

Infections in Patients With End-stage Liver Disease

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Abstract: Infections in patients with end-stage liver disease (ESLD) are an important cause of morbidity and mortality in these patients. Abnormalities in their natural defense mechanisms, alterations in the enteric flora and the growing utilization of invasive procedures increase the risk of infections in these patients. Common bacterial infections in ESLD patients include spontaneous bacterial peritonitis, urinary tract infections, community-acquired pneumonia, dermatologic infections, and bacteremia. Viral infections such as influenza can have a devastating course in ESLD patients. Hepatitis B and C are now among the most common causes of ESLD. They also present an important therapeutic challenge. As patients with human immunodeficiency virus are surviving longer, ESLD due to hepatitis C is now emerging as a leading cause of morbidity in these patients. Prompt detection of infections, use of appropriate antibiotics for treatment and prophylactic measures such as vaccinations can help improve survival in these patients.

Key Words: end-stage liver disease, infection

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End-stage liver disease (ESLD) refers to advanced liver disease with hepatic fibrosis and complications including portal hypertension, ascites, encephalopathy, synthetic dysfunction, and impaired metabolic capacity. ESLD is associated with defects in the immune system, which increase the risk and severity of infections. Both humoral and cell-mediated immunity are depressed in patients with ESLD. These patients typically have a reduction in serum bactericidal, opsonic activity, complements, and fibronectin levels.¹ Community-acquired infections are still the most common source of infections in these patients. However, the increasing use of invasive procedures in the management of ESLD and its complications have led to the emergence of hospital acquired, resistant infections. This article aims at reviewing the common infections encountered in patients with including bacterial, fungal, and viral infections and their diagnosis, prophylaxis, and management.

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BACTERIAL INFECTIONS

Spontaneous bacterial peritonitis (SBP), urinary tract infections, respiratory infections, dermatologic infections, and bacteremia are some of the common bacterial infections seen in patients with ESLD.² As cirrhotic patients are more likely to undergo invasive diagnostic or therapeutic procedures which can alter the host defence barrier, they are at increased risk of acquiring nosocomial infections.³ Furthermore, ESLD patients can develop infections without fever, which can delay the diagnosis. Common organisms include aerobic, gram-negative bacilli with the increasing emergence of gram-positive organisms as well. Early diagnosis and treatment remains the most effective approach in the management of these patients.

SBP

SBP is defined as ascitic fluid infection without an apparent intra-abdominal source of infection.⁴ The incidence of SBP in ESLD patients admitted to the hospital with ascites has been estimated to range between 7% and 23%.^{2,5} The 1-year probability of development of the first episode of SBP in ESLD patients with ascites is approximately 10%.⁶ The diagnosis of SBP is based on the presence of an ascitic fluid polymorph nuclear (PMN) count of more than 250/mm³ and/or positive ascites fluid cultures, in the absence of clinical and laboratory evidence suggesting secondary bacterial peritonitis.

In approximately 50% to 60% of cases, the causative organism is isolated from the ascitic fluid or blood. The remainder including culture negative neutrocytic ascites, monomicrobial non-neutrocytic bacterascites, and polymicrobial bacterascites are considered variants of SBP.^{7,8} Most organisms causing SBP are derived from the intestinal microflora. *Escherichia coli*, *Klebsiella*, and Enterobacteriaceae species are the most frequently isolated organisms.¹ Over the past few years, the microbial etiology of SBP has changed because of the increasing use of invasive procedures and quinolone prophylaxis.^{3,9} In particular, quinolone-resistant gram-negative bacteria and multiresistant gram-positive bacteria are frequently being isolated.

In recent years, the outcomes among patients with ESLD and SBP have improved remarkably. SBP resolution rates in hospitalized patients vary between 70% and 90%. However, despite resolution of the infection, the mortality rate after SBP remains high due to development of complications such as gastrointestinal bleeding, renal dysfunction, and worsening liver failure. Survival expectancy after SBP is relatively poor and patients with ESLD

should be considered for liver transplantation after an episode of SBP.

