REVIEW ARTICLE

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The Evolving Challenge of Infections in Cirrhosis

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Infections in patients with cirrhosis represent a substantial and increasing health and economic burden.[1] Approximately two thirds of patients with cirrhosis and extrahepatic organ failure have sepsis.[1] Hospitalization for these patients is twice as long and almost three times as expensive as hospitalization for patients who have sepsis without cirrhosis, and in-hospital mortality is upwards of 50%.[1] Infections increase the risk of death by a factor of 4 among patients with cirrhosis, and the risk parallels the number of failing organs.[2,3] High mortality has also been observed among patients with cirrhosis who have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[4]

In a global study of infections in patients with cirrhosis, 48% of infections were community-acquired, 26% were associated with health care (i.e., diagnoses were made within the first 48 hr after hospital admission), and 26% were nosocomial (i.e., diagnoses were made >48 hr after admission).[5] In general, health care associated infections are defined as infections acquired in patients who have contact with the health care system that cannot be classified as hospital-acquired or community-acquired. Positive bacterial cultures were obtained in only 59% of patients; the most common infections were spontaneous bacterial peritonitis (27%), followed by urinary tract infections and pneumonia.[5] In a recent North American study, nosocomial infections developed in 15% of hospitalized patients with cirrhosis and were associated with an increased risk of death.[6] In about half of these patients, the nosocomial infection developed after treatment of another infection. Of major concern is the increasing prevalence of infections with multidrug-resistant (MDR) organisms. MDR infections are most prevalent in Asia ó specifically, in India ó where 70% of infections in patients with cirrhosis are due to these organisms.[5] Despite the increasing prevalence of infections among patients with cirrhosis, developing strategies for prevention, early detection, and treatment has been challenging.

Pathogenesis of Infections in Cirrhosis

Cirrhosis is associated with inherent and external factors that synergize to increase susceptibility to and progression of infections.[7] The major internal factors that confer susceptibility to infection are cirrhosis-associated immune dysfunction, reduction in bile flow, and changes in gut microbial composition and function.[7,8] Cirrhosis-associated immune dysfunction affects most lineages of innate and adaptive immunity, with additional impairment of gut immunity and barrier function that confers a predisposition to infections originating from the gut or even other sources, such as the skin, urine, and respiratory tract.[7,8] External factors

are the overuse of proton-pump inhibitors, alcohol intake, frailty, multiple antibiotic courses, and repeated hospital admissions and invasive procedures.[9] These external factors also confer a predisposition to the relative overgrowth of fungi that are important causes of infection.[10]

The intestinal barrier, which consists of multiple physical and immune layers (Fig. 1), is progressively impaired with advancing stages of cirrhosis. Alterations in the gut microbiota, the mucus layer, epithelial cells, and immune function of the lamina propria contribute to an increased rate of bacterial translocation among patients with cirrhosis.[11] This immune impairment in cirrhosis leads to microbial dysbiosis in the stool, upper and lower intestinal mucosa, blood, skin, and saliva.[11] In the gut, these changes include a reduction in autochthonous, or beneficial, taxa and an increase in pathobionts such as gram-negative rods belonging to Enterobacteriaceae (e.g., escherichia and klebsiella) and gram-positive cocci belonging to Streptococcaceae and Enterococcaceae,[12] as well as altered bacterial function. Bacterial translocation is usually monomicrobial, with invasive species belonging to Enterobacteriaceae or Streptococcaceae, and can result in spontaneous bacterial peritonitis and bacteremia.[10] Ultimately, bacterial translocation leading to clinically relevant infections is a balance between pathogen factors, such as causative organisms and virulence, and host factors, such as the severity of liver disease and status with respect to diabetes and malnutrition, as well as to the use of alcohol, proton-pump inhibitors, and glucocorticoids in the context of cirrhosis-associated immune dysfunction.

RECOGNITION AND TREATMENT OF INFECTIONS

The most prevalent infections in patients with cirrhosis are spontaneous bacterial peritonitis and urinary tract infections,[5] followed by pneumonia, spontaneous bacteremia, skin and soft-tissue infections, and *Clostridioides difficile* infection, with variations in the risk of death. Fungal infections occur at a frequency of 10 to 13% among patients with cirrhosis, and patients with dual bacterial and fungal infections have lower survival rates than those with bacterial infections alone.[13] Fungal infections should be suspected in patients presumed to have infection but with negative bacterial cultures, especially in patients with renal insufficiency and recipients of multiple antibiotic courses. Patients with hemochromatosis are at special risk for infections with yersinia, escherichia, vibrio, and listeria organisms, probably because of the effect of excess iron on innate and adaptive immune responses.[14]

As a result of the impaired immune response, most patients with decompensated cirrhosis are unable to mount a febrile response. On the other hand, patients with alcohol-associated hepatitis without infection may have fever, tachypnea, and leukocytosis. Thus, in patients with cirrhosis, an investigation for infections should be triggered by a new onset of acute kidney injury, altered mental status, or signs of organ failure, as well as fever and leukocytosis. C-reactive protein and procalcitonin levels are elevated in patients with cirrhosis, independent of infection, and thus have limited value for the diagnosis of infection; however, persistently elevated C-reactive protein levels identify patients at short-term risk for death.[15]

