Gut flora and bacterial translocation in chronic liver disease

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Abstract
Increasing evidence suggests that derangement of gut flora is of substantial clinical relevance to patients with cirrhosis. Intestinal bacterial overgrowth and increased bacterial translocation of gut flora from the intestinal lumen, in particular, predispose to an increased potential for bacterial infection in this group. Recent studies suggest that, in addition to their role in the pathogenesis of overt infective episodes and the clinical consequences of sepsis, gut flora contributes to the pro-inflammatory state of cirrhosis even in the absence of overt infection. Furthermore, manipulation of gut flora to augment the intestinal content of lactic acid-type bacteria at the expense of other gut flora species with more pathogenic potential may favourably influence liver function in cirrhotic patients. Here we review current concepts of the various inter-relationships between gut flora, bacterial translocation, bacterial infection, pro-inflammatory cytokine production and liver function in this group.

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Key words: Gut flora; Bacterial translocation; Cirrhosis

INTRODUCTION
Disturbances of the microecology of the indigenous gut flora are prevalent in patients with chronic liver disease. Significantly increased viable counts of both Gram-positive and negative bacterial species have been recovered from faeces of cirrhotic patients[1]. A high prevalence of small intestinal bacterial overgrowth, in particular, has been demonstrated in this group[2-5]. This has been attributed, at least in part, to a decrease in small intestinal motility associated with increased adrenergic activity and portal hypertension[6-8]. Studies performed in experimental animals demonstrating important effects of gut flora on intestinal motility[9,10] suggest that the development of small intestinal bacterial overgrowth in the setting of intestinal stasis may further impair intestinal motility, thereby creating a self-perpetuating vicious cycle.

In addition to the range of symptoms and consequences of bacterial overgrowth per se[11], increasing evidences suggest that derangement of gut flora is of substantial clinical relevance to patients with cirrhosis. Intestinal bacterial overgrowth and increased bacterial translocation of gut flora from the intestinal lumen, in combination with failure of immune defence mechanisms to efficiently remove these translocating microorganisms, predispose to an increased potential for bacterial infection in this group[12]. Impaired immune defences include reduced opsonic activity due to low hepatic synthesis of complement, deranged function of macrophage Fc gamma receptors and reduced phagocytic and killing capacity of neutrophils[13-16]. Impairment of mucosal immunity may also be important. The high prevalence of associated malnutrition in cirrhotic patients[17] exacerbates the potential for infection to occur.

Recent studies suggest that, in addition to their role in the pathogenesis of overt infective episodes and the clinical consequences of sepsis, gut flora contributes to the pro-inflammatory state of cirrhosis even in the absence of overt infection[18]. Furthermore, manipulation of gut flora using either a Gram-positive symbiotic (probiotic and fermentable fibre) regimen or fermentable fibre alone to augment the intestinal content of lactic acid-type bacteria at the expense of other gut flora species with more pathogenic potential may favourably influence liver function in cirrhotic patients[19]. Here we review current concepts of the various inter-relationships between gut flora, bacterial translocation, bacterial infection, pro-inflammatory cytokine production and liver function in this group.

BACTERIAL TRANLOCATION IN CIRRHOSIS
Bacterial translocation is defined as the migration of bacteria from the intestinal lumen to mesenteric lymph nodes or other extra-intestinal sites[20]. Gram-negative...
Intestinal bacterial overgrowth is a major factor promoting bacterial translocation and available evidence suggests that factors that promote intestinal bacterial overgrowth in particular, such as impaired intestinal motility, are important in facilitating bacterial translocation in cirrhosis. In experimental animals with cirrhosis, strategies to increase the intestinal transit rate, such as treatment with propranolol or cisapride, have been shown to reduce bacterial overgrowth and bacterial translocation. In the clinical setting, cisapride has been shown to increase small intestinal motility and reduce bacterial overgrowth in patients with cirrhosis, with a trend towards a lower incidence of infection in treated patients.