Pathogenesis

The pathogenesis of SBP is not entirely known. The most accepted hypothesis is the seeding of ascitic fluid with blood-borne bacteria. Development of ascitic fluid infection is probably the final step in a series of events, namely intestinal bacterial overgrowth, bacterial translocation with colonization of mesenteric lymph nodes, bacteremia, and ultimately seeding of bacteria into the ascitic fluid.^{1,10,11} Once bacteria reach the ascitic fluid, the development of SBP depends on the defensive capacity of the ascitic fluid which correlates directly with ascitic fluid protein and complement concentration. This event is preceded by prolonged bacteremia due to impaired phagocytic activity in the reticuloendothelial system.¹¹

ESLD predisposes to the development of bacterial overgrowth, possibly because of altered small intestinal motility¹² and the presence of hypochlorhydria.¹³ However, the role of bacterial overgrowth in the pathogenesis of SBP remains controversial. Whether or not this is an initiating step remains a matter of debate. The bacteria then traverse the intestinal wall, and colonize mesenteric lymph nodes by a process called bacterial translocation. The altered permeability of the intestinal wall, as a consequence of portal hypertension and decreased mucosal blood flow, facilitates this. The ascitic fluid then becomes colonized if the lymphatic carrying the contaminated lymph ruptures because of the high flow and elevated pressure associated with portal hypertension.^{1,10,11}

Bacteria that cause SBP can also originate from infections in sites other than the intestine via bacteremic seeding. These include cellulitis, urinary tract infections, upper respiratory infections, pneumonia, and dental infections.¹⁴ This pathogenic mechanism is favored during diagnostic and therapeutic maneuvers, which create a break in the mucocutaneous barrier, thus creating a portal of entry.

Risk Factors

Many patients with SBP may have advanced liver disease. Other risk factors include an ascitic fluid protein concentration of less than 1 g/dL, prior episode of SBP, a serum bilirubin concentration above 2.5 mg/dL, and variceal hemorrhage.¹⁵⁻¹⁸ Decreased prothrombin activity and increased aspartate aminotransferase level were also associated with an increased risk of developing SBP. However, only low protein content in the ascitic fluid had an independent predictive value.^{6,17} The 1-year probability of the first episode of SBP in patients with an ascitic fluid protein level less than 1 g/dL was 20%.^{17,18} Iatrogenic factors including diagnostic and therapeutic procedures can also alter the host defense barrier and predispose to infections.

Clinical Features

SBP can be minimally symptomatic in the initial stages. Currently the threshold for performing a paracentesis is low and as a result, infections are being detected at a much earlier stage.

Fever is the most common manifestation of SBP. A temperature of 37.8 or greater is worrisome, as patients with ESLD may be mildly hypothermic.¹⁹ Diffuse abdominal pain is another clinical manifestation of SBP. Presence of ascites usually precludes the development of a rigid abdomen by separating the visceral from the parietal peritoneal surfaces.²⁰ Altered mental status is a frequently overlooked symptom.²¹ Ammonia levels do not correlate well with changes in mental status.²² Other signs and symptoms, such as vomiting, ileus, diarrhea, renal impairment, septic shock, and hypothermia may be present in many patients. Alteration in gut flora with overgrowth of one organism has been postulated as a cause of the diarrhea.²³ Occasionally, patients may have no obvious signs or symptoms, but may have subtle laboratory signs. These include leukocytosis, metabolic acidosis, and azotemia. Unexplained presence of any of the above symptoms or signs should prompt a diagnostic tap in a patient with ascites.

Diagnosis

The diagnosis of SBP is based on the presence of an ascitic fluid PMN count of more than 250/mm³ and/or positive ascites fluid cultures, in the absence of clinical and laboratory evidence suggesting secondary bacterial peritonitis.