Spontaneous bacterial peritonitis is an infection most commonly associated with cirrhosis, and affected patients may be asymptomatic or may present with abdominal pain, diarrhea and ileus, fever or hypothermia, leukocytosis, hepatic encephalopathy, or worsening of hepatic and renal function. An ascitic fluid neutrophil count of at least 250 per cubic millimeter has the highest sensitivity for the diagnosis of spontaneous bacterial peritonitis, but a cutoff point of 500 neutrophils per cubic millimeter has the highest specificity.[16] Ascitic fluid cultures may be negative unless inoculation of ascitic fluid (usually 10 ml) into the culture bottles is performed at the bedside. Two bottles (for aerobic and anaerobic cultures) are inoculated with the use of a sterile needle that is separate from the needle used for paracentesis in order to avoid contamination of the ascitic fluid sample with skin flora.

Neither the choice of antibiotics nor the duration of treatment for spontaneous bacterial peritonitis depends on whether cultures are positive or negative, since mortality is similar among culture-positive and culture-negative patients when the infection is diagnosed on the basis of the absolute neutrophil count and when there is a low risk of MDR infection. Bacterascites, the

term used when bacterial cultures of ascitic fluid are positive but the neutrophil count in the fluid is normal, represents colonization of ascitic fluid and typically does not require treatment. Some cases of bacterascites may represent early spontaneous bacterial peritonitis, and antibiotic therapy may be required if the patient is, or becomes, symptomatic. Follow-up paracentesis is recommended to confirm the absence of neutrophilic ascites.[17] The use of intravenous albumin (1.5 g per kilogram of body weight on day 1 and 1 g per kilogram on day 3), in addition to appropriate antibiotics (Tables 1 and 2), is the standard of care for reducing the risk of renal impairment and death.[22] Of concern is bacterial resistance in nosocomial cases of spontaneous bacterial peritonitis, which doubles the risk of death.[40] The increased use of carbapenems may be associated with the emergence of carbapenem-resistant Enterobacteriaceae. Since proton-pump inhibitors increase the risk of spontaneous bacterial peritonitis and *C. difficile* infection, these agents should be discontinued whenever possible.

The presentation of patients with cirrhosis and infections other than spontaneous bacterial peritonitis is similar to the presentation of patients with such infections who do not have cirrhosis. The specific treatment of these infections in patients with cirrhosis is outlined in Table 1.

Management of infections in patients with cirrhosis requires, first, identification of the causative organism, including fungal pathogens; second, prevention of multiorgan failure; third, avoidance of nosocomial infections; and finally, determination of the prognosis. In addition, management entails decisions about referring patients for critical care evaluation, liver transplantation, and end-of-life care (Fig. 2).

Empirical antibiotic therapy needs to be guided by consideration of the following factors: the health care setting (i.e., whether the patient is in a critical care setting), the severity of the presentation, the source of the infection (health care associated, nosocomial, or community-acquired), and regional or national patterns of antibiotic resistance. For patients with septic shock, identification of the causative organism (or organisms) is critical and time-sensitive. Effective antibiotics need to be administered as early as possible, even in the emergency department before the patient is admitted, since each hour that antimicrobial therapy is delayed in patients with cirrhosis increases the risk of death by a factor of 1.86.[41] Therapy is de-escalated as early as is warranted on the basis of the treatment response and antibiotic susceptibility.[28]

CRITICAL CARE MANAGEMENT

Infections in patients with cirrhosis may be uncomplicated or may lead to hepatic and extrahepatic organ failure, a condition termed acute-on-chronic liver failure.[42] Infections may progress to septic shock, a form of distributive shock characterized by profound circulatory, cellular, and metabolic abnormalities. The cardiac response to hypotension may be impaired because of cirrhotic cardiomyopathy.[43] The mortality associated with septic shock in patients with cirrhosis is as high as 65% but is considerably lower than the near-fatal outcome around 20 years ago.[44] Septic shock is identified on the basis of a mean arterial pressure of less than 65 mm Hg or a serum lactate level exceeding 2 mmol per liter (18 mg per deciliter) in the absence of hypovolemia.[45] However, these criteria have not been validated in patients with cirrhosis. Management of septic shock involves a combination of early goal-directed therapy, administration of antibiotics within 1 hour after presentation, intravascular volume resuscitation, monitoring of tissue oxygenation through lactate clearance, support of failing organs, and liver transplantation in selected patients (Fig. 2).