Structural changes in intestinal mucosa Most clinical studies performed to investigate structural changes of intestinal mucosa in patients with cirrhosis have focussed on the small intestine. Shorter and thicker microvilli have been described. Morphologically intact tight junctions, which join together the apical poles of enterocytes and represent the first line of mucosal defence against paracellular absorption, have been reported in a small cohort of clinically stable cirrhotic patients with no prior history of infection with gut-derived bacteria. Whether tight junctions are also intact in cirrhotic patients with a history of such infection and those with elevated nitric oxide levels may be more relevant, since nitric oxide, which is discussed in more detail below in relation to the clinical course of SBP, has been shown to reversibly dilate tight junctions in cultured intestinal epithelial cells. Notably, dilatation of the intercellular space below tight junctions, the second line of defence against paracellular absorption, has been documented in patients with cirrhosis. Mucosal alterations attributed to oxidative stress, including disturbed enterocyte mitochondrial function and increased lipid peroxidation of brush border membranes, have been reported in experimental animal models of cirrhosis, although the relevance of these changes to the pathogenesis of bacterial translocation is uncertain.

Thick-walled, dilated capillaries along with oedema of the lamina propria, fibromuscular proliferation, a reduced villus/crypt ratio and thickened muscularis mucosa in the small bowel have been found in cirrhotic patients with portal hypertension and it has been proposed that an increased potential for bacterial translocation may exist in this setting. However, in a study of cirrhotic patients with an elevated mean portal venous pressure in the order of 25 mm Hg, it has not been suggested that the increased local levels of pro-inflammatory cytokines, although the validity of this approach and the full clinical relevance of a positive result remain to be firmly established. Increased serum levels of lipopolysaccharide-binding protein, a phenomenon attributed to translocation of bacteria from the gut to the circulation, have been documented in a proportion of cirrhotic patients without overt infection and to predict the later development of severe bacterial infection in this group.
Luminal factors contributing to intestinal barrier function

Other factors that contribute to the normal intestinal barrier against bacterial translocation (BT), including luminal factors, such as levels of bile acids, secretory immunoglobulin A, mucus, defensins, lysozyme and phospholipase A2, have been little studied in cirrhotic patients. Bile acids exert a trophic effect on intestinal mucosa and inhibit intestinal bacterial overgrowth, especially of Gram-positive species. An increased incidence of bacterial translocation in patients with obstructive jaundice has been reported. However, whether the reduced intestinal luminal levels of bile acids that may be found in cirrhotic patients, as a consequence of reduced hepatic secretion and luminal deconjugation by overgrowth bacteria, contribute importantly to the potential for increased bacterial translocation in this group has not been established.

Intestinal immunity

Little is known concerning the functional capacity of intestinal immunity in patients with cirrhosis and whether any disturbance of intestinal immune mechanisms contributes importantly to bacterial translocation, especially in the clinical setting. An increased number of intraepithelial lymphocytes with markedly impaired proliferative activity and capacity for production of interferon-γ have been reported in a murine model, with these changes correlating with increased bacterial translocation. Whether this mechanism is important in the clinical situation is unknown. Notably, modest increases in small intestinal intraepithelial lymphocyte counts are found in patients with small intestinal bacterial overgrowth, raising the possibility that the increased levels found in cirrhotic animals may be explained on this basis. Whether the number or function of dendritic cells and other mononuclear cells in intestinal mucosa are deranged and contribute to the pathogenesis of bacterial translocation in patients with cirrhosis remains to be defined.

Anatomical site of bacterial translocation in cirrhosis

The anatomical site(s) from which bacterial translocation in cirrhosis occurs remains to be determined. Data in the non-cirrhotic setting suggest that the small intestine rather than the colon may be the major site of bacterial translocation. In particular, experimental studies involving inoculation of various regions of the gastrointestinal tract with equal quantities of Escherichia coli suggest that translocation occurs preferentially from the small bowel rather than the colon. Similarly, in experimental animals with impaired intestinal motility, treatment with the prokinetic agent, cisapride, is associated with a reduced rate of bacterial translocation that parallels a reduction in jejunal but not caecal bacterial counts.