A diagnosis of culture-negative neutrocytic ascites is made when a patient has ascitic fluid PMN count more than 250 cells/mm³ with a negative ascitic fluid culture.⁸ Secondary bacterial peritonitis must be considered when at least 2 of the following are present in the ascitic fluid: glucose level less than 50 mg/dL, protein content greater than 1 g/dL, and an lactate dehydrogenase concentration higher than normal serum level.²⁰

The concentration of bacteria is very low in ascitic fluid; hence the results of gram stain are frequently negative. However, inoculation of blood culture bottles at the bedside result in a positive culture in 50% to 80% of cases.^{7,24}

The most common organisms isolated are *E. coli*, *Klebsiella*, and Enterobacteriaceae species, but there has been a recent increase in the emergence of gram-positive bacteria including Methicillin-resistant *Staphylococcus aureus*.^{1,3}

The fear of hemorrhagic complications should not preclude a diagnostic paracentesis. The benefits outweigh the risks in most situations.

Treatment

Antibiotics

Third generation cephalosporins are the drugs of first choice and cefotaxime has been widely studied for this indication.^{4,21,25} It should be used at a dose of 2 gm every 12 hours for a minimum of 5 days. Ceftriaxone is

also very effective in the management of SBP with a resolution rate of more than 90%.²⁶ Intravenous amoxicillin-clavulanate has also been found to be effective in the treatment of SBP.²⁷ Oral ofloxacin is as successful in the management of uncomplicated SBP.²⁸ However, it should not be used in patients in whom SBP develops while on quinolone prophylaxis, because of the possibility of quinolone-resistant bacteria causing the infection.

Treatment with aminoglycosides is a risk factor for acute renal failure among patients with advanced liver disease. Nephrotoxicity (impairment of renal function with increase in urinary β 2-microglobulin) was observed by Felisart et al²⁵ in cirrhotics with severe infections treated with ampicillin-tobramycin combination. Avoidance of aminoglycoside antibiotics may reduce the occurrence of renal dysfunction, especially, in hospitalized patients with ESLD.

Albumin

A multicenter, controlled trial has shown that intravenous albumin along with antibiotics reduces the incidence of renal impairment and improves hospital survival.²⁹ In this study 126 patients with SBP were assigned to receive treatment with cefotaxime alone or cefotaxime plus albumin. Albumin was given at a dose of 1.5 g/kg of body weight at the time of diagnosis, followed by 1 g/kg of body weight at day 3. Renal impairment developed in 33% of the patients in the cefotaxime alone group but in only 10% of those in the cefotaxime-plus-albumin group. The mortality rates in-hospital were 28% and 6%, respectively, and at 3 months, the mortality rates were 41% and 22%.

A follow-up ascitic fluid analysis to document resolution of the infection is generally not needed in many patients with SBP.³⁰ However, repeat paracentesis should be performed if no clinical improvement is seen, the previous fluid analysis or the organism is unusual and response to treatment is atypical. Lack of resolution raises the possibility of secondary bacterial peritonitis. If the initial culture grows only a single organism and repeat fluid analysis reveals lower PMN count than the pretreatment value, then the patient probably has SBP.

Prophylaxis

Risk factors for the development of SBP include low ascitic fluid concentration, prior episode of SBP, and variceal bleed among others. The identification of risk factors and the recognition that most of the causative organisms originate in the gut have led to randomized controlled trials looking into selective intestinal decontamination. A meta-analysis of 13 such trials showed an overall mortality benefit [risk ratio 0.70, 95% confidence interval (CI) 0.56-0.89] and a decrease in bacterial infection (risk ratio 0.39, 95% CI 0.32-0.48).³¹

The recurrence of SBP 1 year after treatment can be as high as 70%.³² Cirrhotic patients who have had a prior episode of SBP benefit from prophylaxis indefinitely or until liver transplantation. It is also clearly indicated in the care of patients with gastrointestinal bleed indepen-

dent of ascites.³³ These patients are prone to develop infections during or after the episode. The third group of patients who may benefit from selective intestinal decontamination include cirrhotic with low ascitic fluid protein levels during hospitalization.⁵