In patients with cirrhosis, the recommended target mean arterial pressure is 60 mm Hg or higher, rather than 65 mm Hg or higher, without specific targets for ventricular filling pressure, volume, lactate level, or central venous oxygen saturation.[46] Placement of an arterial catheter and central venous access in patients with circulatory shock and the use of echocardiography for monitoring during fluid resuscitation are also recommended. Assessment of volume status by means of central venous pressure monitoring may be inaccurate when intraabdominal pressure is raised because of tense ascites. However, routine measurement of bladder pressure as a means of determining intraabdominal pressure is not recommended and does not inform the need for paracentesis.[47]

Echocardiographic measurement of dynamic changes in response to fluid boluses is recommended to assess volume status. Respiratory

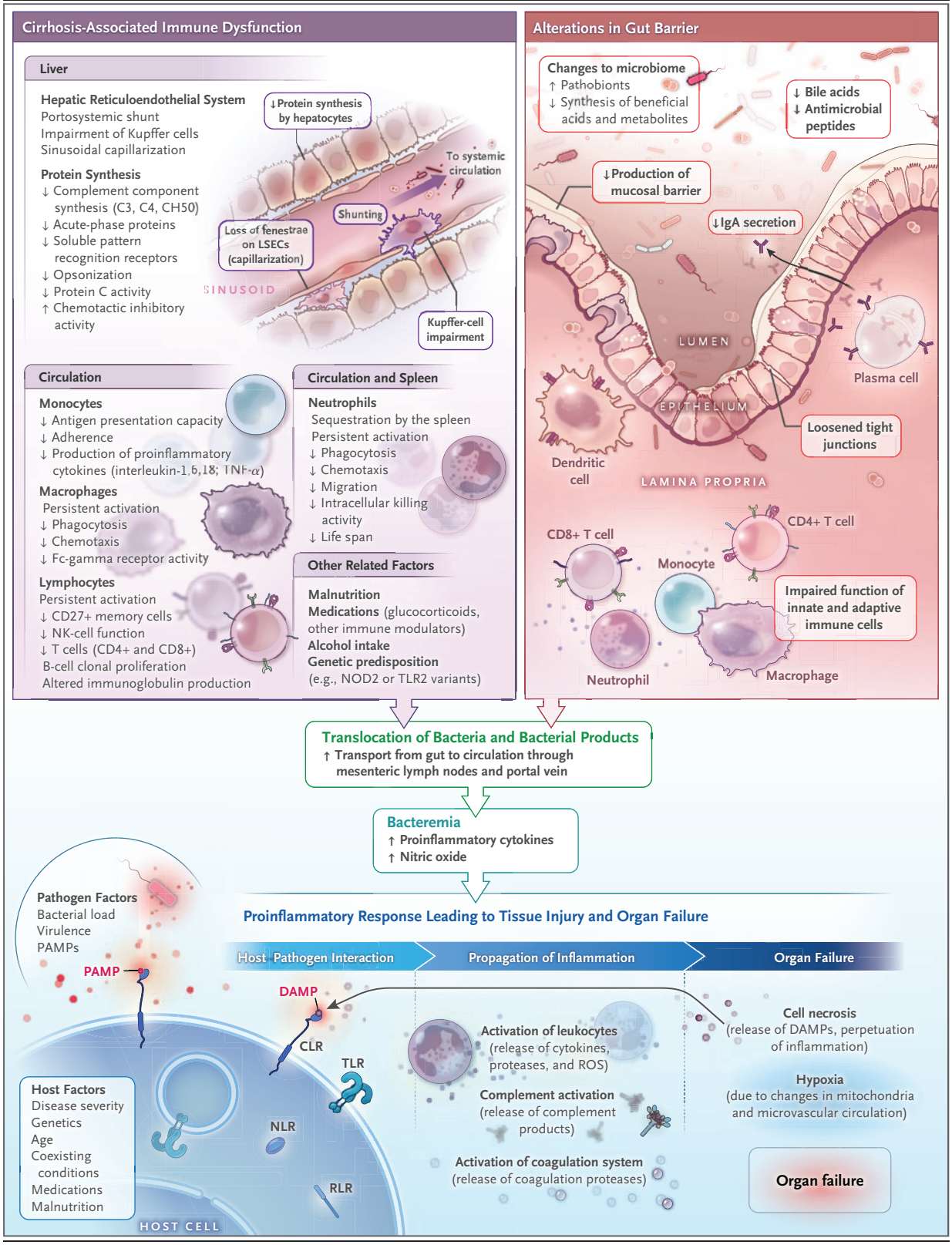

Figure 1 (facing page). Role of Changes in the Gut Liver Axis and Cirrhosis-Associated Immune Dysfunction in the Development of Infections.

