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# Novel Prevention Strategies for Bacterial Infections in Cirrhosis

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## Abstract

**Introduction—**Bacterial infections are a serious complication of cirrhosis, as they can lead to decompensation, multiple organ failure, and/or death. Preventing infections is therefore very relevant. Because gut bacterial translocation is their main pathogenic mechanism, prevention of infections is mostly based on the use of orally administered poorly absorbed antibiotics such as norfloxacin (selective intestinal decontamination). However, antibiotic prophylaxis leads to antibiotic resistance, limiting therapy and increasing morbidity and mortality.

Prevention of bacterial infections in cirrhosis should therefore move away from antibiotics.

**Areas Covered—**This review focuses on various potentially novel methods to prevent infections in cirrhosis focusing on non-antibiotic strategies. The use of probiotics, nonselective intestinal decontamination with rifaximin, prokinetics and beta-blockers or fecal microbiota transplant as means of targeting altered gut microbiota, bile acids and FXR agonists are all potential alternatives to selective intestinal decontamination. Prokinetics and beta-blockers can improve intestinal motility, while bile acids and FXR agonists help by improving the intestinal barrier. Finally, granulocyte colony stimulating factor (G-CSF) and statins are emerging therapeutic strategies that may improve immune dysfunction in cirrhosis.

**Expert Opinion—**Evidence for these strategies has been restricted to animal studies and proof-of concept studies but we expect this to change in coming years.

### Keywords

cirrhosis; bacterial infections; bacterial translocation; selective intestinal decontamination; probiotics; rifaximin; fecal microbiota transplant; prokinetics; beta-blockers; bile acids; FXR agonist; statins; GCSF

## 1.0. Introduction

Bacterial infections are present in 25-40% of hospitalized patients with cirrhosis [1, 2]. They can lead to further decompensation of cirrhosis (recurrent variceal hemorrhage, hepatorenal

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syndrome) and are the main precipitant of multiorgan failure in cirrhosis, the so-called acute-on-chronic liver failure (AOCLF) [Figure 1]. Therefore, they are associated with a high mortality; with a four-fold increase in in-hospital mortality [3], and a post-discharge mortality rate of 28-30% [4, 5]. As such, prevention of bacterial infections in cirrhosis is crucial.

Patients at higher risk of developing bacterial infections are those with poor liver function, upper gastrointestinal (GI) bleeding, low-protein ascites, and a prior episode of spontaneous bacterial peritonitis (SBP) [5, 6]. The most common infections in cirrhotic patients are SBP, urinary tract infections, pneumonia, and skin and soft tissue infections; any one of these may cause bacteremia and sepsis. SBP itself accounts for about 31% of the infections in patients with cirrhosis [2, 7]. Most infections are caused by gram-negative bacteria of intestinal origin; as such, bacterial translocation, defined as the passage of bacteria from the intestinal lumen to mesenteric lymph nodes or other extra-intestinal sites, has been implicated as a major mechanism in the development of these infections (particularly, spontaneous infections such as SBP). Perhaps more importantly, bacterial translocation is responsible for a pro-inflammatory state that worsens the hemodynamic status of patients with cirrhosis and leads to decompensation. This state of immune activation (“cytokine storm”) also leads to the development of cirrhosis-associated immune dysfunction [8, 9] that increases the susceptibility to other infections, including those due to Gram-positive or other bacteria not originating from the gut [Figure 2]. For example, patients with cirrhosis and pneumonia have a higher risk of developing bacteremia than patients without liver disease [10].

Therefore, preventing bacterial translocation will prevent infections and their deleterious consequences in patients with cirrhosis. Bacterial translocation occurs physiologically, but the healthy individual is able to eliminate translocating bacteria. In cirrhosis, a number of gastrointestinal abnormalities make it more likely for bacteria to translocate and spread to the systemic circulation; these abnormalities are as follows: 1) altered gut microbiota (changes in both the quantity and quality of gut bacteria); 2) altered intestinal permeability and 3) decreased phagocytosis. [Figure 3]. This review will focus on current and future novel strategies for preventing bacterial infections in cirrhosis, based on these mechanisms.

## 2.0. Current strategy

Currently, the prevention of bacterial infections is focused solely on use of prophylactic antibiotics, usually norfloxacin, which target the most common organisms implicated in spontaneous infections in cirrhosis, Enterobacteriaceae and non-enterococcal streptococci. This is the strategy of “selective intestinal decontamination” [Figure 4], in which a poorly absorbable antibiotic such as norfloxacin changes the altered intestinal microbiome of cirrhosis to promote the growth of “good” anaerobic bacteria and suppress “bad” gram-negative bacteria[11]. In addition to the benefit of preventing infections, selective intestinal decontamination has also been shown to prevent the early recurrence of variceal hemorrhage [12], hepatorenal syndrome [13], and death [13, 14].

The major drawback of routine antibiotic prophylaxis is the emergence of multidrug resistant organisms [2, 15] which cause infections for which there are limited therapeutic

antibiotics and are thereby associated with a greater incidence of septic shock and death [2]. Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant Enterococcus (VRE), and Extended-Spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are the most prevalent multiresistant organisms reported in patients with cirrhosis [16]. *Clostridium difficile* infection is another infection on the rise, and a major risk factor for its development is antibiotic use; it causes higher mortality and longer hospitalizations in patients with cirrhosis [17].

Hence, routine prophylaxis should be limited to only patients specified below that are at the highest risk of developing a bacterial infection as is currently recommended in practice guidelines of both the American Association for the Study of Liver Diseases (AASLD) [18] and the European Association for the Study of the Liver (EASL) [19].

1. Patients with cirrhosis presenting with upper GI hemorrhage: Antibiotic prophylaxis with norfloxacin 400mg / 12 h PO for 7 days should be instituted from the time of admission, per Baveno VI recommendations [20]. Intravenous ceftriaxone at 1g/ 24h for 7 days should be considered in patients with advanced cirrhosis, in hospital settings with a high prevalence of quinolone-resistant bacterial infections and in patients on previous quinolone prophylaxis.
2. Patients who have survived an episode of SBP: Secondary prophylaxis with norfloxacin at 400mg/day PO is the recommended prophylaxis. Alternatively, since norfloxacin is no longer available in the U.S., ciprofloxacin at a dose of 500 mg/day can be used instead. Treatment should continue until liver transplant, death, or resolution of ascites or improvement in liver function to a compensated status.
3. Patients with ascitic fluid protein <1.5g/dL along with impaired renal function (creatinine ≥1.2, BUN ≥25, or serum Na ≤130) or liver failure (Child score ≥9 and bilirubin ≥3mg/dL): Primary prophylaxis with long-term norfloxacin 400mg/day PO or ciprofloxacin 500mg/day is recommended in these patients. This is particularly relevant in patients awaiting liver transplantation for whom the development of an infection would prompt removal from the transplant list.

## 3.0. Novel Strategies

As currently recommended antibiotic prophylaxis is associated with the development of infections due to multiresistant organisms, other methods for preventing bacterial translocation and bacterial infections are necessary. Novel therapies have been proposed based on their ability to alter bacterial translocation but the evidence for their use is limited and all require further studies. These strategies are outlined below together with their main purported mechanism of action (although many of them act at more than one level).

