the cause (56,57). Because of this wide possibility of causative pathogens, gram stain smears of infected tissue should be immediately collected and broad- spectrum antibiotic treatment should be commenced as soon as possible (32).

When encountering skin and soft tissue infections in the combination of cirrhosis, the possibility of severe cellulitis and necrotizing fasciitis should be always kept in mind. This is due to the fact, that many times a clear portal entry cannot be identified in the skin of these patients.

Hence, in the presence of severe pain or other inflammatory signs, early surgical debridement should not be delayed, even if there is no evidence of a significant wound entry (32).
Overall mortality of severe cellulitis and necrotizing fasciitis ranges from 6-76%, depending on the causative agent, progression of the disease, presence of hemorrhagic bullae, initiation time of treatment and stage of cirrhosis (56,58).

4.5. Bacteremia

Bacteremia is defined by the presence of bacteria in the blood and occurs in around 11% of cirrhotic patients (36,37). It can be subdivided into primary or spontaneous bacteremia and secondary bacteremia.
Primary or spontaneous bacteremia is the presence of bacteria in the blood without an obvious source of infection (32). Blood cultures are usually positive for gram negative enteric bacilli and enterococci, suggesting bacterial translocation as a possible underlying mechanism (39).
Secondary bacteremia has a clear source of pathogen entrance, e.g. gastrointestinal bleeding, wounds, catheters, etc. (32). It occurs 17-45% of the time after an episode of gastrointestinal bleeding and also in this case gram negatives are usually the source (39,59).
Health- care associated bacteremia is typically associated with procedures like intravenous catheter insertion, transarterial chemoembolization or therapeutic endoscopy (28). Frequently encountered bacteria are *S. aureus* and *S. epidermidis* and in up to 35% of the cases bacteremia is culture positive for MRSA strains (38).
The higher incidence of bacteremia in cirrhosis is mainly due to its associated immune dysfunction and this is also the reason why these patients are at higher risk for developing sepsis (38). If untreated, this inevitably leads to decompensation of the liver disease and multiple organ failure, a state known as acute- on- chronic liver failure (ACLF).

5. Complications and Consequences

Indeed, infections are considered to be one of the most common causes of ACLF, being present in 33% of the cases (60). The Chronic Liver Failure (CLIF) – Sequential Assessment of Organ Failure (SOFA) is widely used to define and grade the severity of ACLF according to the number of present organ failures. SOFA can also be used as a mortality predictor, since studies have been shown that higher grades are associated with higher mortalities (grade 1 (22 %) vs. grade 3 (77%)) (58). Specific aspects of the most common failing organs will be discussed in the following sequence of this review.

5.1. Renal failure

Infection related acute kidney injury (AKI) is present in 27- 34% of decompensated liver disease and significantly contributes to increased mortality in these patients (around 40 % vs 7%) (61). It used to be commonly defined as a serum creatinine level of > 1,5 mg/ dL, but the International Club of Ascites (ICA) has suggested a new definition. This is due to numerous factors, like age, bodyweight, race, gender, muscle wasting, etc., influencing baseline values of serum Creatinine. According to ICA AKI should be redefined as an increase of serum creatinine by >0,3 mg/dl within 48 hours or by 50% from a stable baseline within 6 months, regardless of its absolute value. Also a subdivision into three stages has been defined and the differentiation between progressive and regressive AKI (61).

The development of AKI in liver cirrhosis is linked to the increased production of vasodilators, such as nitric oxide, during infection, which results in worsening vasodilation in the splanchnic circulation. This in turn leads to increased cardiac output, decreased systemic vascular resistance and activation of the renin- angiotensin system, all leading to reduced renal perfusion and GFR (43).

Risk factors associated with the development of AKI are advanced liver disease, pre- existing kidney disease, hypovolemia or low cardiac output and unresolved infections (61–63).

A specific entity of infection related renal failure in cirrhosis is termed hepatorenal syndrome (HRS). It is defined as AKI in liver cirrhosis in the absence of any apparent cause. It is a diagnosis of exclusion and it is important to exclude hypovolemia, shock, including septic shock, parenchymal renal diseases and recent use of nephrotoxic drugs (see Table 1) (45).

Table 1: Criteria for diagnosis of hepatorenal syndrome in cirrhosis

Presence of ascites
Serum creatinine >1.5 mg/dl
Absence of shock
Absence of hypovolemia
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal renal disease

Adapted from Ginés P, et al., EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. Journal of Hepatology. 2010

Based on its clinical course hepatorenal syndrome is subdivided into two types, namely HRS type 1 and HRS type 2. HRS 1 is considered to be more severe and progressive and is defined by a serum creatinine increase of greater than 100% to a level higher than 2,5mg/dl in less than 2 weeks. On the contrary, Type 2 is known as renal failure, that is less severe and progressive (45).

The development of HRS is associated with a rapid increase in mortality and requires prompt intervention (discussed in 8.5. Management of hepatorenal syndrome), since the overall medial survival time of all patients with HRS is around 3 months (64,65). Overall mortality for HRS is around 20 % and higher MELD scores and type 1 HRS are associated with even worse prognosis (66,67).