Acid, bile, pancreatic juice, and IgA in the gut lumen, the tight junctions between intestinal epithelial cells, and immune cells in the lamina propria normally work in conjunction to prevent the entry of gut bacteria into the systemic circulation. The lamina propria, made up of loose connective tissue immediately beneath the epithelium, has multiple functions, including defense against bacteria. Hepatic synthesis of complement components, acute-phase proteins, and soluble pattern-recognition receptors, which constitute some of the defense systems against bacteria, diminishes with impaired hepatic function (upper left panel). Gut microbiome alterations, increased gut mucosal permeability, and decreased function of the hepatic reticuloendothelial system, combined with portosystemic collaterals, allow gut bacteria to bypass the liver and enter the systemic circulation. In cirrhosis, the composition of gut microbiota is altered (upper right panel), with increased pathobionts and reduced autochthonous taxa, leading to lower synthesis of beneficial short-chain fatty acids, secondary bile acids, and tryptophan metabolites that strengthen the intestinal barrier and local immune response. These changes confer a predisposition to cirrhosis-associated immune dysfunction, affecting monocytes, macrophages, lymphocytes, and neutrophils. Immune dysfunction results in diminished resistance against the ensuing bacteremia and can also confer a predisposition to infectious processes in sites other than the gut. The proinflammatory response resulting from bacteremia leads to tissue injury (lower panel). The severity of the inflammatory response depends on both host-related factors (e.g., the severity of cirrhosis, age, and the presence or absence of malnutrition, glucocorticoid use, and coexisting conditions) and pathogen-related factors (e.g., bacterial load, virulence, and pathogen-associated molecular patterns [PAMPs] that interact with pattern-recognition receptors). Inflammation is propagated through activation of leukocytes, complement, and coagulation systems. The resulting necrotic cell death releases damage-associated molecular patterns (DAMPs) that are recognized by pattern-recognition receptors, and the inflammation is perpetuated. Changes in the microvascular circulation and mitochondria in specific organs that are due to the inflammation result in hypoxia, which in turn leads to organ failure. Proton-pump inhibitors, malnutrition, alcohol use, and antibiotic therapy increase the risk of bacterial translocation, which is amplified with multiple exposures. The risk and severity of infection parallel the severity of the cirrhosis-associated immune dysfunction, which increases with the severity of liver disease. Current antibiotic therapy is aimed at both treating bacterial infection and preventing further infections. CLR denotes C-type lectin receptor, LSECs liver sinusoidal endothelial cells, NLR nucleotide-binding oligomerization domain (NOD) like receptor, NK natural killer, RLR retinoic acid inducible gene I like receptor, ROS reactive oxygen species, TLR toll-like receptor, and TNF-α tumor necrosis factor α.

variations in the diameter of the inferior vena cava and the velocity time integral of the left ventricular outflow tract have been used to measure fluid responsiveness in patients with sepsis, but it may be difficult to measure inferior vena cava collapsibility in patients with ascites when the inferior vena cava is compressed. Placement of a pulmonary arterial catheter is not recommended because of the risk of bleeding, except in patients with right ventricular dysfunction or pulmonary arterial hypertension. Monitoring of urine output is ideal, since oliguria reflects initial stages of hypovolemia more accurately than does an elevated serum creatinine level; however, routine insertion of a bladder catheter is not recommended.[46] Hypoxia is assessed by measuring serum lactate levels; rising levels are indicative of hypoxia.[48] Though lactate clearance is impaired in patients with cirrhosis, an elevated lactate level in a hemodynamically unstable patient is attributed to septic shock until proved otherwise.

Structural and functional changes in albumin in patients with cirrhosis result in immunodeficiency and an increased risk of infection, which is attenuated by means of albumin infusions.[49] Individual studies have not shown the benefit of albumin over crystalloids in patients with sepsis, but a meta-analysis of all studies addressing volume expansion in sepsis suggests that albumin administration is associated with improved 90-day survival.[50] Plasma volume expands by the amount approximately equal to the volume infused when 5% albumin is used. When 25% albumin is used, plasma volume expands by an amount equal to 3 to 5 times the volume infused but at a slower rate. Therefore, 5% albumin is preferred for rapid volume resuscitation. In adults with cirrhosis and type 1 hepatorenal syndrome, terlipressin with albumin is more effective than placebo with albumin in improving renal function but is associated with a higher risk of respiratory failure.[51]

Norepinephrine is the first-line agent administered when the mean arterial pressure remains below 60 mm Hg despite volume resuscitation and antibiotic therapy for 24 to 48 hours (Fig. 2). Norepinephrine increases cardiac preload and inotropic function, but prolonged use can lead to bradycardia, arrhythmias, and tissue ischemia. Hydrocortisone is administered when hypotension persists, since adrenal insufficiency is com-

Table 1. Spectrum of Infections in Patients with Cirrhosis.*

Infection	Common Organisms in Community-Acquired Infections	Prevalence among Patients with Cirrhosis	90-Day Overall Mortality	Therapeutic Intervention[18,19]	
				Community-Acquired Infection	Nosocomial and Health Care Associated Infection
		percent of patients			
Bacterial					
Spontaneous bacterial peritonitis	*Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *S. viridans*	23	27,[2,5] 3.5 among outpatients[20]	13 41[21,22]	First-line therapy: IV third-generation cephalosporins (cefotaxime or ceftriaxone) Other options: IV ciprofloxacin or oral ofloxacin (in uncomplicated infection); piperacillin tazobactam recommended in countries with high bacterial resistance	Low no. of MDROs: piperacillin tazobactam High no. of MDROs: meropenem with or without glycopeptide
Urinary tract infection	*E. coli*, *K. pneumoniae*, enterococcus species, *Pseudomonas aeruginosa*	22	29[2,5]	19[23]	Uncomplicated infection: oral quinolones or trimethoprim sulfamethoxazole Sepsis: IV third-generation cephalosporins or piperacillin tazobactam	Uncomplicated infection: fosfomycin or nitrofurantoin Sepsis with low no. of MDROs: piperacillin tazobactam Sepsis with high no. of MDROs: meropenem
Pneumonia	*S. pneumoniae*, gram-negative bacilli, staphylococci		19[5]	25[23]	Ceftriaxone plus macrolide, piperacillin tazobactam, levofloxacin, moxifloxacin For aspiration pneumonia: levofloxacin plus metronidazole	Low no. of MDROs: piperacillin tazobactam High no. of MDROs: meropenem or ceftazidime plus levofloxacin (with or without glycopeptide or linezolid for patients at risk for MRSA infection)
Spontaneous bacteremia	*E. coli*, *S. viridans*, other streptococcus species	8	13[2,5]	33[23]	Piperacillin tazobactam preferred for hemodynamically unstable patients Cefotaxime, ceftriaxone, or amoxicillin clavulanic acid for hemodynamically stable patients	Low no. of MDROs: piperacillin tazobactam High no. of MDROs: meropenem with or without glycopeptide
Skin and soft-tissue infection	Group A streptococci, *Staphylococcus aureus*	8	12[2,5]	9.5[23]	Third-generation cephalosporin or oxacillin, or piperacillin tazobactam or cefazolin Vancomycin (for MRSA)	Meropenem, ceftazidime, or glycopeptide Vancomycin or daptomycin for MRSA