Intestinal permeability and its relation to bacterial translocation in cirrhosis

Functional studies have demonstrated that increased intestinal permeability, as reflected by dual sugar absorption tests or absorption of other test substances, occurs in patients with cirrhosis, especially in those with advanced liver disease. Factors predisposing to this increased permeability in cirrhosis remain to be defined. In particular, any relationships with the structural changes of intestinal mucosa described above are uncertain. Enhanced intestinal permeability, likely via the paracellular route, has been reported in association with small intestinal bacterial overgrowth with Gram-negative gut flora in the non-cirrhotic setting, raising the possibility that this entity may at least contribute to the increased intestinal permeability in patients with cirrhosis. The relationship between intestinal permeability and the potential for bacterial translocation is uncertain, as increased permeability results have been found to correlate with a history of septic complications in some, but not all, reports.

GUT FLORA AND BACTERIAL INFECTION IN CIRRHOSIS

Bacterial infection, especially with intestinal-type flora, is a common complication in patients with cirrhosis. Spontaneous bacterial peritonitis (SBP), urinary tract infection, respiratory tract sepsis (pneumonia and spontaneous bacterial empyema) and bacteremia are the most frequent infective complications occurring in this group. The incidence of infection with Gram-positive cocci, in particular, has increased in recent years, with such flora now the most frequent isolates in hospitalised cirrhotic patients with nosocomial infection, especially those admitted to intensive care units, presumably due to the high rate of invasive procedures, including placement of indwelling vascular and bladder catheters, performed in this group. Recent data suggest that between 15% and 35% of cirrhotic patients admitted to hospital develop nosocomial bacterial infection, substantially higher than the rate of hospital-acquired infection in the order of 5% to 7% in the general hospital setting.

Complicating infection may have severe adverse clinical consequences in cirrhotic patients. The associated pro-inflammatory response exacerbates hepatic dysfunction, encephalopathy and the haemodynamic disturbances that underlie the development of portal hypertension and hepatorenal syndrome. Increasing evidence suggests that bacterial infection is a trigger for variceal haemorrhage in patients with cirrhosis, possibly as a consequence of both activation of hepatic stellate cells, leading to increased intrahepatic vascular resistance, and prostacyclin-related inhibition of platelet aggregation. Conversely, variceal haemorrhage predisposes cirrhotic patients to bacterial infection with gut-derived flora, setting up a vicious cycle between gastrointestinal bleeding and infection in this group. This is a phenomenon of substantial clinical importance, as complicating infection is independently associated with early mortality in bleeding cirrhotic patients. Worsening coagulopathy, due to the consumption of clotting factors by the extrinsic coagulation pathway and the production of endogenous heparinoid, occurs in patients with cirrhosis and complicating bacterial infection. Sepsis is a common cause of death in cirrhotic patients. The mortality rate associated with bacterial infection in this group is more than twenty times higher than in the general population.
SPONTANEOUS BACTERIAL PERITONITIS (SBP)

SBP, an infection of ascitic fluid typically with a single bacterial species in the absence of any other primary intra-abdominal source, is the most characteristic and serious infection occurring in patients with cirrhosis. Prospective studies suggest that SBP, including culture-negative and non-neutrocytic cases, is present in up to 23% of all cirrhotic patients with ascites admitted to hospital. Gram-negative gut flora, especially *Escherichia coli* and *Klebsiella* species, are isolated in approximately 70% of culture-positive cases of community-acquired SBP. Aerobic Gram-positive bacteria belonging to *Streptococcus* and *Staphylococcus* spp constitute most of the remaining isolates. Pathogens belonging to *Aeromonas*, *Plesiomonas*, *Listeria*, *Salmonella*, and *Neisseria* spp are occasionally responsible. In keeping with their reduced potential for translocation from the intestine discussed above, obligate anaerobes are isolated in fewer than 5% of cases. In hospitalised cirrhotic patients with nosocomial SBP, Gram-positive pathogens are predominant, accounting for over 70% of isolates, with methicillin-resistant *Staphylococcus aureus* accounting for nearly 25% of cases in one recent series.