5.2. Adrenal insufficiency

Relative adrenal insufficiency (RAI) or critical illness related corticosteroid insufficiency (CIRCI) are terms used to describe a state of dysfunctional cortisol production in the context of critical illness or stress (68).

There is still controversy about the exact mechanisms of the development of adrenal insufficiency (AI) in liver cirrhosis. Many of the proposed pathophysiological mechanisms share common features with the development of RIA in critically ill patients with sepsis and no cirrhosis. However, a significant amount of cases (7-83%) have been reported in non- critically ill patients with cirrhosis, introducing the theory that certain pathophysiological mechanisms may be attributed to the liver dysfunction per se (68). Several studies have observed decreased levels of serum HDL cholesterol in liver cirrhosis and anti-inflammatory mediators, like TNF-α, Il-1 and Il-6, decrease hepatocyte synthesis of apolipoprotein A1, a major constituent of HDL cholesterol (69,70). Furthermore, endotoxins like LPS can also limit the delivery of HDL cholesterol to the adrenal gland (71). All in all, this leads to reduced steroidogenesis, since cholesterol is known to be the main substrate for steroid synthesis (69–71).

Besides cholesterol deficiency, other factors may play a role as well. For instance, coagulopathy (see Chapter 5.5. Coagulopathy), which is another comm complication of liver cirrhosis, may cause adrenal hemorrhage and infarction. This further limits its steroidogenic capacity (72).
The prevalence of AI is not very clear, since there are no standardized test and criteria to diagnose AI. Hence numbers vary between studies, ranging from 10-87% in critically ill cirrhotic patients and 7 – 83% in stable cirrhotic patients (68).
The use of hydrocortisone as a treatment still remains controversial. Whereas some studies report decreased mortality, reversal of septic shock and reduced vasopressor requirements, other studies report no survival benefits or even higher incidences of infections (68).

5.3. Encephalopathy

Infections are known to be an important trigger of hepatic encephalopathy and do not only serve as precipitants but may also worsen already pre-existent hepatic encephalopathy (73). This might be linked to the potential capacity of inflammatory mediators and reactive oxygen species to aggravate cerebral effect of ammonia and hence, precipitate or worsen hepatic encephalopathy. A study has illustrated this by the fact, that induced hyperammonemia during SIRS results in deterioration of neuropsychological function, whereas resolution of SIRS does not cause these effects (74,75). Another study showed that injection of LPS in cirrhotic rats caused pre-coma and exacerbation of cerebral edema, due to the synergistic effect of cirrhosis associated hyperammonemia and infection related inflammatory response (20).

5.4. Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is common in decompensated liver cirrhosis. Pulmonary cellular function seems to be altered in cirrhosis, with alveolar macrophages exhibiting reduced antibacterial activity, differentiation of T – lymphocytic subsets and altered capillary permeability (76,77). Furthermore, reduced altered mental status in the context of hepatic encephalopathy predisposes to aspiration pneumonia. Pressure exerted by tense ascites limits basal lung expansion, further reducing pulmonary function. These factors in addition to local inflammatory effects result in a higher incidence of ARDS in patients with cirrhosis and sepsis than in others and it is associated with a higher mortality rate (78).

5.5. Coagulopathy

Coagulopathy is a common feature of liver cirrhosis and is caused by the deficient hepatic synthesis of coagulation factors VII, V, X, prothrombin, Vitamin K and platelets (34). The incidence of coagulation abnormalities is higher in cirrhotic patients with sepsis than without. This is due to the contribution of inflammatory cytokines causing impaired platelet function, increased fibrinolysis and consumption of clotting factors, known as consumptive coagulopathy (79).

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5.6. Variceal Bleeding

Variceal bleeding is well known to predispose to bacterial infections, but also vice versa infections seem to be closely associated with a higher risk of variceal bleeding (55). This might be due to the fact, that endotoxins cause further increase in portal pressure in already pre-existing high-pressure varices and thus make them more prone to bleeding (30). Indeed, evidence has shown that cirrhotic patients with infections have a higher prevalence of uncontrolled bleeding, early rebleeding and mortality (80).

6. Early Diagnosis and Biomarkers

Early diagnosis and subsequent treatment of infections is crucial, in order to prevent fatalities in patients with liver cirrhosis. Since many cirrhotic patients may have subtle or nonspecific symptoms and signs, it is important to always keep a high clinical suspicion. Whenever a cirrhotic patient is hospitalized or clinical deterioration occurs, a complete workup should be conducted. This includes a detailed physical examination, closed microbiological surveillance, repeated blood work up and other tests like, chest- X ray, urine and ascitic fluid culture (41).