### 3.1. Prevention Strategies That Target the Altered Intestinal Microbiota

Though there are countless bacteria in the human gastrointestinal tract, most of them reside in the colon. There are hundreds of times more anaerobic bacteria than aerobic bacteria, with the latter being responsible for most cases of bacterial translocation [21]. Aspirates of the colon may reveal concentrations up to $10^{12}$ colony-forming units (CFU) /mL, whereas aspirates of the jejunum are much less concentrated at $10^{3}$-$10^{4}$ CFU/mL [22]. The small intestine harbors significantly fewer bacteria than the colon due to its constant peristaltic motion and presence of antimicrobial gastric acid [23]. Bacterial overgrowth of the small intestine may occur in certain disease states, and is defined as at least $10^{5}$ total CFU/mL in jejunal secretions. Small intestinal bacterial overgrowth is prominent in both cirrhotic rats with ascites and patients with cirrhosis [24-27], and is thought to be the most common site of bacterial translocation [28]. It is related to the severity of liver disease [27], and increases the risk of bacterial translocation and infection [24, 29, 30]. Proposed strategies to target this bacterial overgrowth involve decreasing the overall bacterial burden or changing the taxonomy of intestinal microbes to favor the growth of anaerobic bacteria [Figure 3].

**3.1.1. Decreasing the overall burden/function of intestinal bacteria: Rifaximin —**Rifaximin is an antibiotic with broad-spectrum activity that was thought to eliminate gut microbes non-selectively, hence reducing the overall burden of intestinal bacteria [31, 32]. However a recent study shows that, rather than changing the stool microbiome, it seems to have a direct effect on bacterial function by impairing their ability to translocate [33]. Rifaximin's activity is specific to the gut as its absorption into the systemic circulation is practically nil, which limits systemic toxicity or side effects. The lack of systemic availability also limits the selective pressure for the development of widespread resistance that is seen with systemically available antibiotics; in addition, resistance to rifaximin is not efficiently transferred [34].There is already strong evidence for the use of rifaximin in maintaining remission from hepatic encephalopathy in cirrhosis [32, 35] and in this setting, it has not been associated with the development of infections due to multidrug resistant organisms [15]. The role of rifaximin in preventing infections is being investigated. Non-randomized studies have shown mixed results: there is both a positive effect and a lack of effect of rifaximin in preventing SBP or cirrhosis decompensation. Rifaximin was shown to lower the infection rate in cirrhotic patients compared to no treatment [35, 36], with as much as a 72% decrease in the risk of primary SBP [37], as well as lowering other complications of cirrhosis such as hepatorenal syndrome and variceal bleeding [36]. However, in a prospective cohort study comparing prophylaxis with rifaximin to prophylaxis with systemically absorbed antibiotic versus no prophylaxis, rifaximin did not reduce SBP occurrence in hospitalized cirrhotic patients compared to no treatment; only systemic antibiotic had an effect on reducing risk of SBP [38]. The major drawback is that none of these studies were randomized, placebo-controlled trials, which are needed to truly delineate the effect of rifaximin in preventing infections in cirrhosis.

**3.1.2. Changing the taxonomy of intestinal microbes: Probiotics, prebiotics, and synbiotics—**Probiotics are live bacteria that replace or add to the beneficial bacteria normally present in the gastrointestinal tract. Species such as *Lactobacillus* spp. have protective effects on the intestinal mucosa, such as lowering intestinal pH, preventing

colonization by pathogenic species, and modulating the immune response; hence, they help to improve overall gut function [39]. Prebiotics are nondigestable food ingredients that promote the growth of the beneficial bacteria, such as fermentable fibers, which the bacteria break down for their nutrition and survival. Synbiotics are merely the combination of probiotics and prebiotics.

In rats with cirrhosis, administration of *Lactobacillus johnsonii* La1 with antioxidants reduced bacterial translocation and endotoxemia compared to control [40]. Other combinations of lactobacilli were also shown to be effective at reducing bacterial translocation and serum alanine aminotransferase levels in a rat model of acute liver injury [41]. An 8-species probiotic cocktail (3 bifidobacteria species and 5 lactobacilli species) called VSL#3 decreased bacterial translocation and improved intestinal permeability (measured by ileal occludin expression and oxidative damage) in rats with cirrhosis [42] [Table 1].

Randomized controlled trials (RCT) in liver transplant recipients demonstrated a significant reduction in infections in patients treated with *Lactobacillus plantarum* 299 and fiber compared to selective bowel decontamination with a mix of antibiotics [39], as well as in patients treated with a mixture of four lactic acid bacteria species and four fibers versus fibers only [43]. An RCT featuring administration of *Escherichia coli* Nissle improved the gut microbial profile and lowered endotoxemia, a marker of bacterial translocation, and mildly improved liver function [44]. A synbiotic preparation containing 4 species (*Pediacoccus pentoseceus*, *Leuconostoc mesenteroides*, *Lactobacillus paracasei*, *Lactobacillus plantarum* 2592) and 4 fibers (beta glucan, inulin, pectin, resistant starch) was effective at improving gut flora, reducing endotoxemia, and reversing minimal hepatic encephalopathy in 50% of patients with cirrhosis [45]. Together, these studies suggest a beneficial effect of probiotics in preventing infections in cirrhosis. [Table 2].

However, there are also negative studies with probiotics, including case reports of *Lactobacillus* sepsis with probiotic therapy. In a rat model of cirrhosis, *Lactobacillus rhamnosus* strain GG proved ineffective at preventing bacterial translocation and ascitic fluid infection compared to control [46]. A randomized controlled trial in humans showed that addition of a 4-species probiotic (*Enterococcus faecalis* JPC, *Clostridium butyricum*, *Bacillus mesentericus* JPC, *Bacillus coagulans*) to norfloxacin did not reduce the occurrence of spontaneous bacterial peritonitis or mortality [47]. These negative results may be the result of various factors; the first of which is that not all probiotics are created equal, and different probiotics were used in all these studies; some species may be more effective than others, and the number of different species may make a difference as well. Also, the addition of norfloxacin to probiotic may have affected probiotic viability in the latter study. Further studies are needed to determine the optimal combination of probiotics and prebiotics, as well the dosing and duration of administration. These studies would need to compare pro/prebiotics to standard antibiotic prophylaxis and not in addition to it.

**3.1.3. Changing the taxonomy of intestinal microbes: Fecal microbiota transplant—**Fecal microbiota transplant (FMT) is an emerging therapy for the treatment of gastrointestinal dysbiosis, usually in *Clostridium difficile* infections [48]. It involves the

transfer of feces from a healthy donor to the recipient via one of three routes: gastric, jejunal, or colonoscopic. It is capable of reestablishing intestinal homeostasis and preventing recurrent infections [48, 49]. However, the evidence for FMT outside of *C. difficile* infection is scant. In one case report, a 14-year-old girl colonized with highly resistant Klebsiella pneumonia leading to successive infections was successfully treated with fecal microbiota transplant, after which stool studies showed clearance of the organism that was sustained over several months [50]. In another case report, fecal microbiota transplant in a patient with cirrhosis and hepatic encephalopathy improved cognitive function and brought the gut flora taxonomy closer to normal, though this effect was not sustained beyond 7 weeks following transplant [51]. To date there are no studies examining the use of fecal microbiota transplant for preventing bacterial infections in patients with cirrhosis, though it remains a promising therapy.