The overall likelihood of a cirrhotic patient with ascites developing SBP at one year is in the order of 10%.[80] Clinical studies have identified several sub-groups of patients with cirrhotic ascites at particularly high risk for SBP. Over 70% of cases occur in those classified as Child-Pugh C.[83] An increased prevalence of SBP has been reported in patients with small intestinal bacterial overgrowth compared to their non-overgrowth counterparts, presumably due to the increased propensity for bacterial translocation.[84] Gastrointestinal haemorrhage is another important precipitant of SBP in this group. Bacteraemia and/or SBP, typically with Gram-negative enteric-type flora, develop within 48 hours of gastrointestinal haemorrhage in nearly 50% of Child-Pugh C patients with ascites.[81] The likelihood of SBP is related to the functional activity of Kupffer cells, which is impaired in patients with advanced liver disease.[80] However, the most powerful predictive factor identified in several series is an ascitic fluid total protein level ≤ 10 g/L, which reflects a low complement protein C3 concentration and, hence, opsonisation capacity. Patients with such low levels are at a six- to ten-fold increased risk of a first episode of SBP compared to cirrhotic counterparts with ascitic fluid total protein levels > 10 g/L.[87,88]

CLINICAL COURSE

Despite a trend towards earlier diagnosis and commencement of antibiotic treatment, along with overall improvements in the general medical care of cirrhotic patients, the in-hospital mortality rate associated with SBP remains 30-50%.[89] This is largely related to underlying hepatic decompensation and a high prevalence of complicating hepatorenal syndrome. The latter occurs in approximately 30% of patients with SBP, predominantly in those with pre-existing renal impairment, and is progressive despite cure of infection in half of these cases.[89] Ascitic levels of nitric oxide, which are significantly increased in cirrhotic patients with SBP and persist for over two weeks despite appropriate antibiotic treatment,[90,91] independently predict renal impairment in this setting.[92]

Use of nephrotoxic antibiotics adds to the risk of renal failure in this setting.[93]. The development of renal failure is the most important predictor of in-hospital mortality associated with SBP. This is in the order of 50% in those with complicating renal failure compared to only 6% in those without.[89] Albumin infusion improves systemic haemodynamics, prevents renal failure and improves survival compared to antibiotic treatment alone in patients with SBP. Beneficial effects are related to reduction in arterial vasodilatation and improved cardiac function.[94] Other correlates of poor outcome include increased ascitic levels of the pro-inflammatory cytokines, interleukin-6 and tumor necrosis factor-α (TNF-α).[95] A recent report suggests a higher mortality rate in patients with nosocomial infection with staphylococcal species compared to that in patients with community-acquired SBP.[89] A trend towards a higher mortality rate when infection is with encapsulated strains of *Escherichia coli* associated with tissue invasiveness has also been reported.[96]

The medium term prognosis for cirrhotic patients who have recovered from an episode of SBP is similarly poor, with a mortality rate at one year in the order of 30-80%.[89] Approximately 20% of patients who die within one year of an episode of SBP succumb to a further episode of spontaneous peritoneal infection, the remainder dying of causes, such as variceal haemorrhage, hepatorenal syndrome or hepatocellular carcinoma.[95,97,98] The risk of SBP recurrence within one year varies from 40-70% and, as for an initial episode, is influenced mainly by the degree of underlying liver dysfunction and the ascitic fluid total protein level.[81,89,90] Survivors of an episode of SBP should be evaluated for liver transplantation in view of the high risk of recurrence and poor overall prognosis.

PROPHYLAXIS

Antibiotic prophylaxis against SBP may be beneficial in three high risk groups of cirrhotic patients, namely those who have survived a previous episode, those with low ascitic fluid total protein levels and those presenting with gastrointestinal haemorrhage.[97,98,100-103]. Most prophylaxis studies have aimed to reduce or eradicate aerobic Gram-negative bacilli from the intestine using norfloxacin, a poorly absorbed quinolone with activity against these flora. The importance of antibiotic prophylaxis in patients with cirrhosis presenting with variceal haemorrhage is increasingly recognised. Treatment with norfloxacin, 400 mg twice daily either orally or via a nasogastric tube for seven days commencing immediately after emergency endoscopy, was associated with a significantly reduced in-hospital incidence of bacteraemia and/or SBP, especially with aerobic Gram-negative flora, compared to patients receiving no prophylactic antibiotics (3% vs 17%)[89]. Ciprofloxacin, 500 mg twice daily either orally or via nasogastric tube for 7 d immediately following endoscopy, has similarly been shown to significantly reduce the incidences of bacteraemia, SBP and urinary tract infection compared to placebo (0% vs 23%, 3% vs
13% and 5% vs 18%, respectively)