Clostridioides difficile infection	*C. difficile*	2.4 4[2,5]	14 (30-day mortality)[24]	Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode; FMT may be recommended in patients with recurrent infection	Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode; FMT may be recommended in patients with recurrent infection
Tuberculosis	*Mycobacterium tuberculosis*	<1[25]	27 (30-day mortality)[25]	No consensus, but first-line drugs include isoniazid, rifampicin, pyrazinamide, and ethambutol; potential hepatotoxicity is a concern	No consensus, but first-line drugs include isoniazid, rifampicin, pyrazinamide, and ethambutol; potential hepatotoxicity is a concern
Fungal					
Candidiasis	*Candida albicans* and other candida species	5 10[13,26]	Worse survival with dual bacterial and fungal infections than with bacterial infections alone[13]	Echinocandin (IV caspofungin, micafungin, or anidulafungin)	Echinocandin (IV caspofungin, micafungin, or anidulafungin)
Other liver disease related infections					
Cholangitis	*E. coli*, klebsiella species, enterobacter species	2.8[5]	11[23]	Piperacillin tazobactam	Cefepime, ceftazidime, or cefozopran, plus or minus metronidazole; meropenem, as well as aztreonam plus or minus metronidazole, may also be considered
Hemochromatosis	*E. coli*, *Vibrio vulnificus* and other vibrio species, *Listeria monocytogenes*	NR	NR	Progression to septic shock may occur despite appropriate antibiotic therapy	Progression to septic shock may occur despite appropriate antibiotic therapy

* FMT denotes fecal microbiota transplantation, IV intravenous, MDROs multidrug-resistant organisms, MRSA methicillin-resistant *Staphylococcus aureus*, and NR not reported. Testing for echinocandin susceptibility should be considered in patients who have had prior treatment with an echinocandin and those who have infection with *C. glabrata or C. parapsilosis*; fluconazole is an acceptable alternative to an echinocandin as initial therapy in selected patients who are not critically ill; testing for azole susceptibility is recommended for all bloodstream and other clinically relevant candida isolates.[27]

Table 2. Infection, Prophylaxis, and Multidrug Resistance in Patients with Cirrhosis.*

Infection	Risk Factors	Prophylaxis	Factors Related to Multidrug Resistance	Other Considerations
Spontaneous bacterial peritonitis	GI bleeding	Primary prophylaxis if oral intake is not possible during GI bleeding and in cases of advanced liver disease: IV ceftriaxone, 1 g every 24 hr for 7 days[28,29]	Significant increase in MDROs over time, causing sepsis and death[29,30] Rifaximin has a low potential for resistance and has been investigated as a potential prophylactic agent, with mixed results; it may be associated with a pretransplantation survival benefit[31,32]	Half of such peritonitis episodes manifest at hospital admission, and half develop after admission[33] 50% of episodes may be asymptomatic
	Advanced cirrhosis (Child Pugh score ≥9 and serum bilirubin ≥3 mg/dl) and low ascites protein (<1.5 g/dl),[34] with either impaired renal function (serum creatinine ≥1.2 mg/dl or blood urea nitrogen ≥25 mg/dl) or hyponatremia (serum sodium ≤130 mmol/liter)[35]	Primary prophylaxis: oral norfloxacin where available, 400 mg/day, or ciprofloxacin, 500 mg/day, or trimethoprim sulfamethoxazole, one double-strength tablet daily, until liver transplantation or death[28,29,34,36]	Significant increase in MDROs over time, causing sepsis and death[29,30] Rifaximin has a low potential for resistance and has been investigated as a potential prophylactic agent, with mixed results; it may be associated with a pretransplantation survival benefit[31,32]	Half of such peritonitis episodes manifest at hospital admission, and half develop after admission[33] 50% of episodes may be asymptomatic
	Previous spontaneous bacterial peritonitis	Secondary prophylaxis: oral norfloxacin where available, 400 mg/day, or ciprofloxacin, 500 mg/day, or trimethoprim sulfamethoxazole, one double-strength tablet daily, until liver transplantation, death, or resolution of ascites[28,36]	Significant increase in MDROs over time, causing sepsis and death[29,30] Rifaximin has a low potential for resistance and has been investigated as a potential prophylactic agent, with mixed results; it may be associated with a pretransplantation survival benefit[31,32]	Half of such peritonitis episodes manifest at hospital admission, and half develop after admission[33] 50% of episodes may be asymptomatic
Urinary tract infection	Urinary catheterization	Avoid unnecessary catheterization, remove catheter as soon as it is not required, and follow infection prevention policies and consider alternatives; prophylaxis with systemic antimicrobial agents is not recommended unless clinically indicated	High prevalence of MDR infections (28 39%), especially of nosocomial origin (35 57%)[5,23,37]	Asymptomatic infections related to residual urinary volume are common[38]
Pneumonia	Ventilator use, previous antibiotic therapy	Pneumococcal vaccine	Prevalence of MDR infections is 32% among nosocomial infections vs. 14% and 9% among health care associated and community-acquired infections, respectively[37]	High mortality among patients with cirrhosis[23]
Fungal infections	Impaired renal function, health care associated or nosocomial settings, alcohol-associated cirrhosis on glucocorticoid therapy for alcohol-associated hepatitis, higher incidence among women than among men	Fluconazole or liposomal amphotericin B to reduce invasive fungal infections in liver-transplant recipients[39]		Failed treatment of bacterial infections may be due, in part, to the possibility of fungal infections[26]