### 3.2. Prevention Strategies that Target Abnormal Intestinal Motility in Cirrhosis

One of the causes of intestinal bacterial overgrowth in cirrhosis is that intestinal transit times are prolonged, particularly in patients with decompensated cirrhosis (the ones most prone to infection). The regular cyclical contractions of the gastrointestinal tract in the fasting state is due to waves of electrical activity known as migrating motor complexes (MMCs), which generate peristaltic waves that propel material through the intestinal lumen. It consists of three phases: phase I, the quiescent phase; phase II, characterized by a buildup of action potentials and contractility; and finally phase III, the peak of electrical and mechanical activity. Phase III of the MMC acts as the intestinal housekeeper, with its well-defined aborad migration that clears the gut, along with increased biliary secretions that act as a detergent [52, 53]. Intestinal peristalsis, gastric acid, and mucosal immunity work in concert to prevent bacterial overgrowth in the small intestine [54].

Abnormalities in small bowel motility in patients with cirrhosis include a prolonged MMC cycle duration, a prolonged phase II, and various changes in the contraction pattern of phase II in patients with cirrhosis compared to healthy controls, such as increased clustered contractions, less cyclic contractions, and more retrograde pressure waves [52, 55, 56]. The abnormalities in migrating motor complexes and increased clustered activity are more severe in Child-Pugh stage C cirrhotic patients compared to stage A patients; also, the extent of small bowel dysmotility is related to the degree of liver failure [52, 57, 58] and presence of portal hypertension [56]. Furthermore, these abnormalities in intestinal motility are reversed following liver transplantation [59].

These changes in intestinal motility in cirrhotic patients likely cause ineffective intestinal peristalsis, which delays the intestinal transit time and favors bacterial overgrowth. Indeed, decompensated cirrhotic patients have slower intestinal transit times than patients with compensated cirrhosis [58], with a significant correlation between small bowel transit time and Child-Pugh score ($R=0.77$, $p=0.0003$) [58]. These abnormalities in bowel motility and transit times are conducive to bacterial overgrowth, as patients with cirrhosis and a history of SBP have a significantly higher incidence of bacterial overgrowth compared to cirrhotic patients without SBP [52]. Other studies have also demonstrated the association of small intestinal bacterial overgrowth with intestinal dysmotility in both rats and patients with

cirrhosis [24, 60, 61], and specifically in those cirrhotic patients with portal hypertension [56].

**3.2.1. Improving intestinal motility: Cisapride—**Since altered intestinal motility is one of the factors predisposing to infections in patients with cirrhosis, prokinetic agents represent a therapeutic strategy to target this complication. Cisapride is the best studied agent for this purpose; it is unique among prokinetics as it does not have antidopaminergic properties, instead exerting its effect by increasing the physiologic release of acetylcholine from post ganglionic nerve endings of the myenteric plexus. It significantly reduces bacterial translocation in cirrhotic rats, namely by accelerating intestinal transit time and reducing intestinal bacterial overgrowth [62, 63]. Its administration in humans with cirrhosis improves fasting cyclical activity, reduces orocecal transit time and is associated with abolishment of bacterial overgrowth [60, 62]. A prospective randomized controlled trial in a heterogeneous group of cirrhotic patients with ascites showed that the combination of norfloxacin and cisapride significantly reduces the incidence of spontaneous bacterial peritonitis compared to norfloxacin alone [64]. However, the inclusion of patients at different risks for SBP and adding the prokinetic to norfloxacin rather than comparing it to norfloxacin, limit the validity of this study. Cisapride is associated with QT prolongation that has led to its discontinuation from the market. Further studies using other prokinetic agents, such as the 5-HT4 receptor antagonist prucalopride, would be worthwhile although there is no preliminary data.

**3.2.2. Improving Intestinal Motility: Non-selective beta adrenergic-blockers—**Cirrhosis is a state of increased adrenergic activity that results from vasodilatation (splanchnic and systemic), the hemodynamic hallmark of patients with decompensated cirrhosis. This increased sympathetic stimulation results in delayed intestinal transit, which may be reversed with beta-blockers. Since norepinephrine also increases the growth of gram-negative rods and increases intestinal permeability [65, 66], beta-blockers may also act as an antibacterial and target multiple mechanisms responsible for bacterial translocation in cirrhosis. Beta-blockers are already used to prevent variceal hemorrhage in cirrhosis, their main effect being a reduction in portal pressure.

In cirrhotic rats with ascites, propranolol significantly accelerated intestinal transit, reducing rates of bacterial overgrowth in the bowel and bacterial translocation [61]. In patients with cirrhosis, propranolol reduced intestinal permeability, measured by urinary sucrose levels, and bacterial translocation, measured by serum LPS-binding protein (LBP) and IL-6 [67]. A meta-analysis that included studies of beta-blockers in the prevention of hemorrhage (studies in which infection was not an outcome) suggested that patients with cirrhosis on propranolol have a lower risk of SBP and that this effect was independent on their portal pressure-reducing effect [68]. A recent prospective study also found a significant protective effect of beta-blockers against infection in cirrhotic patients; these patients had lower infection-related morbidity and mortality when taking beta-blockers [69]. Until more data is available beta-blockers should not be used with the objective of preventing infections. In fact, a recent controversial issue pertains to a potentially deleterious effect of beta-blockers in patients with cirrhosis and refractory ascites (the most prone to develop infections) [70]. Until this

issue is resolved, and per Baveno recommendations, beta-blockers should not be discontinued in all patients with refractory ascites but only in those with a systolic blood pressure <90 mmHg, hyponatremia (<130 mEq/L) or increases in serum creatinine >0.3 mg/dL from baseline [20].

### 3.3. Prevention Strategies that Target the Impaired Intestinal Barrier in Cirrhosis

Normal intestine contains a mucosal barrier with secretory and physical components to prevent microbial translocation [71]. Mucins from epithelial goblet cells shield the microvillus membrane from bacteria [72]. Immunoglobulin A (IgA) antibodies is another important player in antimicrobial defense; it binds epitopes on pathogens and traps them in the mucus layer (immune exclusion), and neutralizes toxins [71, 73]. Bile acids also contribute by inhibiting bacterial overgrowth, promoting growth of the intestinal mucosa [74], and acting as a detergent to prevent bacterial adherence [75]. The intestinal epithelium itself maintains a critical barrier through the use of tight-junction complexes to maintain selective permeability, as well as through the active production of antimicrobial peptides and proteins [71].

This well-evolved intestinal barrier is compromised in cirrhosis. Markers of intestinal permeability and bacterial translocation are significantly correlated with [67]degree of liver dysfunction [76] in patients with cirrhosis. There are various factors involved in this breakdown in intestinal integrity, including altered expression of tight junction proteins occludin and claudin-1 [77], upregulation of tumor necrosis factor-α in the gut-associated lymphatic tissue [78], and deficiency of mucosal protective factors, such as bile acids [79], secretory IgA [80], and antimicrobial peptides [16, 81].

**3.3.1. Protecting the Intestinal Barrier: Bile acids—**Bile acids are bacteriostatic [82, 83], prevent bacterial overgrowth in the small intestine, and maintain intestinal barrier function. Decreased bile flow in cirrhosis results from bile duct obstruction, which fosters bacterial overgrowth and bacterial translocation, including leakage of endotoxin and bacterially-driven products from the gut into the systemic circulation [84]. The oral administration of bile acids cholic acid, deoxycholic acid, or whole bile) inhibits bacterial overgrowth and bacterial translocation in common bile duct ligated rats [85]. In a more relevant model of cirrhosis, the rat with carbon tetrachloride (CCl4)-induced cirrhosis, oral bile acids also reduced intestinal bacterial overgrowth and bacterial translocation, in addition to reducing mortality [79]. There are no relevant studies in humans but experimental studies suggest that bile acids, through both their antimicrobial effects and intestinal barrier effects, may prevent bacterial translocation and infections in cirrhosis.