Quinolones like norfloxacin are the drug of choice for prophylaxis. This has led to the development of SBP caused by quinolone-resistant gram-negative bacteria. Despite this observation, the incidence of SBP caused by the resistant strains is still low. Trimethoprim-sulfamethoxazole has been shown to be an efficacious and cost-effective agent for SBP prophylaxis in patients with ESLD.³⁴

Intermittent prophylaxis has been shown to be an effective strategy for the prevention of SBP. Regimens include a single weekly dose of 750 mg of ciprofloxacin,³⁵ One double-strength tablet of trimethoprim-sulfamethoxazole 5 days per week,³⁴ or restricting the use of norfloxacin for the indication of ascitic fluid protein < 1 g/dL to inpatients only, with discontinuation of the drug at the time of discharge.³⁶

Bacteremia

In ESLD patients, bacteremia can be spontaneous or occur as a sequela of infections at specific sites like the skin, lungs, bladder, etc. Although transient bacteremia associated with therapeutic invasive procedures is a relatively common phenomenon, the risks of clinically relevant infections secondary to certain procedures like trans-catheter arterial chemoembolization,^{3,37} percutaneous ethanol injection, and sclerotherapy^{3,38} are relatively low and do not warrant antibiotic prophylaxis. Early prophylaxis with antibiotics has shown to significantly decrease the incidence of bacterial infections in ESLD patients, with or without ascites, presenting with an upper gastrointestinal hemorrhage.³³ Antibiotic prophylaxis is also recommended before transjugular intrahepatic portosystemic shunt (TIPS) insertion and surgical interventions.³⁹ It is well established that routine endoscopy and therapeutic paracentesis do not increase the risk of infections in cirrhosis.^{3,40}

Pneumonia

Pneumonia is seen in about 21.37% patients with ESLD.² The mortality rate can be as high as 41%. Certain clinical conditions like hepatic encephalopathy and procedures like tracheal intubations can predispose to the development of pneumonia.

Community-acquired pneumonia still remains the most common type with *Streptococcus pneumoniae* being the most frequent pathogen. In alcoholic cirrhosis, infection with anaerobes, *Hemophilus influenzae*, and *K. pneumoniae* are of particular concern. Hospital-acquired pneumonia is predominantly caused by gram-negative bacilli and staphylococci. Most of the time, the causative organism is not isolated and empiric treatment is necessary. Third generation cephalosporins are generally recommended, with nosocomial pneumonia needing

broader coverage or coverage for pseudomonas, depending on the situation.

All patients with ESLD must undergo vaccination against pneumonia. A single revaccination is recommended in adults ≥ 65 years of age if they were vaccinated more than 5 years previously at a time when they were less than 65 years of age.

Urinary Tract Infections

Urinary tract infections are one of the most common complications of ESLD, the incidence being higher in females. Incomplete bladder emptying due to ascites has been postulated as a possible mechanism.² Most patients are asymptomatic with pyuria being seen in only about 60% of patients. This can give rise to a diagnostic dilemma because of the high incidence of bacteriuria in these patients. Gram-negative bacilli are still the most common organism and treatment should be directed against these. Although debate still exists as to whether women with primary biliary cirrhosis are at a higher risk, most studies support the hypothesis that there is a positive association between primary biliary cirrhosis and urinary tract infection.^{41,42} These patients have also been noted to have frequent recurrences after treatment. Various hypotheses have been put forward regarding the pathogenesis including similarities existing between epitopic regions of *E. coli* and certain primary biliary cirrhosis-specific autoantibodies serving as targets of direct cross-reactive immunity.⁴³⁻⁴⁵

Other Bacterial Infections

Chapoutot et al found that 56% of cirrhotic patients had nasal colonization of *S. aureus*.⁴⁶ Given the fact that *S. aureus* is an important cause of mortality in patients with cirrhosis, eradication of *Staphylococcus* colonization from the nasal mucosa may reduce these numbers.