* GI denotes gastrointestinal, and MDR multidrug-resistant.
Advanced liver disease is defined as at least two of the following: ascites, severe malnutrition, encephalopathy, or jaundice.
To convert the value for bilirubin to micromoles per liter, multiply by 17.1. To convert the value for creatinine to micromoles per liter, multiply by 88.4. To convert the value for urea nitrogen to millimoles per liter, multiply by 0.357.
A double-strength tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole.

mon in patients with cirrhosis and sepsis.[52] Glucocorticoids result in quicker resolution of shock but without a long-term survival benefit and may be associated with gastrointestinal bleeding.[53] Patients whose condition deteriorates despite adequate treatment may be candidates for liver transplantation. Patients with multiorgan failure are at higher risk for death, but it is unclear currently whether organ failure scores[54,55] should be used to exclude patients from liver transplantation for reasons of futility or, conversely, whether scores should be used to assign a higher priority for organ allocation. Selecting very sick patients for transplantation is as much an art as a science. Patients with infection who have been treated with antibiotics for 24 to 48 hours may be considered for transplantation, whereas sarcopenia, frailty, increasing vasopressor requirements, and ventilatory support for acute respiratory distress syndrome are factors that generally exclude patients from being considered for transplantation. Patients who are not candidates for transplantation may be evaluated for end-of-life care. Such decisions are often multidisciplinary, and the goals of care in these situations need to be discussed with the family members and palliative care teams as early as possible and updated frequently.

PREVENTION OF INFECTIONS

Because of the relatively grim prognosis for patients with cirrhosis and infection, preventive strategies need to be considered. These include antibiotic prophylaxis and vaccinations.

ANTIBIOTIC PROPHYLAXIS

Daily antibiotics for prophylaxis against spontaneous bacterial peritonitis should be considered in three high-risk groups of patients with cirrhosis: patients with acute gastrointestinal bleeding (primary prophylaxis), those with advanced cirrhosis who are at high risk for infection (primary prophylaxis), and those with a history of spontaneous bacterial peritonitis (secondary prophylaxis) (Table 2). In patients with gastrointestinal hemorrhage, the administration of antibiotics has been associated with reductions in the rates of infection and rebleeding and improved survival. Primary prophylaxis is recommended in patients who have advanced cirrhosis (Child Pugh score ≥9 [on a scale from 5 to 15, with higher scores indicating more severe liver disease] and serum bilirubin level ≥3 mg per deciliter [51 μmol per liter]) and a low ascites fluid protein level (<1.5 g per deciliter)[34] with either impaired renal function (serum creatinine level ≥1.2 mg per deciliter [106.1 μmol per liter] or blood urea nitrogen level ≥25 mg per deciliter [9 mmol per liter]) or hyponatremia (serum sodium level ≤130 mmol per liter).[35] Long-term secondary prophylaxis against a subsequent bout of spontaneous bacterial peritonitis is recommended until liver transplantation or death. However, prophylactic strategies are associated with the risk of antibiotic resistance.