Markers of Infection

In many cirrhotic patients infection is accompanied by the systemic inflammatory response syndrome (SIRS). Even though SIRS has been diagnosed in 57- 70% of cirrhotic patients with infections, its presence can still not be used solely as a marker for infection (81,82). This is attributable to the fact that, because of hyperdynamic circulation, hepatic encephalopathy, tense ascites and hypersplenism, altering heart and respiratory rate, many times SIRS is diagnosed in cirrhotic patients in the absence of infections. On the other side, SIRS is often undiagnosed in cirrhotic patients with infections, due to the use of beta blockers and an apparently normal white blood cell count caused by hypersplenism (23).
The use of the acute phase proteins procalcitonin (PCT) and C- reactive protein (CRP) as early markers of infection has been found to have a similar predictive power for detecting infection in patients with and without cirrhosis. Furthermore, CRP and PCT levels have been shown to correlate with the severity, course and outcome of sepsis in patients with cirrhosis (83,84). Nevertheless, potential limitations on its usefulness in these patients have been proposed as well. Accordingly, inflammation and bacterial translocation can induce increased synthesis of PCT and CRP without the presence of infection, leading to false interpretation of the values (23). Furthermore, since CRP is produced exclusively in the liver, bacterial infection in decompensated liver disease may present with a reduced CRP response and this can result in underdiagnosis of early infection (85).
Another factor is that in the majority of cases CRP levels remain elevated even after the resolution of the infection (86). This limits its role as a clinical course predictor and thus some research assumes that procalcitonin plays a superior role in this case. However, this hypothesis is still under discussion and until now the use of the combination of CRP and PCT as markers of infection and its severity is recommended (87).

New tools for pathogen identification

The use of real time PCR essays where shown to be also beneficial when it comes to diagnosing infections. They target DNA sequences of bacteria and fungi directly and unlike culture methods do not require a prior incubation period, hence results can be obtained in less than 6 hours (23).
In addition, sensitivity and specificity for detecting bacteria from ascitic fluid is higher in this method compared to conventional culture methods (88). However, the use of real time PCR is expensive and special equipment and expertise for DNA extraction is required. Due to the inconsistency with culture results and frequent isolation of environmental organism with unknown pathogenicity, real time PCR essays can still not fully replace microbiological culture techniques (88).
Recently, new methods, known as direct susceptibility tests (DST), have been introduced to early identify resistant bacteria from positive blood cultures and to determine their antibiotic susceptibility. Even though this method seems to operate faster than others, it cannot be used for mixed culture results or infections caused by yeasts and results still need to be confirmed by classical methods (23). Yet it is in the light of future research, since it might be beneficially used for targeted antibiotic therapy and prevention of multidrug resistance (see Chapter 10. Conclusion and future research).

7. Treatment

7.1. Antibiotic Treatment

Once infection in patients with cirrhosis is suspected, it is crucial to initiate antibiotic treatment immediately, since increased mortality is usually associated with inappropriate choice and delayed start of therapy (45). Antibiotics should be chosen according to type, severity and origin of infection (community- acquired (CA) vs. health care – associated (HCA)) (see Table 2). Regarding the treatment of HCA infections, one should be familiar with the local epidemiological pattern of antibiotic resistance, which might vary between hospitals. If the causative organism is identified (in 50% of cases), empirical treatment should be tapered down according to the results, in order to prevent emergence of antibiotic resistance (27).

Table 2. Recommended empirical antibiotic treatment for community- acquired and nosocomial bacterial infection in cirrhosis.

Type of Infection	Community-acquired infections	Nosocomial infections
SBP and spontaneous bacteremia	Cefotaxime **or** ceftriaxone **or** amoxicillin/clavulanic acid **or** ciprofloxacin[6]	Piperacillin/tazobactam[1] **or** meropenem[2] ± gylcopeptide[3]
UTI	**Uncomplicated:** ciprofloxacin **or** cotrimoxazole **If sepsis:** Cefotaxime **or** ceftriaxone **or** amoxicillin/clavulanic acid	**Uncomplicated:** nitrofurantoin or fosfomycin **If sepsis:** Piperacillin/tazobactam[1] **or** meropenem[2] ± glycopeptide[3]
Pneumonia	Amoxicillin/clavulanic acid **or** ceftriaxone + macrolide **or** levofloxacin **or** moxifloxacin	Piperacillin/tazobactam[1] **or** meropenem/ceftazidime+ ciprofloxacin ± glyocpeptide[3], if patient with risk factors for MRSA5
Cellulitis	Amoxicillin/clavulanic acid **or** ceftriaxone + oxacillin	Meropenem/ceftazidime[4] + oxacillin **or** glycopeptides[3]

[1] In areas with low prevalence of multiresistant bacteria
[2] to cover extended spectrum β- lactamase producing *Enterobacteriaceae*
[3] IV vancomycin or teicoplanin in areas with a high prevalence of MRSA and vancomycin-susceptible enterococci. Replacement of glycopeptides by IV linezolid in areas with high prevalence of vancomycin-resistant enterococci.
[4] active against *Pseudomonas aeruginosa.*
[5] Ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage.
[6] Do not use in patients with previous fluoroquinolone SPB prophylaxis, due to risk of resistance

Adapted from Jalan R, et al., Bacterial infections in cirrhosis: A position statement based on the EASL Special Conference 2013. Journal of Hepatology. 2014

7.2. Management of spontaneous bacterial peritonitis

Empirical antibiotic therapy

As already mentioned before the crucial point in treating SPB lies in commencing empirical antibiotic therapy (table 2) as soon as possible, since SPB mortality can be drastically improved (from 90% to 20%) in patients, who are treated on time (89) . However, ascitic fluid, blood and urine cultures should be obtained before starting antibiotic administration (46).