Other infections in cirrhotics include cellulitis, cholangitis, bronchitis, endocarditis, meningitis, and gastroenteritis. Spontaneous bacterial empyema is associated with the development of infections in a preexisting hepatic hydrothorax.⁴⁷ This is seen only in cirrhotic patients.

Tuberculosis is now being increasingly encountered, especially in patients with alcoholic cirrhosis.⁴⁸ Such patients usually have a left side pleural effusion. Many patients may not mount a typical reaction to the tuberculin skin test. The development of low grade fever and ascites with a high protein and lymphocyte count in patients with cirrhosis should raise the suspicion of peritoneal tuberculosis.⁴⁹ It is not always possible to culture *Mycobacterium tuberculosis* from the ascitic fluid, in which case laparoscopy and biopsy may be needed to make the diagnosis. They usually respond to antituberculous drugs.

VIRAL INFECTIONS

Common viral infections like influenza can have a devastating course in patients with ESLD. Viral hepatitis

due to hepatitis C and B, which are now among the most common causes of ESLD, also present an important therapeutic challenge. With transplantation becoming an important modality of treatment for chronic liver diseases, the goal is to eradicate these infections pretransplantation, so as to prevent posttransplantation recurrence. It also becomes increasingly important that these individuals be screened for evidence of immunity to hepatitis A and B early during the disease course, and be vaccinated if they are not. Due to shared routes of transmission, human immunodeficiency virus (HIV) and hepatitis C coinfection remains an important problem.

Influenza

Influenza infections cause increased morbidity and mortality in ESLD patients. Influenza infection can lead to hepatic decompensation in these individuals.⁵⁰ As early recognition and treatment of influenza in ESLD patients is important, these patients presenting with an upper respiratory illness should be screened for influenza. Rimantadine is preferred to amantadine for therapy in the presence of decreased liver function.⁵⁰ Effective prevention with vaccination should be undertaken annually in these patients.

Hepatitis A

The clinical outcome of acute hepatitis A virus infection in patients with ESLD is dismal. The Center for Disease Control and Prevention has reported that hepatitis A super-infection in other causes of chronic liver disease had a 23-fold increased risk of death.^{51,52} Super-infection with hepatitis A virus in patients with ESLD, particularly in patients with hepatitis C, can develop fulminant hepatitis. The Center for Disease Control and Prevention recommends that patients with cirrhosis, especially those who have ESLD secondary to hepatitis C, be tested for evidence of immunity to hepatitis A.⁵³ If they do not demonstrate anti-HAV seroprevalence, then administration of hepatitis A vaccine should be strongly considered. Patients should be immunized as early as possible after the diagnosis of chronic liver disease, even before transplantation is being considered, as liver failure seems to blunt the immune response to the vaccine.

Hepatitis B

An estimated 350 million persons worldwide are chronically infected with hepatitis B virus. The 5-year survival rate for chronic hepatitis B patients with cirrhosis and early decompensation has been estimated as 55% to 84%,^{54,55} and only 14%⁵⁶ in patients with decompensated cirrhosis. Also, patients with hepatitis B virus related ESLD and high levels of serum HBV DNA have a greater likelihood of developing hepatic failure and hepatocellular carcinoma.

Patients with hepatitis B related ESLD with evidence of HBV viral replication should be treated with anti-HBV viral medications. Treatment with interferon is generally not recommended unless well compensated.