**3.3.2. Improving intestinal permeability—**Farnesoid X Receptor (FXR) agonists Farnesoid X Receptor is a nuclear receptor and transcription factor activated by bile acids such as cholic and chenodeoxycholic acid. It is a chief regulator of the metabolism of bile acid, lipid, and carbohydrates. In the intestine, FXR induces genes involved in enteroprotection, from restoring intestinal permeability to reducing inflammation, and thus represents an enticing target for preventing bacterial translocation in cirrhosis. FXR-deficient rats demonstrate high rates of bacterial translocation and increased intestinal

permeability [86]. In bile-duct ligated rats, administration of an FXR agonist GW4064 significantly reduced the number of bacteria both in the ileum and the mesenteric lymph nodes [87]. In humans with cirrhosis, a polymorphism in the FXR receptor gene, the rs56163822 genotype, significantly increased the risk of developing spontaneous bacterial peritonitis and was confirmed as a predictor of SBP [88].

Obeticholic acid (6-ethylchenodeoxycholic acid) is a potent semisynthetic bile acid and agonist of FXR, and was shown in bile duct-ligated rats to reduce intestinal inflammation and the number of bacterial strains that translocated to mesenteric lymph nodes, compared to animals treated with ursodeoxycholic acid (UDCA) [86]. In rats with CCl4-induced cirrhosis, administration of obeticholic acid significantly reduced bacterial translocation (from 83% to 20%, $p<0.01$) and improved markers of inflammation and fibrosis in the gut and liver (e.g, IL-17, TNF-α, TLR-4, and collagen) compared to placebo [89]. In humans, obeticholic acid was recently shown to improve liver fibrosis in patients with non-cirrhotic, non-alcoholic steatohepatitis, and was shown to be safe [90]. Even though it has not been specifically investigated in patients with cirrhosis, it is a promising therapeutic target that should be further explored regarding its capacity to prevent infections.

### 3.4.Prevention Strategies that Target Immune Dysfunction in Cirrhosis

The immune dysfunction in cirrhosis involves at once a state of immunodeficiency as well as a pro-inflammatory state [9, 91]. The pro-inflammatory state in cirrhosis is a result of continuous stimulation of immune cells by products of bacterial translocation that eventually leads a population of immune cells to become dysfunctional (“immune paralysis”) [92]. Not only is the quantity of lymphocytes, neutrophils, and other phagocytes reduced (partly because of pooling in the spleen resulting from portal hypertension), but these cells also demonstrate poor functional activity [93]. Additionally, the presence of porto-systemic shunting and liver dysfunction (with decreased hepatic production of complement) results in decreased clearance of bacteria by the liver [94].

**3.4.1. Repopulating the liver with functional immune cells Granulocyte Colony-Stimulating Factor—**One novel potential therapy that actually gets at the root cause of liver disease itself is the use of granulocyte colony-stimulating Factor (G-CSF). This 175-amino acid-long recombinant cytokine protein is the most potent agent available for mobilizing hematopoietic stem cells from the bone marrow. This therapy works by repopulating the liver [95] with both hepatocytes and non-parenchymal cells, which includes immune cells (e.g. neutrophils, T cells) that can help prevent infection. In recent randomized controlled trials, G-CSF was shown to decrease risk of infection and/or sepsis in patients with acute-on-chronic liver failure [96, 97] and, in combination with erythropoietin, to lower the incidence of septic shock to 7%, compared to 38% in the placebo group ($P<0.005$) [98]. Importantly, both trials showed a survival benefit in patients with advanced liver disease and therefore this strategy would appear to be particularly promising if confirmed by other groups.

**3.4.2. Modulating inflammation: Statins—**Statins seem to have a protective effect against bacteremic infections, although they appear to have no effect on mortality. It is

thought to work through its anti-inflammatory and immunomodulatory properties [99]. A retrospective cohort study in veterans with compensated cirrhosis showed a decrease in severe bacterial infections in statin users compared to non-statin users (HR 0.42, 95% CI 0.36-0.48) [100], suggesting that statin use may reduce the risk of infections in cirrhosis. However, these results must be taken with caution because of methodological issues, importantly its retrospective nature. Statin use has further benefits in cirrhotic patients in that it lowers portal pressure and portal hypertension, allowing improved liver perfusion and function [101] and has recently been shown to prevent decompensation and death in patients with compensated hepatitis C-related cirrhosis [102]. Overall, further studies are necessary to confirm these findings of the beneficial effects of statins in liver disease.

## 4.0.Conclusion

Prevention of bacterial infections in cirrhosis is currently limited to selective intestinal decontamination with antibiotics. Although effective, this management strategy is not ideal as it has led to the development of antibiotic resistance and should therefore be restricted to very specific populations of patients with cirrhosis with an especially high-risk of developing infections. Increasing knowledge regarding the mechanisms of infection, inflammation and immune deficiency in cirrhosis have led to potentially novel and useful strategies to prevent bacterial translocation and the development of infections in cirrhosis. Emerging alternatives to selective intestinal decontamination include: nonselective decontamination with rifaximin, probiotics, and fecal microbiota transplant, all of which target bacterial overgrowth; prokinetics like cisapride and beta-blockers to target intestinal dysmotility; bile acids and FXR agonists to target the impaired intestinal barrier; G-CSF and statins to restore the immune imbalance in cirrhosis. Ultimately, prevention of bacterial translocation and the resultant risk of immune activation and/or overt bacterial infection will result in prevention of decompensation and multiorgan failure and an improvement in survival. Hopefully, in the upcoming years the efficacy of many of these strategies and the specific population of patients with cirrhosis that would benefit from specific strategies will be clarified.

## 5.0.Expert Opinion

The research on antibiotic prophylaxis of bacterial infections in cirrhosis is solid in the settings of patients with gastrointestinal hemorrhage and in the prevention of recurrent spontaneous bacterial peritonitis (SBP). In these studies the key findings are that antibiotics not only prevent infections but could prevent recurrent variceal hemorrhage, recurrent SBP and death. It is not as solid in the area of primary prophylaxis of SBP/infections in general because further patient stratification is necessary. However, if restricted to patients with very severe liver disease, antibiotic prophylaxis can prevent hepatorenal syndrome and prolong survival. Research on non-antibiotic prophylaxis has mostly been restricted to animal studies and to some proof-of concept studies in patients with cirrhosis so, at this time, evidence is insufficient to recommend any of these non-antibiotic strategies.

The potential of this research is not only to prevent infections in cirrhosis but also to prevent the deleterious consequences of translocation of bacteria and its products from the gut by

triggering a pro-inflammatory state that can lead to further immune dysfunction, creating a vicious cycle. Ultimately, the goal would be to prevent the development of decompensation, multiorgan failure and death in cirrhosis. Basic research to further define the mechanisms vis-à-vis different stages of cirrhosis is necessary so that an individualized approach can be applied to clinical trials. The potential strategies are many and it is unclear which one will be the best in general or, more importantly, which approach will be best for specific patient populations.