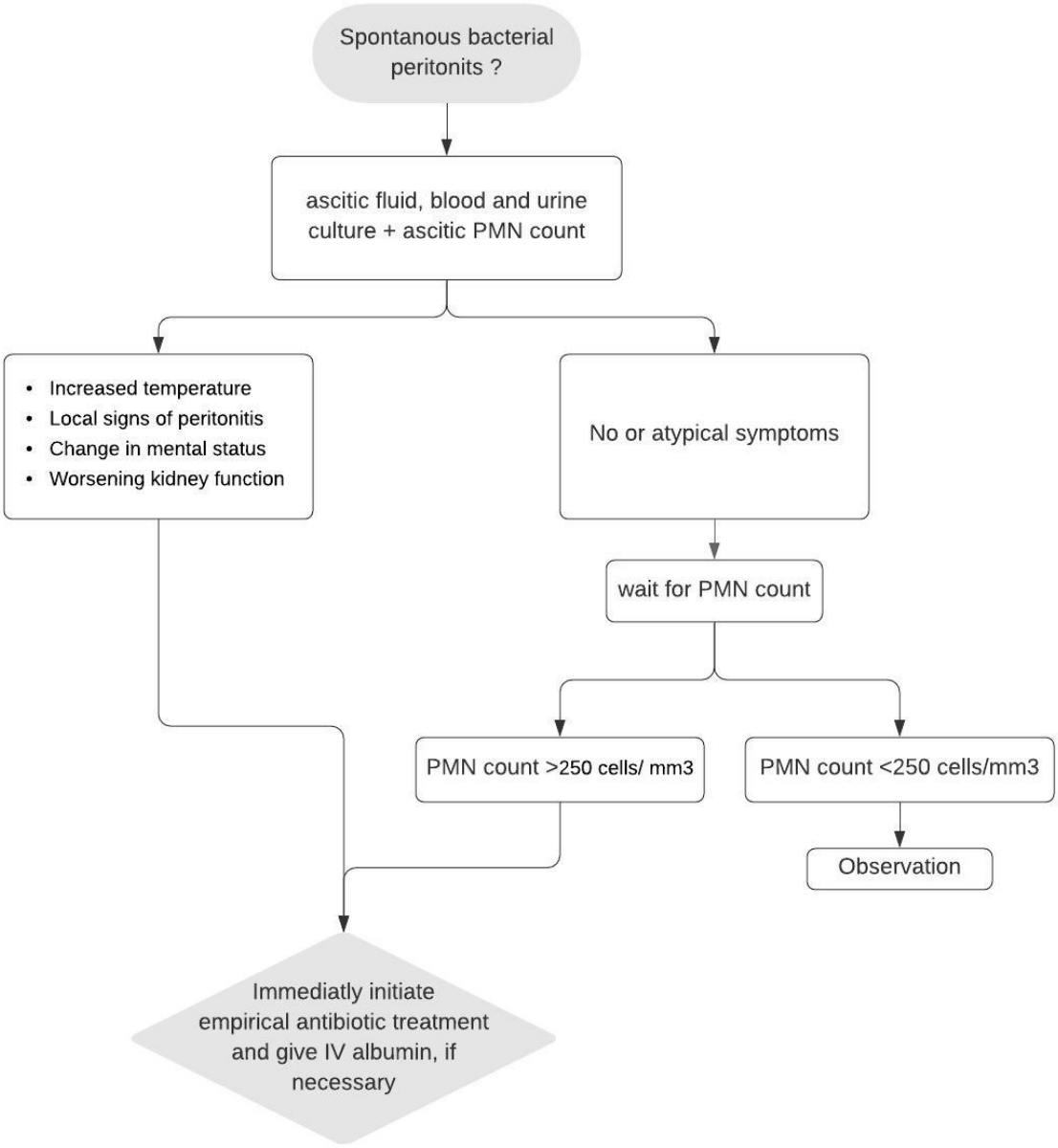

Figure 3: Management algorithm for spontaneous bacterial peritonitis

In the presence of the following indications, treatment for SPB should be initiated as soon as samples for culture and analysis are obtained and there is no need to wait for any results (90):

- Increased temperature
- Local signs of peritonitis (abdominal pain and tenderness, vomiting, diarrhea, ileus)
- Change in mental status
- Worsening kidney function

Regarding patients who do not present with the afore mentioned symptoms, it is recommended to wait until PMN counts are available and if they present with ≥ 250 cells/mm^3 antibiotic treatment should be initiated (46). Collection and analysis of ascitic PMN count should not take more than a few hours and culture results are not required for initiation of treatment, since they take much longer (90) (see Figure 3).

When it comes to choosing the type of antibiotic, cefotaxime should the first line choice. It is a safe and effective drug, with rash being its main adverse reaction in approximately 1 percent of patients. 2 g intravenously every 8 hours have been shown to be most effective, but lower doses or less frequent dosing, e.g. 2g every 12 hours, can be used in patients with impaired renal function, as well. Other treatment options are summarized in Table 2 (91).