Nucleoside analogs are the accepted modality of treatment.⁵⁷ Currently available drugs are lamivudine, adefovir, and entecavir. Lamivudine is economical and efficacious; however, development of drug-resistant HBV mutants is a well-established risk with long term use.⁵⁸ It has been shown that inhibition of viral replication with lamivudine results in the improvement of liver function in decompensated HBV cirrhosis and also prevents the development of HCC.⁵⁹ Di Marco et al⁶⁰ studied the relationship between HBV suppression, development of viral resistance, and disease outcome in 59 patients with cirrhosis due to hepatitis B when treated with lamivudine. Fifty patients achieved virologic response during the first 6 months of therapy. The YMDD mutation was detected in 26 patients. Patients who continued to maintain viral suppression demonstrated a longer event-free survival. In patients with advanced cirrhosis, liver decompensation occurred more in patients after the emergence of YMDD mutations. However, recent reports demonstrate that stopping treatment with lamivudine in patients with resistant mutants does not invariably lead to decompensation. Nevertheless, patients with cirrhosis should be switched to adefovir before stopping treatment. Renal function should be monitored closely on treatment with adefovir. Schiff et al⁶¹ demonstrated that adefovir is associated with suppression of HBV deoxyribonucleic acid to undetectable levels in 81% of patients and stabilization or improvement in Child-Turcotte-Pugh (CTP) score of 92% after 6 months in patients with decompensated cirrhosis and lamivudine-resistant HBV.

Entecavir, a deoxyguanosine analog, is a relatively newer drug. It is a potent inhibitor of HBV DNA polymerase, is not associated with any major adverse effects, and has a limited potential for resistance.⁶² Recent studies have demonstrated significantly higher rates of histologic, virologic, and biochemical improvement with entecavir when compared with lamivudine.^{63,64}

Maintenance of viral suppression as evidenced by undetectable serum HBV DNA reduces the rate of recurrent infection posttransplantation. If infection does occur after transplantation, the severity is reduced if we can reduce pretransplantation viremia. It may even obviate the need for transplantation.

Although there are no specific recommendations for vaccination against hepatitis B, screening for preexisting immunity to hepatitis B should be undertaken and if nonimmune and at risk for exposure, then hepatitis B vaccination should be offered.⁵³ Pre vaccination serology should include anti-Hepatitis B core to identify patients with isolated core antibody as the only serologic manifestation of HBV infection. There is a lower rate of seroconversion in patients with chronic liver disease. Conversion rates have ranged from 69% to 100% using different doses of HBV vaccinations.⁶⁵⁻⁶⁷ Roseman et al⁶⁸ showed that an accelerated, high dose regimen (40 µg at 0, 1, 2, and 6 mo) achieved a 75% seroconversion rate when compared to the standard regimen (20 µg at 0, 1, and 6 mo) (46%). Another study found only a 36% serocon-

version rate using an even more accelerated, double-dose vaccination schedule (40 µg at 0 weeks, 2 weeks, 4 weeks, and 6 months).⁶⁹ Given the low rates of seroconversion in patients with chronic liver disease, postimmunization serologic testing may be appropriate. Patients who have not responded may benefit from additional vaccine doses.

Hepatitis C

ESLD due to chronic hepatitis C is the leading indication for liver transplantation in the United States. Early cirrhotics may be asymptomatic with a normal laboratory profile. Current data suggest that 41% of patients with genotype 1 hepatitis C virus infection and 73% with genotype 2 or 3 infection with advanced fibrosis or early cirrhosis can achieve sustained virologic response with the standard combination antiviral therapy with pegylated interferon and ribavirin.^{70,71} Liver transplantation is the treatment of choice for patients with decompensated cirrhosis.

The vast majority of chronic hepatitis C patients with ESLD on the wait list for liver transplantation has well compensated disease and may benefit from antiviral therapy. The Model for End-Stage Liver Disease (MELD) score that is used to categorize the severity of ESLD, indicate that 93% of HCV patients have a MELD score ≤ 18 , which corresponds to a CTP score of ≤ 7 , or bilirubin 2.5 mg/dL, INR 1.5, and creatinine 1.5 mg/dL. In fact 62% of patients with Hepatitis C on the waiting list have MELD scores between 11 and 18.⁷⁰ These patients with early cirrhosis might tolerate and benefit from antiviral therapy. Recurrence of hepatitis C in the allograft is an almost universal occurrence. Eradication of the virus with pretransplantation clearance of HCV RNA from the blood reduces the likelihood of HCV recurrence after transplantation. Treatment of hepatitis C may slow the progression of the fibrosis and could also improve the degree of decompensation in these patients.