Hopefully, antibiotic stewardship and restriction of antibiotic prophylaxis to only those patients that really need it will lead to a decrease in infections due to multiresistant organisms. Concomitantly, further development of benign, non-antibiotic strategies may lead to randomized clinical trials that will prioritize among the different strategies outlined in this review.

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## List of abbreviations

| | |
|---|---|
| **AOCLF** | Acute-on-chronic liver failure |
| **SBP** | spontaneous bacterial peritonitis |
| **MDR** | multidrug-resistant |
| **ESBL** | extended spectrum β–lactamase |
| **CDI** | *Clostridium difficile* infection |
| **CFU** | colony-forming units |

| | |
|---|---|
| **RCT** | randomized controlled trial |
| **FMT** | fecal microbiota transplant |
| **LPS** | lipopolysaccharide |
| **LBP** | LPS-binding protein |
| **MELD** | Model for End-Stage Liver Disease |
| **FXR** | Farnesoid X-Receptor |
| **$CCl_4$** | carbon tetrachloride |
| **UDCA** | ursodeoxycholic acid |
| **OCA** | obeticholic acid |
| **TNF** | tumor necrosis factor |
| **TLR** | toll-like receptor |
| **Ig** | Immunoglobulin |

## Highlights

- Bacterial translocation is the main mechanism in the pathogenesis of spontaneous infection in cirrhosis, and results from the following physiologic alterations in cirrhosis: altered gut microbiota, intestinal dysmotility, gut barrier dysfunction, and immune dysfunction
- Our current strategy for preventing infections is the method of selective intestinal decontamination, which uses an antibiotic such as norfloxacin to change the taxonomy of gut microbiota. However, it is associated with the development of antibiotic-resistant organisms
- Novel approaches to preventing bacterial infections include the following strategies: targeting altered gut microbiota using probiotics and rifaximin; targeting intestinal dysmotility with prokinetics, and beta-blockers; improving the intestinal barrier with bile acids and FXR agonists; and targeting immune dysfunction with G-CSF and statins.
- Of these approaches, there is most evidence in human studies for probiotics, rifaximin, and beta-blockers.
- There is insufficient evidence to officially recommend any of these strategies at this point.