VACCINATIONS

Patients with cirrhosis require influenza, pneumococcal infection, herpes zoster, hepatitis A and B, tetanus diphtheria acellular pertussis, measles mumps rubella, and varicella vaccines. The immune response to vaccinations correlates inversely with the degree of hepatic decompensation. Thus, immunization against hepatitis A and B is best carried out in the early stages of cirrhosis. The clinical trials of coronavirus disease 2019 (Covid-19) vaccines have not included patients with cirrhosis.[56] Yet it is reasonable to consider vaccinating patients with cirrhosis, given the high risk of death associated with Covid-19 that these patients face.[57]

EMERGING APPROACHES TO MANAGEMENT

CULTURE-INDEPENDENT IDENTIFICATION OF CAUSATIVE ORGANISMS

Rapid multiplex polymerase-chain-reaction syndromic panels can simultaneously detect and identify multiple pathogens associated with typical clinical syndromes, such as bloodstream, respiratory, gastrointestinal, or central nervous system infections,[58] and may be of value in patients with cirrhosis. The use of metagenomics, the study of a collection of genomic material from a mixed community of organisms, in the diagnosis of specific infections is relatively new. Metagenomics could be important in the diagnosis of infections, since the microbiome on hospital admission in infected patients with cirrhosis differs from the microbiome in uninfected patients.[59] In studies involving patients with prosthetic joint infections, diabetic foot infections,

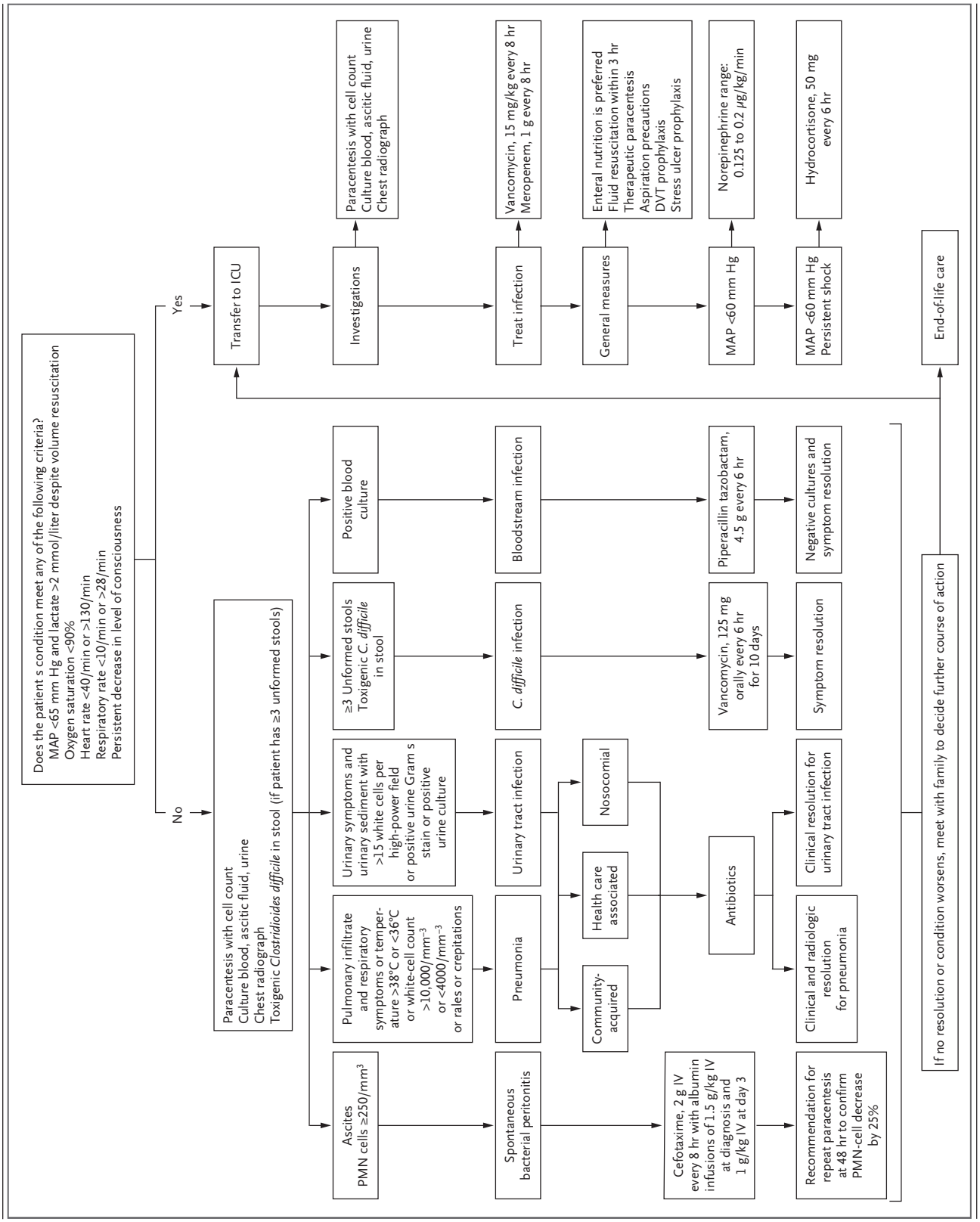

Figure 2 (facing page). Algorithm for the Care of Patients with Cirrhosis and Suspected Infection.

These broad guidelines may be superseded by local practice patterns, regional and national bacterial resistance patterns, and clinical judgment. DVT denotes deep-vein thrombosis, ICU intensive care unit, IV intravenous, MAP mean arterial pressure, PMN polymorphonuclear.

and unexplained encephalitis, metagenomics has detected organisms at a much higher yield than traditional culture-based methods, leading to successful therapy.[60] Specific metagenomic techniques can also be used to detect MDR and extensively drug-resistant genes in the identified organisms.[58] Challenges with metagenomics include cost, turnaround time, contamination with host DNA, an inability to distinguish between dead and live bacteria, and the need for bioinformatics expertise. These drawbacks have diminished over time, and at this stage, metagenomics may be explored to detect organisms in fluids if infections are suspected but cannot be cultured.