Everson et al⁷² evaluated the effectiveness, tolerability and outcome of a low accelerating dose regimen of antiviral therapy in the treatment of patients with advanced HCV and cirrhosis. They treated 124 patients, 70% genotype 1 with the low accelerating dose regimen protocol. They used either interferon α -2b 1.5 MU 3 times a week or peg interferon α -2b 0.5 µg/kg/wk plus ribavirin 600 mg/d initially. Adjustments were made with dose increments every 2 weeks to reach maximally tolerated or target standard doses. Growth factors were used for treatment-associated anemia in only 5% of patients with the anemia mostly being managed by ribavirin dose reduction. Granulocyte-colony stimulating factor was administered in 33% of patients for leucopenia. Sixty-three percent of the patients had decompensated cirrhosis at time of treatment. The mean CTP score was 7.4 ± 2.3 , and the mean MELD score was 11.0 ± 3.7 . Forty-five percent were CTP class A. Forty-six percent were HCV RNA negative at the end of treatment and SVR was seen in 13% of genotype 1 infected patients. They found that the 12 of 15 patients who were HCV RNA negative before transplantation remained negative 6 months after

transplant. A second study which included predominantly Child's B and C cirrhosis was less encouraging. Many patients had severe treatment-related side effects.⁷³

Anemia, neutropenia, and thrombocytopenia are more common in ESLD and hence treatment requires close monitoring. Dose modifications and appropriate use of growth factors may be needed to counter these side effects.

Maintenance therapy with interferon α in previous nonresponders in hepatitis C-related cirrhosis has been shown to inhibit histologic progression and the development of hepatocellular carcinoma.⁷⁴ Schiffman et al showed that continuous interferon therapy improved the hepatic histology score in 80% of patients despite persistence of viremia. Any treatment that decrease inflammation can reduce the rate of disease progression and thereby progression of cirrhosis and its consequent complications.

HIV

ESLD is one of the leading causes of death in patients with HIV. Shared risk factors for viral acquisition have led to the high prevalence of HIV/HBV and HIV/HCV coinfections. Patients with HCV and underlying HIV progress faster to ESLD than patients infected with HCV alone. Risk factors associated with higher rates of fibrosis progression include alcohol use, age, and CD4 counts $< 200/\mu\text{L}$.⁷⁵⁻⁷⁷

HIV-associated mortality has significantly decreased because of the advent of highly active antiretroviral therapy. This has led to the emergence of ESLD from hepatitis C as the leading cause of mortality in HIV patients making treatment of hepatitis C increasingly important. Treatment, regardless of genotype, with peginterferon α and ribavirin for 48 weeks of duration should be considered as long as the patients are well compensated. Genotypes 2 and 3 have a more favorable response than genotype 1.⁷⁸ Due to the potential for increased toxicity, coinfecting patients with decompensated liver disease should not be treated with peginterferon and ribavirin.⁷⁹ Liver transplantation may be an option for such individuals at some select liver transplant centers.

Cytomegalovirus Infections

Polymerase chain reaction studies have demonstrated that cytomegalovirus (CMV) is often detected in the mononuclear cells of seropositive patients with cirrhosis (63%). This suggests that because of depressed cellular immunity, reactivation of CMV may have already occurred in cirrhotics. Such patients may be at risk for endogenous reactivation of CMV after liver transplantation. Although infections can be mild and asymptomatic, CMV infections should be identified and treated promptly in patients with ESLD.