Treatment with cefotaxime is generally recommended for 5 days and if clinical improvement is observed it can be stopped (91). Otherwise resolution of infection has to be proven by a decrease of ascitic neutrophil count to <250/mm^3 and negative ascitic fluid cultures, if they were positive before (42). On the contrary, if there is worsening of the clinical status and/ or no reduction in ascitic fluid neutrophil count, response to antibiotic therapy is most likely failing (46,92). This can be either due to the development of secondary spontaneous peritonitis or emergence of antibiotic resistance. It is important to exclude secondary bacterial peritonitis first and then readjust antibiotic therapy (42).

Discontinuation of nonselective beta blockers

Nonselective β blockers are commonly prescribed to patients with cirrhosis, in order to reduce portal hypertension and thus prevent variceal hemorrhage. They reduce cardiac output and splanchnic vasoconstriction by non-selectively inhibiting β_1 and β_2 adrenoreceptors (93). In the presence of bacterial infections like SPB peripheral vasodilation and a compensatory increase in cardiac output occurs (94). The adrenoreceptor blocking effect from NSBB use could inhibit this adaptive response and lead to circulatory collapse with inadequate organ perfusion. Indeed, a research has shown that the use of NSBB in the presence of SPB is associated with increase in mortality by 58%, higher incidence of hepatorenal syndrome (24 vs 11%) and longer length of hospital stay (95).

Intravenous Albumin

In about 30 % of patients, being treated with antibiotics alone, SPB is complicated by renal failure and is associated with a poor prognosis. Recently, a randomized controlled study has shown, that the administration of albumin (1,5g/kg body weight at diagnosis and 1g/kg on day 3) decreases the incidence of HRS type 1 from 30 to 10% and reduces mortality from 29 to 10%. This effect was mostly observed in patients with total bilirubin >4 mg/dl and creatinine >1 mg/dl and remains unclear in patients with values below these limits, since the incidence of HRS is generally lower in this subgroup (96). Nevertheless, it is recommended to treat all patients, who have SPB, with albumin regardless of their total bilirubin and albumin level. For infections other than SPB, so far, no significant improvement of overall mortality with the addition of albumin could be demonstrated, despite the fact that an increased resolution of ACLF and reduced development of nosocomial infections were observed (97,98).

7.3. Management of hepatorenal syndrome

General measures

Once there is a diagnosis of HRS treatment should be started as soon as possible to prevent further deterioration of renal function. Patients vital signs, urine output, fluid balance and arterial pressure should be assessed on a regular base. In ideal cases central venous pressure should be monitored in order to keep a precise fluid balance and prevent volume overload. For initial assessment and diagnosis all diuretics should be stopped, but otherwise diuretics like furosemide can be continued in order to maintain urine output or treat potential volume overload. Potassium sparing diuretics like spironolactone are absolutely contraindicated in cirrhotic patients with HRS, because of the high risk of severe hyperkalemia (45).

Drug therapy

Even though resolution rate of HRS and 30- day survival seem to be similar between treatment with norepinephrine and terlipressin (each in combination with albumin), the latter showed a higher incidence of adverse events (99,100). Furthermore, treatment with norepinephrine is more than three times cheaper than treatment with terlipressin (99). Hence, when available, e.g. in the ICU, treatment with norepinephrine plus albumin is recommended. Norepinephrine is administered intravenously as a continuous infusion (0,5 – 3mg/h) and albumin as an intravenous bolus (1g/ kg on day 1 followed by 40g/ day) (45).

Terlipressin should be also given in combination with albumin. It is usually initiated with a dose of 1mg/ 4-6h and increased to 2mg/4-6h if there is no adequate response to therapy (42). The average time to respond is around 14 days and depends on the pretreatment serum creatinine level, with lower levels requiring less time to respond (101). Terlipressin is generally effective in approximately 40-50% and recurrence of HRS after treatment is rare (65,102). However, 12% of the patients reported cardiovascular or ischemic side effects, thus it is important to closely monitor them for arrythmias and signs of ischemia. Ischemic vascular disease, like coronary artery disease, is a contraindication (65,102).
Another treatment option is the triple use of midodrine plus octreotide plus albumin. Therefore, midodrine is given orally at a dose of 2,5-7,5mg/ 8h (max. 15mg/8h) and octreotide subcutaneously with a dose of 100 μg/ 8 h (max. 200 μg/8 h). Even though this regimen shows to be effective as well, more data is available on the afore mentioned options (103,104).

Table 3: Pharmacological treatment options for hepatorenal syndrome

Norepinephrine	0,5 – 3 mg/ h IV
+ Albumin	1g/ kg on day one followed by 40g/ day IV
Terlipressin	1 – 2 mg/ 4-6 h IV
+ Albumin	1g/ kg on day one followed by 40g/ day IV
Midodrine	2,5 – 7,5 mg/ 8h p.o.
+ Octreotide	100 μg/ 8 h s.c.
+ Albumin	1g/ kg on day one followed by 40g/ day IV

The goal of the treatment is to reach creatinine values below 1,5 mg/dl and an increase in arterial pressure, urine volume and serum sodium concentration (42).