Implementation of treatment protocols that incorporate antibiotic prophylaxis led to a fall in post-variceal bacterial infection rates from 38% to 14% over the past two decades in a large French centre. Antibiotic prophylaxis has been shown to reduce the incidence of not only bacterial infection, but also early re-bleeding following variceal haemorrhage, especially in Child-Pugh class C patients, those requiring ventilatory support and those initially treated with balloon tamponade.

Several cost analysis studies have shown that prokinetic treatment with norfloxacin in each of these high risk groups is cost effective, as a consequence of the reduced incidence of SBP and its associated resource utilisation. Short-term prophylaxis with trimethoprim-sulphamethoxazole is also cost-effective, especially in those at high risk for SBP. Most studies report a reduction in overall mortality associated with prophylactic antibiotic treatment, although a statistically significant survival benefit has been more difficult to demonstrate. This is not surprising, as the likelihood of dying as a result of progressive liver failure, variceal haemorrhage, hepatocellular carcinoma or other causes is unaffected by the use of prophylactic antibiotics. More recently, a meta-analysis of 13 randomized controlled trials has suggested that antibiotic prophylaxis of hospitalized cirrhotic in-patients is efficacious in reducing the relative risk of in-hospital death (relative risk of dying 0.70), irrespective of underlying risk factors. In addition, a meta-analysis of 534 cirrhotic patients with gastrointestinal bleeding has shown that short-term antibiotic prophylaxis significantly increases short-term survival rates by a mean 9% in this setting.

A particular concern, especially with long-term antibiotic prophylaxis, is the potential for the development of infection with antibiotic-resistant bacteria. Initial studies of norfloxacin prophylaxis against SBP reported a low incidence of infection with quinolone-resistant Gram-negative bacterial species. More recent studies, however, suggest an increased prevalence of infection with such microorganisms. Over 20% of cases of SBP due to Escherichia coli were with a norfloxacin-resistant strain in a recent series from Spain, while 50% of cases of culture-positive SBP in patients receiving long-term norfloxacin prophylaxis and 16% of instances in patients not treated with this drug were caused by norfloxacin-resistant Gram-negative bacteria in another Spanish report. A high rate of SBP due to trimethoprim-sulphamethoxazole-resistant Gram-negative flora in excess of 40% was also documented in norfloxacin-treated patients. An increased proportion of infections with Gram-positive bacterial species has also been reported in this setting, including instances of severe hospital-acquired staphylococcal infections. An increased incidence of carriage of methicillin-resistant Staphylococcus aureus has also been documented in cirrhotic patients treated with norfloxacin prophylaxis.

Such experiences highlight the need for non-antibiotic-based strategies to prevent intestinal motility, reversal of bacterial overgrowth and a tendency towards a reduced incidence of infection with gut-derived flora in a cohort of cirrhotic patients. Unfortunately, cisapride has been withdrawn from use in some countries because of potential for cardiac arrhythmia. Alternatively, treatment with either symbiotics (in the form of four species of lactic acid bacteria and fermentable fibre) or fermentable fibre alone has recently been shown to significantly reduce viable counts of potentially pathogenic Gram-positive and Gram-negative gut flora in patients with cirrhosis. In another study, a lower rate of post-operative bacterial infection was documented in liver transplant recipients treated with an early enteral supply of a symbiotic regimen that included Lactobacillus plantarum and fermentable fibre than in patients receiving selective intestinal decontamination. A follow-up randomised double-blind trial in liver transplant recipients showed that early enteral nutrition supplemented with a mixture of lactic acid bacteria and fermentable fibre significantly reduced the incidence of post-operative bacterial infection compared to supplementation with fermentable fibre alone. Based on these reports, the possible use of symbiotics for prophylaxis against SBP in cirrhotic patients warrants investigation. Conversely, probiotic treatment with a lactobacillus strain without additional fermentable fibre was ineffective in preventing bacterial translocation and SBP in rats with experimental cirrhosis, despite successful intestinal colonisation.