Manifestations are myriad and include pneumonia, colitis, retinitis, and gastrointestinal ulcers, etc.^{80,81}

Fungal Infections

Candida, *Cryptococcus*, *Aspergillus*, and *Coccidioidomycosis* are some of the fungi causing infections in cirrhotics. An increased incidence of fungal infections is seen in primary biliary cirrhosis.⁸² ESLD was shown to be the third most common underlying condition associated with cryptococcal peritonitis in the series reported by Mabee et al.⁸³ The pathogenesis of *C. neoformans* in cirrhotics is usually multifactorial. Low index of suspicion and consequent delay in treatment can be fatal. Unfortunately, a lack of signs and symptoms and nondiagnostic ascitic fluid findings further compound the issue. Unless diagnosed and treated appropriately, dissemination of infection ensues, ultimately leading to the demise of the patient. Multiple paracenteses and appropriate fungal cultures are necessary to make the diagnosis. Bedside inoculation of culture medium, India ink preparations, and testing for serum cryptococcal antigen is recommended to facilitate a timely diagnosis.

Funguria with *Candida* species could be either a super-infection or a true infection of the urinary tract. Use of antibiotics could be related to the funguria. Patients with ESLD should have urine fungal cultures in the presence of symptoms suggestive of UTI. Blood cultures may need prolonged incubation to detect fungal growth.

Coccidioidomycosis is an endemic fungal infection of southwestern United States. Blair et al⁸⁴ prospectively evaluated 290 patients with ESLD and found 2.1% to have active coccidioidal infection and of the 184 patients listed for transplantation, the 1 year incidence was 4.2%. Identifying coccidioidal infections need awareness, especially in nonendemic areas. Serologic testing for coccidioidomycosis can be done by enzyme immunoassay, complement fixation test, or immunodiffusion. Patients with ESLD and active coccidioidomycosis can be treated with fluconazole until the infection resolves.

TIPS-associated Infections

The development TIPS has led to a change in the management of the complications of portal hypertension. TIPS are now being more widely used for the control of variceal bleeding and also are effective in the management of refractory ascites. The increasing use of TIPS has led to the development of a number of complications including portosystemic encephalopathy, hemolysis, TIPS stenosis, and infections.

Primary infection of the TIPS, also known as endotipisitis, is a relatively uncommon but sometimes fatal complication. It is important to recognize this entity, thereby facilitating the diagnosis. It can manifest as fever, tender hepatomegaly, hypoxemia, and neutrophilia. Most of these patients can be treated with antibiotics. Sanyal et al⁸⁵ evaluated 8 patients with TIPS and fever. The diagnosis of endotipisitis was made on the basis of positive blood cultures and a vegetation or thrombus on the stent or persistent bacteremia in a patient with TIPS and no other detectable source of infection. Doppler ultrasound of the liver was used to demonstrate an

occluded thrombus or vegetation. Blood cultures were positive for aerobic gram-negative bacteria or *Candida* in all patients.

TIPS infection can be successfully treated with intravenous antibiotics. Duration and type of antibiotics may vary depending on the causative organism, with fungal infections requiring a prolonged course of treatment. There is one report of a patient with endotipsitis who seemed to respond to treatment with antibiotics for 1 month.⁸⁶ But subsequent manipulation of the stent for an episode of bleeding led to bacteremia with the original organism because of bacteria being walled off in the thrombus, leading to subsequent relapse with stent manipulation. As patients with an underlying TIPS thrombosis are more likely to be seeded, it is recommended that such patients be provided with prophylaxis during bacteremia.

TIPS-associated bacteremia, albeit not very frequent, is a clinically significant entity.³⁹ The increasing utilization of this procedure in patients with portal hypertension, has led to the observation that bacteremia associated with this procedure can be serious. Gram-negative bacteremia, especially with *Enterococcus* species is often encountered.^{39,87} Of interest, the median interval between TIPS placement and sustained bacteremia has been observed to be as much as 3 months or more. Although there are no definite recommendations, antibiotic prophylaxis is recommended in patients undergoing TIPS placement.

CONCLUSIONS

Infections in ESLD are a common cause of morbidity and mortality. Abnormalities in cellular and humoral immunity and the increasing use of invasive procedures predispose these patients to a variety of bacterial, fungal and viral infections. Clinicians should have a low index of suspicion as prompt detection and the use of appropriate treatment can improve survival in these patients.

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