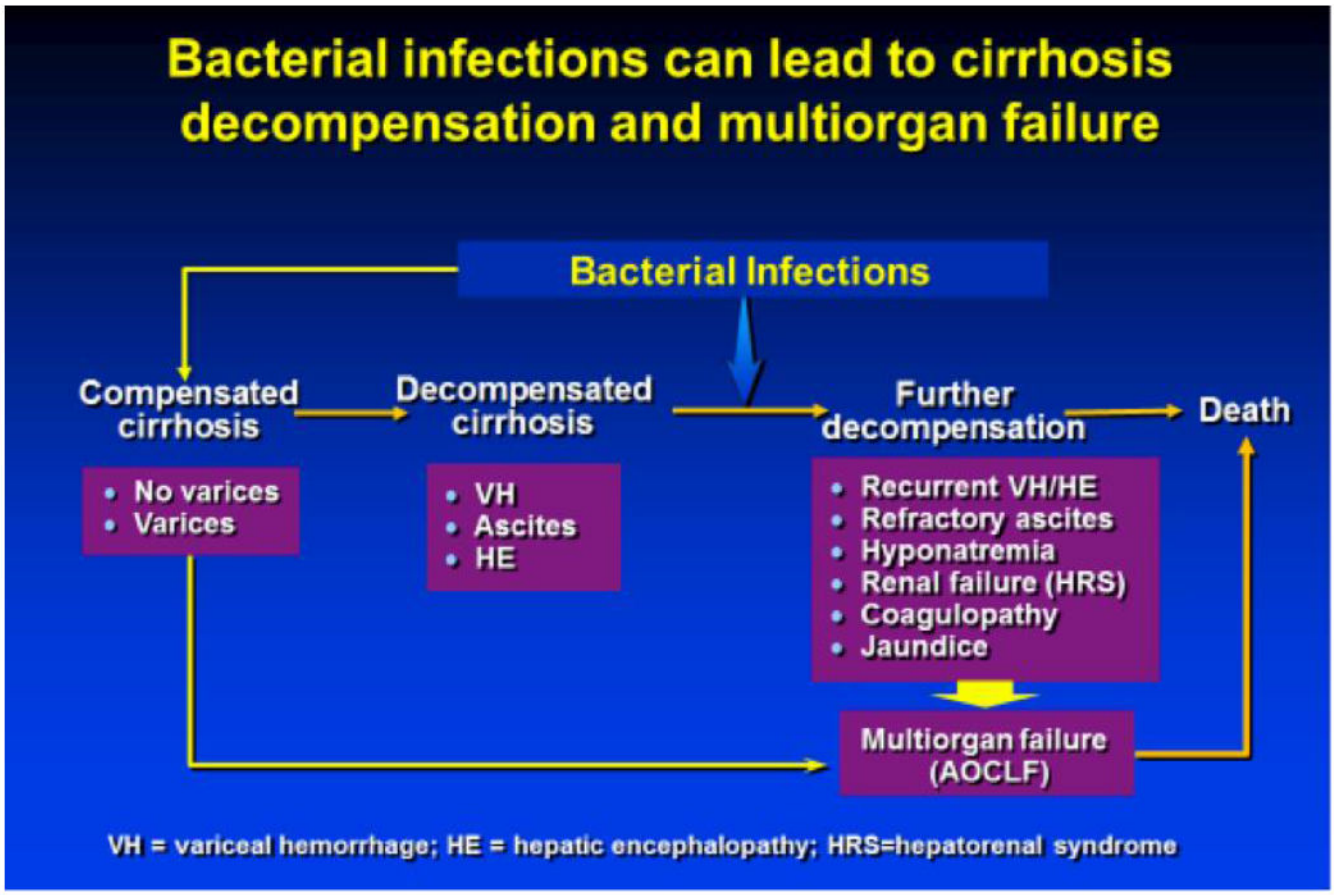


**Figure 1.**
Bacterial infections can lead to decompensation of cirrhosis and multiorgan failure

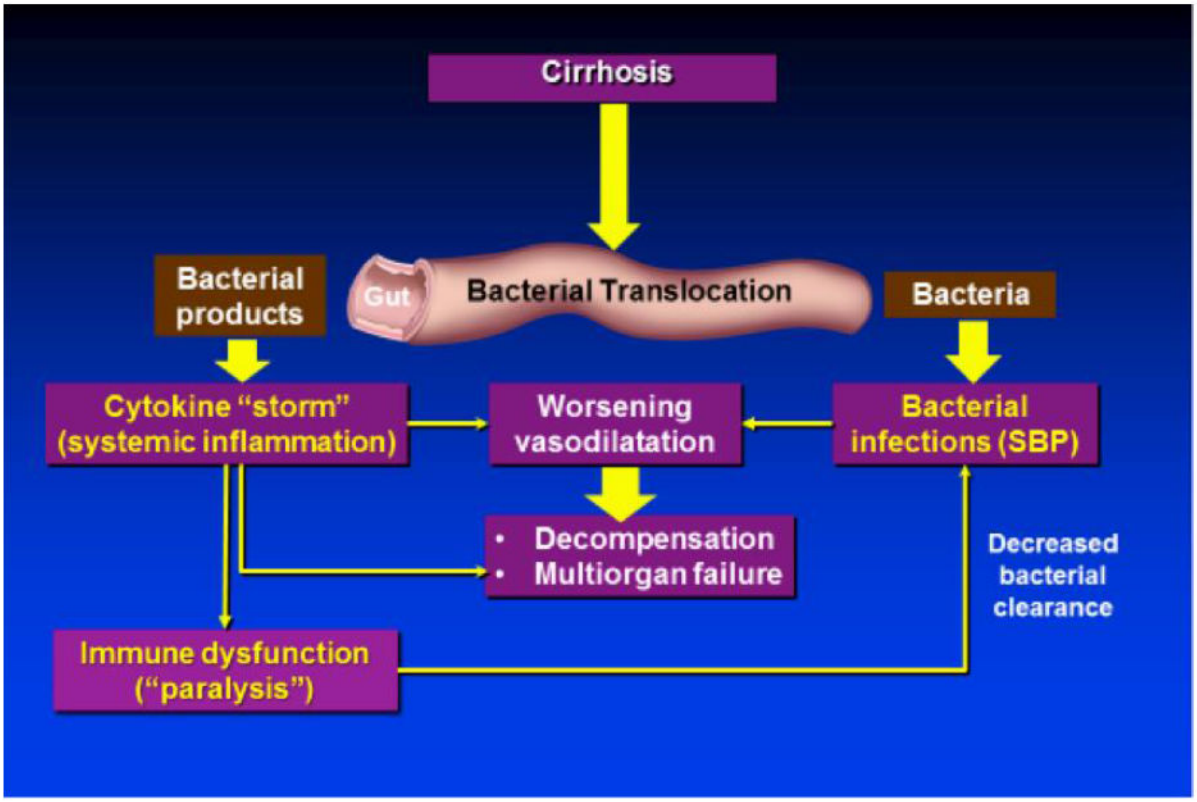


**Figure 2.**
Effect of Bacterial Translocation in Cirrhosis

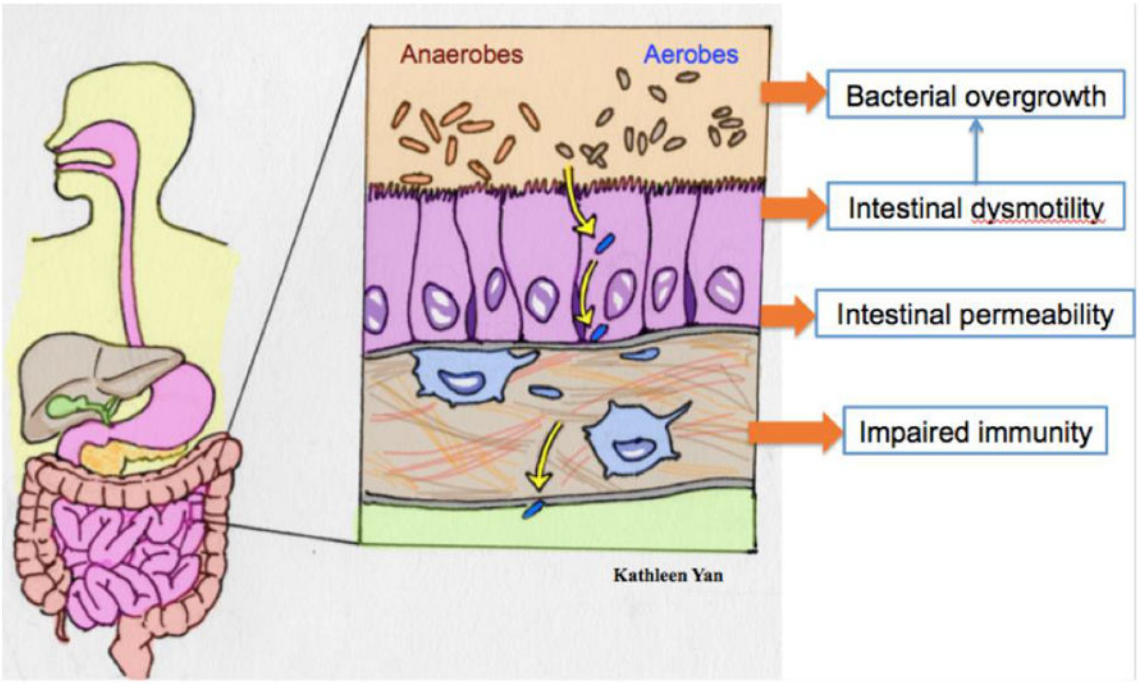


**Figure 3.**
Mechanisms of Bacterial Translocation in Cirrhosis

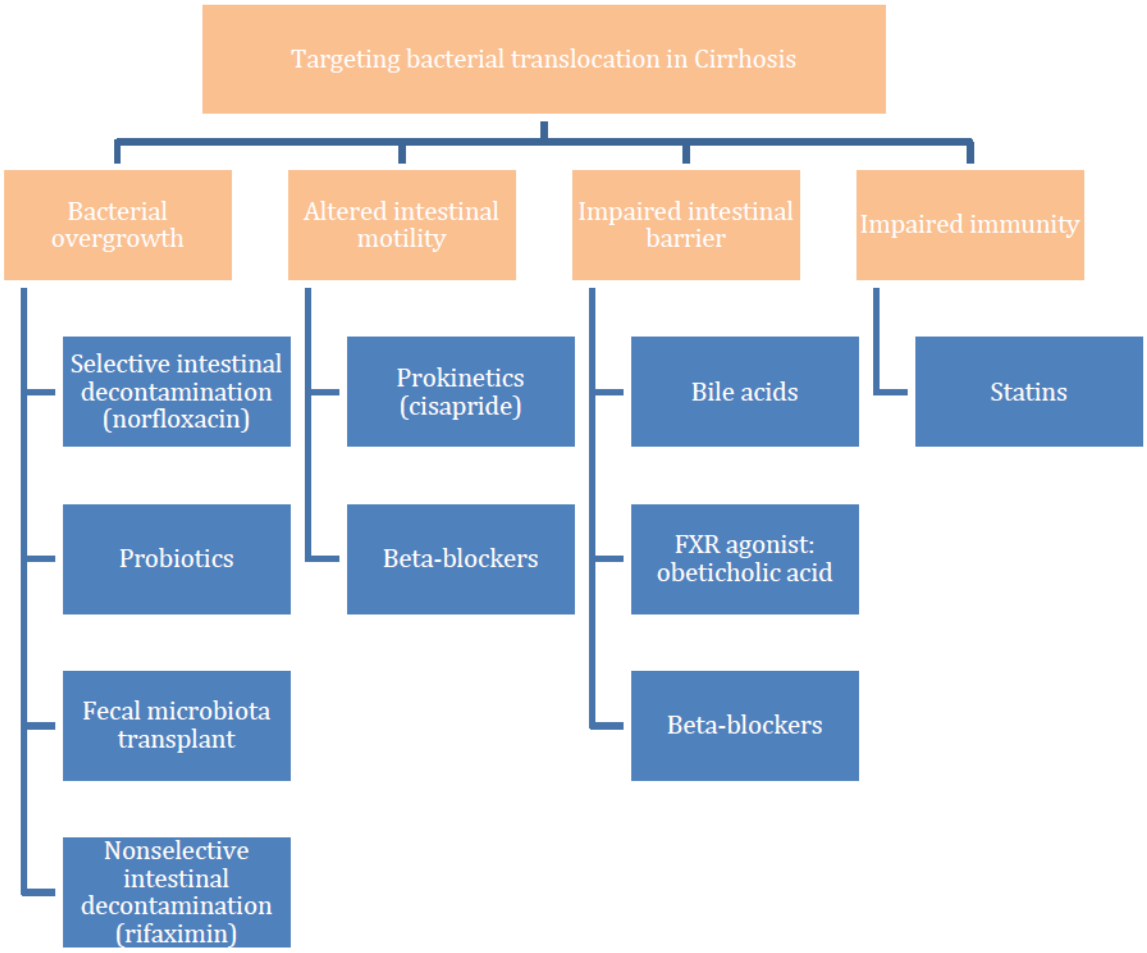


**Figure 4.**

Strategies to target bacterial translocation in cirrhosis. Mechanisms are shown in orange, and treatment strategies in blue.