**GUT FLORA AND PRO-INFLAMMATORY STATE OF CIRRHOSIS IN ABSENCE OF OVERT INFECTION**

Pro-inflammatory cytokines, such as TNF-α, have been shown to be critically involved in the development and/or exacerbation of liver injury in animal models. Activation of macrophages by endotoxin, a cell wall component of Gram-negative bacteria, plays a key role in the over-production of TNF-α and liver injury in these settings. Increased translocation from the gut lumen and reduced hepatic clearance have each been proposed to predispose to endotoxaemia in this situation. In the clinical setting, increased circulating levels of both endotoxin and pro-inflammatory cytokines have been documented in patients with chronic liver disease, even in the absence of overt infection. Based on experiences in experimental animals, it has, until recently, been assumed that endotoxaemia causes the raised pro-inflammatory cytokine levels in this group. However, a significant correlation between circulating endotoxin and pro-inflammatory cytokine levels has generally not been shown, raising the possibility that, unlike in animal models, stimuli other than endotoxin may be important.

Recent analyses of the expression of Toll-like receptors (TLRs) in patients with cirrhosis have helped to clarify this issue. These receptors are the human homologues of the Drosophila Toll protein and comprise a family of at least ten transmembrane receptor proteins, the intracellular domains of which show distinct sequence homology with the interleukin-1 receptor. TLRs play a critical role in the
induction of innate immunity to microbial pathogens via recognition of conserved molecular patterns. In particular, it is known that TLR4, in association with CD14 and MD-2, is responsible for signal transduction leading to TNF-α production in response to endotoxin. In contrast, TLR2 is required for signaling in response to a number of Gram-positive microbial stimuli, including whole bacteria and cell wall components, such as peptidoglycan and lipoteichoic acid[126,131]. Indeed, significantly increased expression on peripheral blood mononuclear cells (PBMCs) of TLR2 but not of TLR4 has recently been demonstrated in patients with cirrhosis but no overt infection[132]. Furthermore, PBMC expression of TLR2 but not that of TLR4 was shown to correlate significantly with circulating levels of both TNF-α and anti-inflammatory soluble TNF receptors[133]. These novel findings suggest that signaling via TLR2 but not TLR4 contributes to the increased circulating levels of TNF-α levels found in cirrhosis and imply, contrary to previous assumptions, an important role for Gram-positive microbial stimuli rather than endotoxin in this process. This contention is supported by in vitro PBMC stimulation data consistent with presensitisation by Gram-positive microbial stimuli but not endotoxin in vivo. In addition, supplementation of cirrhotic patients with a synbiotic regimen including four Gram-positive gut flora and fermentable fibre led to further increases in PBMC expression of TLR2 and circulating TNF-α levels in most cases, suggesting that Gram-stimuli derived from the gut, in particular, may be important in promoting the increased circulating levels of both pro-inflammatory and anti-inflammatory TNF-related molecules found in patients with cirrhosis[134].

GUT FLORA AND HEPATIC FUNCTION IN CIRRHOSIS

Reversal of minimal hepatic encephalopathy has been reported in 50% of predominantly Child-Pugh class B or C cirrhotic patients treated with a lactic acid bacteria-based synbiotic regimen for 30 d, an efficacy comparable to that of treatment with lactulose[19]. In addition, the Child-Pugh class improves in nearly 50% of initially Child-Pugh class B or C synbiotic-treated patients, a proportion significantly higher than that in placebo-treated counterparts (8%). Treatment is associated with a significant increase in the faecal content of lactobacilli at the expense of potentially pathogenic Gram-positive bacteria[135]. These findings are in keeping with reported experiences in experimental animals’ suggesting that oral supplementation with Gram-positive probiotics can protect against hepatocellular damage. In particular, rats fed lactobacilli have been shown to be protected against alcohol-induced liver damage[136], while studies of probiotic use in a murine model of non-alcoholic fatty liver disease have found reductions in the intra-hepatic expression of various molecular markers of inflammation, including nuclear factor kappa-B and TNF-α[134,135].

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