INTRAVENOUS ALBUMIN

In addition to increasing oncotic pressure, intravenous administration of albumin has antiinflammatory and pathogen-reduction effects and is important for binding and transport of drugs. Long-term administration of albumin may reduce complications, including infections, in outpatients with cirrhosis,[61] but it is less effective in patients awaiting liver transplantation.[62] In patients hospitalized with decompensated cirrhosis, albumin infusions do not prevent infections and are associated with more serious adverse events than the current standard of care.[63] Therefore, routine administration of albumin to prevent infections is not recommended.

MICROBE-TARGETED THERAPIES

Microbe-targeted therapies for infections in patients with cirrhosis include probiotics and prebiotics, fecal transplantation, and phage therapy (Table 3).

Probiotics and Prebiotics

Multiple studies involving outpatients colonized with MDR organisms have failed to show the benefit of using multistrain or single-strain probiotics.[64,65] Lactulose, which is a prebiotic used to treat hepatic encephalopathy, is not associated

Table 3. Benefits and Limitations of Current and Emerging Therapies for Infections in Patients with Cirrhosis.*

Therapy	Efficacy and Advantages	Limitations	Regulatory Landscape	Outlook
Antibiotics (current approach)	Highly effective if the causative organism and sensitivities are adequately identified; multiple studies have documented efficacy in patients with cirrhosis	Drug resistance and antibiotic overuse are rampant, may be bacteriostatic or bactericidal, not effective against biofilms, slow discovery process for new antibiotics	Large trials required to show efficacy and safety for FDA approval	If MDR persists, it will be a major cause of death worldwide
Prebiotics	Ineffective as stand-alone agents	Not enough evidence to be recommended for clinical use	Food supplements, but need to be tested formally as IND	New glycans are being produced that could impair pathogen growth
Probiotics	Low efficacy in recent trials	Not FDA-regulated, can by themselves result in infections	Treated as biologics under FDA guidance, with trials for efficacy required	Newer, focused probiotics are needed for greater effectiveness
FMT	Effective for *C. difficile* infection, no. of MDROs and antibiotic-resistant bacteria usually low after FMT, safe in patients with cirrhosis	Antibiotics must usually be avoided, mode of delivery and dose unclear, requires extensive donor testing	Treated as biologics under FDA guidance, with efficacy trials required for conditions other than *C. difficile* infections	Focused products pertaining to bacterial consortia or guilds are being developed, RCTs in process
Phage therapy	Individualized human experience is promising, no large RCTs, can penetrate biofilms, rapid discovery process	Focused on specific strains and therefore only targets single organisms, cannot penetrate eukaryotic cells, resistance can emerge	Unclear regulatory path, since individualized therapies are needed	More studies planned to treat infections, emerging data for phage cocktails as treatment for microbially mediated diseases, not just infections

* FDA denotes Food and Drug Administration, IND investigational new drug, and RCTs randomized, controlled trials.

with any appreciable change in infection rates or carriage of MDR organisms.[66]

Fecal Transplantation

Fecal microbiota transplantation involves the safe transfer of filtrated fecal material, in capsular or liquid formulations, from a donor to a recipient.[67] Studies involving patient groups with high rates of infection due to MDR bacteria, such as patients with neutropenia undergoing bone marrow transplantation, have shown that fecal transplantation results in a reduced risk of antibiotic-resistant infection.[68] Fecal transplantation is safe in patients with cirrhosis, resolves antibiotic-associated structural and functional collapse of the microbiome, and reduces an abundance of antibiotic-resistance genes in recipients.[69,70] If the donor is not carefully chosen, however, the fecal transplantation procedure itself can become a source of infection.[71] Although initial studies in advanced cirrhosis are promising, the use of fecal transplantation to reduce the risk of repeated and antibiotic-resistant infections requires further study.

Phage Therapy

Bacteriophages have been used therapeutically for antibiotic-resistant infections with varying degrees of success.[72] The advantages are their bactericidal nature and penetration of biofilms, whereas disadvantages are related to strain specificity and the risk of resistance.[73] Phage therapy can be administered topically, intravenously, or orally. The lack of regulatory approval for phage therapy in patients with cirrhosis and infection, as well as the need to individualize treatment, makes widespread application of phage therapy difficult at present.

FUTURE DIRECTIONS AND SUMMARY

Infections profoundly affect the natural history of cirrhosis. The epidemiologic characteristics and causative organisms are changing radically, in part because of concomitant medications and indiscriminate use of antibiotics. A high index of suspicion, early diagnosis, rapid administration of effective antibiotics, and prevention of multiorgan failure are required to improve survival. Prevention of further infections and the negative effect of infections on liver transplantation candidacy remain challenges. Effective management strategies are urgently required to improve the poor prognosis for patients with cirrhosis who have infections.

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