**Table 1**

Non-antibiotic preventative strategies – studies in Animals

| Strategy | Author/Year | Model used | Number of animals | Endpoints | Results | Significance |
|---|---|---|---|---|---|---|
| Probiotics | Chiva 2002 [40] | Rats with CCl4-induced cirrhosis | N=29 rats (10 with probiotic + antioxidant, 11 with antioxidant, 8 control) | Intestinal flora, endotoxemia, and bacterial translocation | Rats treated with antioxidants + Lactobacillus or antioxidants only had reduced intestinal bacterial burden and bacterial translocation. Only the group treated with antioxidant + Lactobacillus had decreased endotoxemia. | Positive study |
| Probiotics | Adawi 2001 [41] | Rats with Acute liver injury induced through intraperitoneal injection of D-galactosamine | N=30 rats (6 rats in each of five groups) | Extent of liver injury, bacterial translocation, and intestinal microflora | All lactobacillus probiotics reduced the incidence of bacterial translocation, whereas Bifidobacterium increased the incidence of bacterial translocation. | Positive study |
| Probiotics | Sanchez 2015 [42] | Rats with CCl4-induced cirrhosis | N=46 rats (24 water only, 22 VSL#3+water) | Bacterial translocation, intestinal microbiota, gut barrier / inflammatory response | The probiotic combination VSL#3 decreases bacterial translocation, the pro-inflammatory state and ileal oxidative damage; it increases ileal occludin expression in rats with experimental cirrhosis | Positive study |
| Probiotics | Bauer 2002 [46] | Rats with CCl4-induced cirrhosis | N=34 rats with lactobacillus v. control, N=20 in norfloxacin + lactobacillus v. control | Bacterial translocation, ascitic fluid infection | Rats treated with Lactobacilli showed no difference in bacterial translocation or ascitic fluid infection compared to those with control (with or without norfloxacin pretreatment) | Negative study |
| Cisapride | Pardo 2000 [62] | Rats with CCl4-induced cirrhosis | Cirrhotic rats randomized to cisapride (N=15) or saline (N=15) | Intestinal bacterial overgrowth, bacterial translocation | Cisapride significantly reduced intestinal bacterial overgrowth and bacterial translocation in cirrhotic rats | Positive study |
| Cisapride | Zhang 2003 [63] | Rats with CCl4-induced cirrhosis | Cirrhotic rats divided into no treatment (N=25), cisapride treatment (N=20), and saline treatment (N=20) | Intestinal bacterial overgrowth, bacterial translocation, intestinal transit and permeability | Compared with the placebo group, cisapride-treated rats had lower rates of bacterial/endotoxin translocation and intestinal bacterial overgrowth, which was closely associated with increased intestinal transit and improved intestinal permeability by cisapride. | Positive study |
| Beta-blockers | Perez-Paramo 2000 [61] | Rats with CCl4-induced cirrhosis | Cirrhotic rats randomized to propranolol (N=13) or placebo (N=12) | Intestinal bacterial load, transit and permeability of the bowel, and rate of bacterial translocation | Compared with the placebo group, propranolol-treated animals had significanctly faster intestinal transit, and lower rates of bacterial overgrowth and translocation. | Positive study |
| Bile acids | Ding 1993 [85] | Rats with bile-duct ligation (BDL) | BDL rats received saline (n=15) vs. cholic acid (n=9), | Bacterial translocation; serum endotoxin | Rate of bacterial translocation was signficantly lower in bile-treated animals compared with saline-treated animals. | Positive study |

| Strategy | Author/Year | Model used | Number of animals | Endpoints | Results | Significance |
|---|---|---|---|---|---|---|
| | | | deoxycholic acid (n=12), or whole bile (n=12) | | Assays for endotoxin were negative in bile-treated animals and positive in saline-treated animals | |
| Conjugated bile acids | Lorenzo-Zuniga 2003 [79] | Rats with CCl4-induced cirrhosis | N=60 cirrhotic rats, randomized to cholylsarcosine (n=20), cholylglycine (n=20) or placebo (n=20). N=20 healthy non-cirrhotic controls | Bacterial overgrowth, bacterial translocation, and endotoxemia | Administration of conjugated bile acids reduced ileal bacterial content to normal levels in cirrhotic rats. Bacterial translocation was lower in cirrhotic rats who received conjugated bile acids (33% with cholylsarcosine, and 26% with cholylglycine) than in animals who received placebo (66%). | Positive study |
| FXR agonist: Obeticholic acid (OCA) | Verbeke 2015 [86] | Rats with bile-duct ligation (BDL) | N=28 untreated healthy controls; N=51 BDL (then randomized to vehicle, ursodeoxycholic acid, or obeticholic acid) | Gut permeability, inflammation, and bacterial translocation | After treatment with obeticholic acid, BDL-rats showed decreased markers of inflammation in the gut, normalized gut permeability, and a significant reduction in translocated bacterial strains. | Positive study |
| FXR agonist: Obeticholic acid | Ubeda 2014 [89] | Rats with CCl4-induced cirrhosis | N=22 rats with cirrhosis randomized to OCA or vehicle; N=14 controls | Gut bacterial translocation; ileal inflammation; hepatic fibrogenesis | In cirrhotic rats and compared with vehicle, OCA reduces bacterial translocation (83% vs. 20%, $p<0.01$), reduces markers of ileal inflammation (IL-17, IFNγ, TLR4) and ameliorates hepatic expression of fibrosis markers | Positve study |
| FXR agonist: GW4064 | Inagaki 2006 [87] | Mice with bile-duct ligation (BDL) | BDL mice randomized to vehicle or FXR agonist GW4064 | Gut bacterial overgrowth; bacterial translocation; gut barrier integrity | Administration of GW4064 (FXR agonist) in BDL mice: reduced bacterial overgrowth in the ileum and cecum; reduced bacterial translocation; and restored the intestinal barrier (shown via occludin immunostaining and mucosal damage). | Positive study |