Non- pharmacological therapy

Even though some studies have demonstrated improvement of renal function with the insertion of transjugular intrahepatic portosystemic shunts, there is still insufficient data to implement this as a standard treatment option and many patients have contraindications for it (102, 103, 42).
In addition, renal replacement therapy, like hemodialysis or hemofiltration, have been shown by some studies to be beneficial, but also in this case sufficient data is lacking (107,108). However, in cases of severe hyperkalemia, metabolic acidosis and volume overload renal replacement therapy remains the only treatment option (42).
Liver transplantation is generally recommended in cirrhotic patients with HRS and in some patients combined liver and kidney transplantation should be considered (42).

7.4. Management of sepsis and septic shock

The main principles of managing sepsis and septic shock in cirrhosis are similar to the ones in non-cirrhotic patients. It also includes early antibiotic therapy and hemodynamic support. Mean arterial and central venous pressure, hematocrit and central venous oxygen might be different from non- cirrhotic patients, since these baseline values are often altered in cirrhotic patients, due to its hyperdynamic nature (78). Figure 4 summarizes important steps in evaluating and managing cirrhotic patients with sepsis or septic shock.

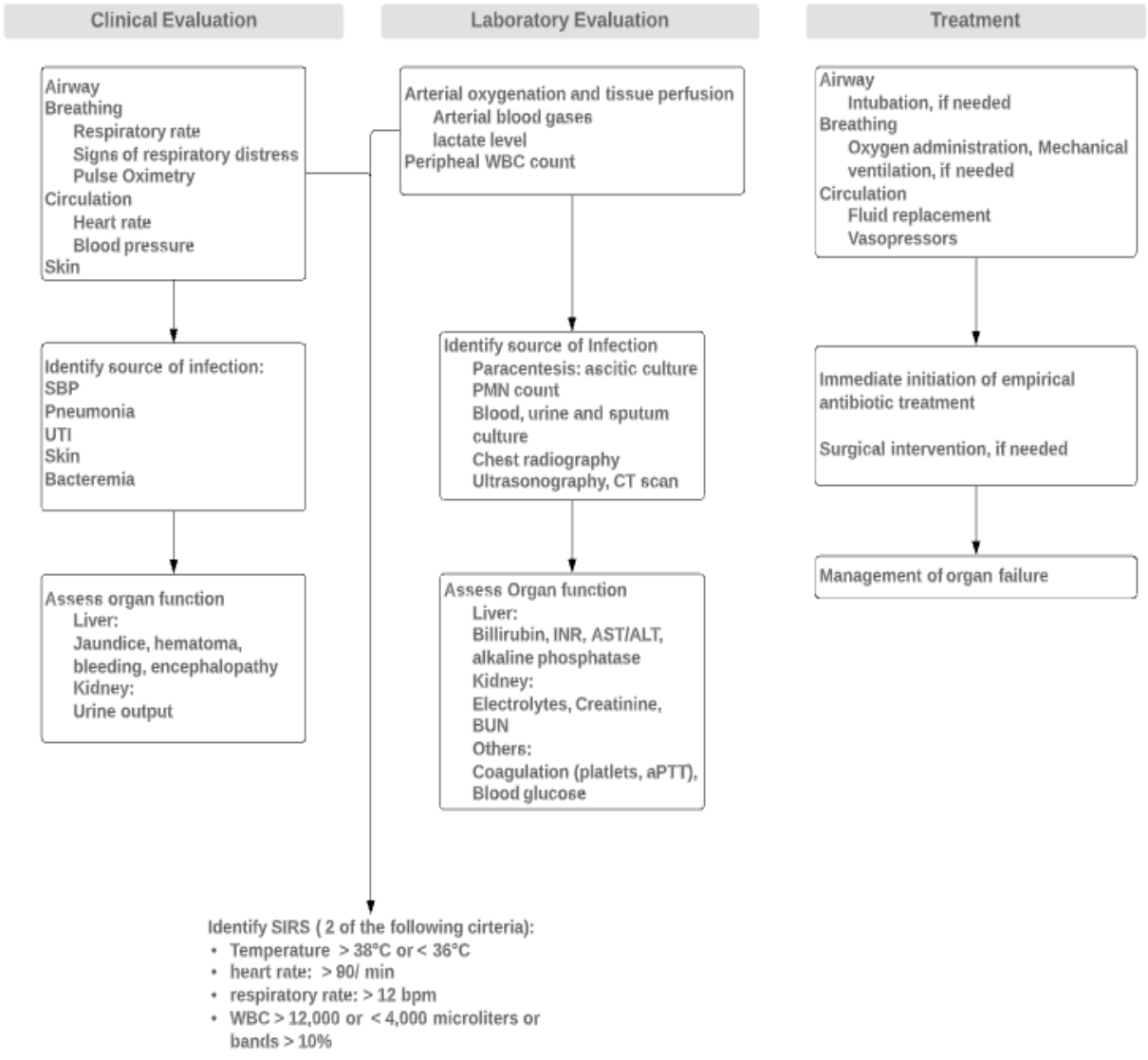

Figure 4: Diagnosis and Management of Sepsis in liver Cirrhosis.
Adopted from Gustot T, et al., Severe sepsis in cirrhosis. Hepatology. 2009

8. Prophylaxis

In order to prevent antibiotic overtreatment and emergence of resistant organisms, prophylactic antibiotics must be strictly reserved for patients, who are at risk of bacterial infections. Belonging to this category are patients with upper gastrointestinal bleeding, advanced cirrhosis and previous history of SPB (42,43,106,108).

8.1. Primary Prophylaxis

Gastrointestinal bleeding

More than half of cirrhotic patients develop bacterial infection within the first week after the hemorrhage and thus belong to a risk group (110,111). Prophylactic administration of antibiotics has shown to be associated with significant reduction in all-cause mortality, bacterial infection mortality, rebleeding events and length of hospitalization (111). The choice of antibiotic is controversially discussed in research. But generally, IV ceftriaxone (1g/day for 7 days) is preferred for advanced cirrhosis, i.e. when two of the following are present: ascites, jaundice, severe malnutrition, or encephalopathy. In other cases, oral norfloxacin (400mg/12h) can be used (27,112).

Spontaneous bacterial peritonitis

Also, regarding antibiotic prophylaxis for SPB, careful selection of the patients is mandatory and only those, who are at risk should receive prophylactic therapy. Antibiotics should be reserved for cirrhotic patients with an ascites protein < 1,5g/dl and liver failure or impaired renal function. For this purpose, liver failure is defined as a Child-Pugh score (113) ≥ 9 and a bilirubin ≥ 3 mg/dl and renal failure as a creatinine ≥ 1,2 mg/dl, a blood urea nitrogen level ≥ 25 mg/dl or serum sodium ≤130 mEq/L (27). In these patients long term prophylaxis with oral norfloxacin (400 mg daily) or oral ciprofloxacin (500mg daily) is often performed (2).

Use of Proton pump inhibitors

Many times, proton pump inhibitors are prescribed to patients with cirrhosis, due to their increased risk for developing peptic ulcers and subsequent bleeding (114). However, the use of PPIs is associated with increased SBO, BT, reduction of gastrointestinal motility and thus increased risk for infection (115,116). For this reason, PPIs should not be given to patients with cirrhosis, unless there is a clinical indication (117).

Other preventive measures

Besides antibiotic prophylaxis, vaccination is an important measure to prevent bacterial infections. Therefore, vaccinations against Hepatitis A and B, influenza and pneumococcus are recommended. It is important to perform them at early stages of the disease, since advanced stages are associated with an inadequate post-vaccination response and loss of immunogenicity. This is due to the immune dysfunction (see chapter 2.1. cirrhosis associated immune dysfunction) associated with progressing liver disease (118).

8.2. Secondary Prophylaxis

Patients who recover from SPB are at higher risk of developing a second episode. Therefore, antibiotic prophylaxis is highly recommended in this subpopulation, as well. Long term norfloxacin (400 mg daily) or ciprofloxacin (500mg daily) can be effectively used (27). In one study for instance, norfloxacin prophylaxis was associated with a reduction of SPB recurrence rate from 68% in the placebo to 20% in the treated group (119) Also liver transplantation should be seriously considered in these patients with a prior episode of SPB (45).

8.3. Antibiotic prophylaxis and emergence of resistance

While being beneficial in preventing infection and reinfection, at the same time antibiotic prophylaxis poses a risk of developing multidrug resistance. Type and extent of resistance largely depend on the local epidemiological patterns and incidence reaches up to 40% in some hospitals. Treatment of resistant bacteria is difficult and might result in a less than 50% resolution rate (3,120,121). These figures emphasize the importance to perform a proper risk stratification and to carefully select the patients for antibiotic prophylaxis. Therefore, the Tarragona strategy gives physicians a clear guide and states the following: 1) Recognize individual risk factors 2) Know local epidemiology 3) Treat immediately and broad enough 4) Treat according to site of infection 5) Reevaluate the patient (122).
Recently, rifaximin was proposed as a prophylactic alternative to norfloxacin (27). According to a case-control study the administration of norfloxacin to patients with hepatic encephalopathy seemed not to be associated with the development of infections with multiresistant bacteria (123). The following mechanisms might explain this theory: 1) rifaximin reaches high fecal concentrations, but is almost not absorbed, 2) it reduces virulence factor expression and capacity for plasmid transfer, which is required for resistance development, 3) despite its high fecal concentrations, it does not alter intestinal microflora extensively (27). Despite these promising figures, more research has to be done on its efficiency and safety compared to that of norfloxacin (27).

9. Prognosis

Mortality during and after infection in patients with cirrhosis is very high compared to cirrhotic patients without any infection. According to a large systematic review, published in the gastroenterology journal, infection is a significant predictor of outcome in liver cirrhosis and seems to increase mortality four fold (43).