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**Table 2**

Non-antibiotic preventative strategies – studies in Humans

| Strategy | Author/Year | Type of study | Number of patients | Endpoints | Results | Significance |
|---|---|---|---|---|---|---|
| Probiotic | Rayes 2002 [39] | Randomized controlled trial | N=95 (32 SBD group, 31 Lactobacillus, 32 placebo) | Incidence of post-operative infections | Patients receiving living lactobacillus plus fiber developed significantly fewer bacterial infections (13%) compared to the group with SBD (48%) | Positive study |
| Probiotic | Rayes 2005 [43] | Randomized controlled trial | N=66 (33 probiotics +fibers group, 33 fibers-only group) | 30-day infection rate; length of hospital stay; duration of antibiotic therapy | Synbiotic treatment reduced the incidence of post-operative bacterial infections from 48% with only fibers to 3% with fibers and probiotic. The duration of antibiotic therapy was also shorter in the synbiotic group. | Positive study |
| Probiotic | Lata 2007 [44] | Randomized controlled trial | N=39 (22 probiotic, 17 placebo) | Serum endotoxin levels, biochemical analysis, stool microbiological analysis | Patients treated with E. coli Nissle demonstrated normalization of fecal flora, reduced endotoxemia and improved liver function | Some results not reaching statistical significance, but suggesting positive results |
| Probiotic | Liu 2004 [45] | Randomized controlled trial | N=55 (20 synbiotic, 20 fermentable fiber, 20 placebo) | Stool microbiological analysis, venous ammonia levels, serum endotoxin levels | Synbiotic treatment increased the fecal composition of Lactobacillus spp at the expense of other species and was associated with a significant reduction in blood ammonia levels, endotoxemia, and reversal of minimal hepatic encephalopathy in 50% of patients. | Positive study |
| Probiotic | Pande 2012 [47] | Randomized controlled trial | N=110 patients: 55 norfloxacin + probiotic, 55 norfloxacin + placebo | Occurrence of SBP within 6 months; mortality | No difference in primary or secondary prophylaxis of SBP or reducing mortality | Negative study |
| Rifaximin | Hanouneh 2012 [37] | Retrospective cohort | N=404 (49 of whom received rifaximin) | Incidence of SBP; transplant-free survival | There was a 72% reduction in the rate of SBP in the rifaximin group vs. controls (HR 0.28, 95% CI 0.11-0.71, p=0.007); as well as a transplant-free survival benefit (P=0.045) | Positive study |
| Rifaximin | Vlachogiannakos 2013 [36] | Retrospective cohort rifaximin, matched with 46 controls | N=23 patients who received | Survival; risk of variceal bleeding, HE, SBP, and HRS | Patients who received rifaximin had a significantly lower risk of developing SBP | Positive study |

| Strategy | Author/Year | Type of study | Number of patients | Endpoints | Results | Significance |
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| | | | | | than controls (4.5% vs. 46%, p=0.027) | |
| Rifaximin | Mullen 2014 [35] | Phase 3, open-label maintenance study (nonrandomized) | N=392 | Rate of infections, complications, and hospitalizations | Infection event rates per person-years of exposure for rifaximin patients was 0.73, lower than that observed in the placebo group (1.33) or historical rifaximin group (1.12) | Positive study |
| Rifaximin | Lutz 2014 [38] | Prospective cohort | N=152 | Frequency of SBP | SBP rate in patients with rifaximin vs. no treatment were comparable (8/27 = 30% vs. 24/108=22%) and significantly higher than in those patients who received systemic antibiotic prophylaxis (0/17=0%). | Negative study |
| Cisapride | Madrid 2001 [60] | Randomized controlled trial | N=34 (12 cisapride, 12 norfloxacin/neomycin, 10 placebo) | Small intestinal motor activity, orocecal transit time, bacterial overgrowth, liver function over 6 months | After 6 months, both cisapride and antibiotics significantly improved fasting cyclic activity, reduced duration of orocecal transit time, and decreased small intestinal bacterial overgrowth compared to placebo | Positive study |
| Cisapride | Pardo 2000 [62] | Cross-sectional study and pilot randomized study | N=46; of these, 10 were randomized to receive cisapride (5) or no treatment (5). | Intestinal bacterial overgrowth, orocecal transit time | Orocecal transit time was significantly decreased in patients who received cisapride therapy compared to no treatment; intestinal bacterial overgrowth was also significantly reduced in patients with cisapride treatment vs. no treatment (P<0.05). | Positive study |
| Cisapride | Sandhu 2005 [64] | Randomized controlled trial | N=94, of whom 48 received norfloxacin and 46 received norfloxacin + cisapride | Probability of developing SBP; mortality | The probability of developing SBP at 12 months was reduced from 56.8% in norfloxacin-only group to 21.7% in the norfloxacin + cisapride group (P=0.026). Probability of death at 18 months was 20.6% in norfloxacin-only group vs. 6.2% in norfloxacin + cisapride group (P=0.1) | Positive study |
| Beta blockers | Reiberger 2013 [67] | Prospective cohort study | N=50 (NSBB therapy initiated in 39 patients) | Intestinal permeability; serum levels of lipopolysaccharide-binding protein (LBP) and IL-6 | Under non-selective beta-blocker (NSBB) therapy, there was an amelioration of intestinal permeability and a significant decrease in | Positive study |

| Strategy | Author/Year | Type of study | Number of patients | Endpoints | Results | Significance |
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| | | | | | bacterial translocation (measured by serum levels of LBP and IL-6), which was not limited to hemodynamic (HVPG) responders. | |
| Beta-blockers | Senzolo 2009 [68] | Meta-analysis | N=644 patients (257 treated with propranolol, 387 receiving no propranolol) | Occurrence of SBP | There was a significantly significant difference of 12.1%, P<0.001 in favor of propranolol in preventing SBP | Positive study |
| Beta-blockers | Merli 2015[69] | Prospective cohort study | N=400 | Occurrence of infections and risk factors | The use of beta-blockers was a protective factor against infection, with an OR 0.46, 95% CI 0.3-0.7, P=0.001. Cirrhotic patients with infection showed lower morbidity and mortality when taking beta-blockers | Positive study |
| G-CSF | Garg 2012 [96] | Randomized controlled trial | N=23 receiving G-CSF, N=24 receiving placebo | 60-day survival; Child-Turcot Pugh score, MELD score, SOFA, complications such as sepsis, HRS, and HE | Patients treated with G-CSF had a significantly higher 60-day survival than those with placebo (69.6% vs. 29%); fewer patients treated with G-CSF developed sepsis compared with those on placebo (14% vs. 41%, p=0.04). There was a significant impact / improvement in other endpoints as well. | Positive study; patients with acute-on-chronic liver failure |
| G-CSF | Duan 2013 [97] | Randomized controlled trial | N=27 receiving G-CSF, N=28 control | Peripheral CD34+ cell count, liver function, and 3-month survival / complications | Survival at 3 months was 48.1% in G-CSF treated patients vs. 21.4% in the control group (p=0.0181). More patients in the control group died of sepsis and HRS compared to those in the G-CSF group (X2 value 4.863, p=0.027). | Positive study; patients with Hep-B acute-on-chronic liver failure |
| G-CSF and EPO combination | Kedarisetty 2015 [98] | Randomized controlled trial | N=29 receiving G-CSF and darbopoietin, N=26 placebo | 12-month survival; Child-Pugh score, MELD score, need for large volume paracentesis, septic shock | Patients treated with G-CSF and Darbopoietin demonstrated a significant increase in 12-month survival compared to placebo (68.6% vs. 26.9%, p=0.003). The incidence of SBP was non-significant between the two groups, although there was a lower incidence of septic shock between G-CSF+EPO-treated and placebo-treated | Positive study |

| Strategy | Author/Year | Type of study | Number of patients | Endpoints | Results | Significance |
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| | | | | | groups (6.9% vs. 38.5% respectively, p=0.005). | |
| Statins | Motzkus-Feagans 2013 [100] | Retrospective cohort study | N=19379 patients with compensated cirrhosis | Hospitalizations with infections | Compared with non-users, the rate of infection or death was significantly lower among statin users (adjusted HR 0.67, 95% CI 0.47-0.95) | Positive study |