Overall Mortality

Overall median mortality in patients with cirrhosis and a prior or ongoing infection lies around 43%. On the contrary mortality in patients without infection seems to be only around 14%. Out of the infected cirrhotic patients approximately 29% die within the first month, 44% within the first three months and 63% within the first year. The high mortality rate even after resolution of infection might be partially explained by the fact that levels of endotoxins, nitric oxide, and cytokines might not return to baseline after resolution and continue compromising systemic, renal and hepatic hemodynamics (43).

Mortality related to specific infection

The median overall mortality for SPB is approximately 43%, for bacteremia around 42% and for respiratory tract infections 37-41 % (43,53,54). For other infections like UTI and skin and soft tissue infections it is hard to obtain clear numbers and skin and soft tissue infection mortality also highly varies between the stage of infection, e.g. mortality in cellulitis compared to mortality in necrotizing fasciitis (56,58).

Prognostic Factors

It is very important to determine individual patient prognosis, meaning survival chances and mortality, in order to adjust therapeutic decisions. There are three main important factors determining mortality in cirrhotic patients with concomitant infection: severity of liver disease, presence of renal failure and non-resolution of infection due to antimicrobial resistance (124).
The severity of the disease can be reflected by using scores, e.g. Child-Pugh or Model for end-stage liver disease (MELD) score (54), which represent the degree of liver dysfunction or the amount of organ failure present. In addition the presence of cirrhosis associated complications, like gastrointestinal hemorrhage, hepatic encephalopathy or hepatocellular carcinoma, can be used as predictors of mortality (124).

Furthermore, the development of AKI is another indicator of worse outcome. Overall fatality rate in patients with cirrhosis and infection, who develop AKI is around 40% compared to a 7% mortality rate in patients without AKI and increases with progression of the disease (61).

The third common factor associated with increased mortality is the initial failure in treating infection, due to the emergence of antibiotic resistance. Resistance is usually common in nosocomial infections and is associated with almost double the risk of a fatal outcome (120,124). Other risk factors for acquiring resistance are previous antibiotic treatment, previous infection by multiresistant bacteria, diabetes mellitus and upper GI bleeding (see Chapter 3. Epidemiology and types of infection and Chapter 8.3. Antibiotic prophylaxis and emergence of resistance) (3,121).

10. Conclusion and future research

It has become clear, that decompensated liver cirrhosis is associated with immunological, structural, and hemodynamic changes, that make these patients susceptible to infections, systemic inflammation, organ failure and death. The presence of infection is associated with increased complications and morbidity. Often, due to the concurrent immune dysfunction, overt clinical signs of infection are lacking, making diagnosis difficult and delaying treatment. Hence, current and future research concentrates on generating models and possible markers to identify these patients and patients at risk.

In addition, new scoring systems need to be developed specifically for patients with liver cirrhosis and concomitant infection, in order to predict mortality more accurately.

Until now higher Child- Pugh scores and MELD scores are generally associated with higher mortality rates and thus are used to reflect severity of disease and extent of organ failure. However, the independent contribution of systemic inflammation and infection is not incorporated into these scoring systems. For instance, in the absence of SIRS a MELD score above 18 is associated with a 12% in-hospital mortality, whereas in the presence of SIRS the same MELD score is associated with 43% mortality (125). Reevaluation and redefinition of these scoring systems is considered as a potential for future research.

Another focus of research is the development of new technologies to qualitatively detect the type of pathogen and thus enable early targeted therapy and prevention of multidrug resistance (see chapter 6. Early diagnosis and Biomarkers) (27).

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13. Biography

Aresa Krasniqi was born in Munich, Germany on September 25th, 1995 as a daughter of Skender (born 1964 in Prishtina, Kosovo) and Arijeta Krasniqi (born 1974 in Prishtina, Kosovo). Her father works as a surgeon in Munich and her mother as a nurse. She is the first child in the family followed by her brother Andet Krasniqi (born 1997 in Munich, Germany) and her sister Lisa Krasniqi (born 2004 in Munich, Germany).

The author´s interest for medicine developed early. In 2010, when she was 14 years old, she completed an internship at Sozialstation Berg- am- Laim, a nursing ambulance in Munich. This was her first encounter with medical work and the fundamental of her future career. From Oktober 2013, after she finished high school, she started working as a nursing assistant at Klinikum Bogenhausen München at the Cardiology department.

In the same year she got accepted at the medical faculty at the University of Zagreb. Besides her studies Aresa Krasniqi would work as a private German teacher in Zagreb and during the summer holidays as a surgical assistant at Orthopädische Klinik München, OCM and a waitress at the restaurant Guido al Duomo in Munich.

Even though the author has already assisted in many surgeries, her main interest lies in internal medicine. Hence, she completed clinical rotations in December 2019 at the emergency department in Klinikum Bogenhausen. Currently, she is doing her rotations at the Cardiology department at the same hospital and department, where she was working as a nursing assistant in 2013/2014.

Besides the medical aspect Aresa Krasniqi loves hiking, skiing, playing piano and spending time with her family and friends. She speaks German, Albanian and English fluently and knows French and Croatian.