

## REVIEW

# Intestinal dysfunction in liver cirrhosis: Its role in spontaneous bacterial peritonitis

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**Abstract** Spontaneous bacterial peritonitis is a common illness in patients with cirrhosis and ascites that occurs without any apparent focus of infection. Bacterial translocation plays an important role in spontaneous bacterial peritonitis and it is evident from a variety of studies that the gut is a major source of this bacteria. Gut motility alterations, along with bacterial overgrowth and changes in intestinal permeability, probably play a role in this bacterial translocation. The present review looks at the role of the intestine in spontaneous bacterial peritonitis induced by liver cirrhosis and the factors influencing bacterial translocation in this disease.

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**Key words:** cirrhosis, intestine, spontaneous bacterial peritonitis.

## INTRODUCTION

Liver cirrhosis is a pathologically defined entity that reflects irreversible chronic injury of the hepatic parenchyma in association with extensive fibrosis. Bacterial infection is responsible for up to one-quarter of the deaths of patients with liver disease,<sup>1</sup> the most susceptible being those with alcoholic cirrhosis.<sup>2</sup> One of the major complications of liver cirrhosis is spontaneous bacterial peritonitis (SBP), which is defined as an abrupt onset of acute bacterial peritonitis without any apparent external or intra-abdominal focus of infection in patients with ascites caused by liver disease.<sup>3</sup> Spontaneous bacterial peritonitis is thought to appear as a consequence of impaired defense mechanisms against infection seen in cirrhotic patients, such as depressed reticuloendothelial system phagocytic activity, reduced serum complement levels and low antibacterial activity of ascitic fluid.<sup>4</sup> Spontaneous bacterial peritonitis is a common illness in patients with cirrhosis and ascites<sup>5</sup> and, although key steps in the pathogenesis of SBP are yet to be elucidated, it is evident from recent research that the gut is a major source of bacteria in SBP. Gut motility alterations, along with bacterial overgrowth and changes in intestinal permeability, probably play a role

in this bacterial translocation. The present review concentrates on the mechanistic etiology of SBP and attempts to collate various studies on this aspect. The diagnosis, treatment and prophylaxis of the disease have been extensively studied and reviewed elsewhere.<sup>6</sup>

## INTESTINE IN LIVER CIRRHOSIS

It has been shown that the gastrointestinal tract is affected during cirrhosis and mucosal abnormalities secondary to portal hypertension exist. Manevska has shown a correlative connection between liver damage and the functional activity of the intestine, manifested by the inhibition of the activity of the membrane enzymes alkaline phosphatase and aminopeptidase, as well as the activity of acid phosphatase and succinic dehydrogenase, in experimental cirrhosis.<sup>7</sup> Triglyceride levels in the small intestine of cirrhotic rats are significantly decreased, probably because of low intestinal apolipoprotein A-IV.<sup>8</sup> Transport of nutrients across the intestine is also affected and intestinal sugar transport is disturbed in experimental cirrhosis, an alteration corrected by insulin-like growth factor-I.<sup>9</sup> D-Galactose

absorption is also reduced in cirrhotic rats and this is accompanied by a significant elongation of enterocyte microvilli.<sup>10</sup> Biliary cirrhosis induces changes in brush border membrane composition in rats, which include decreased structural proteins, microvillus enzymes and triglyceride content. This is accompanied by a threefold decrease in calcium transport in the duodeno-jejunum, probably because of a lower content in brush border membrane calmodulin.<sup>11</sup>

## ALTERED GUT MOTILITY AND BACTERIAL OVERGROWTH IN CIRRHOSIS

Altered small bowel motility has been shown in patients with liver cirrhosis and this depends on the severity of liver disease.<sup>12</sup> The mouth-to-cecum transit time is prolonged, the pylorus-cecum component playing the main role in delaying oro-cecal transit time.<sup>13</sup> Chang *et al.* have shown that small intestine motility dysfunction was also more severe in cirrhotic patients with a history of SBP.<sup>14</sup> Motor abnormalities of the small intestine are present in these patients, along with a decrease in the amplitude of small bowel contractions, suggesting a myogenic involvement.<sup>15</sup> Altered proximal small bowel motility has been observed in patients with cirrhosis with an increase in the mean duration of the migrating motor complex and marked changes in the contraction pattern.<sup>16</sup> It has also been shown that this abnormal migrating motor complex activity and prominent clustered contractions present preoperatively in cirrhotic patients normalized within 6 months after orthotopic liver transplantation.<sup>17</sup>

Intestinal bacterial overgrowth (IBO) is very frequent in patients with chronic hepatopathies. It occurs in approximately one-third of patients with cirrhosis secondary to alcohol, particularly in patients with ascites and advanced liver dysfunction. Moreover, bacterial overgrowth may be a condition favoring infection of the ascitic fluid.<sup>18</sup> Carbon tetrachloride-induced cirrhosis leads to an increased total intestinal aerobic bacteria count, which may play a role in the bacterial translocation seen in this experimental model of cirrhosis in rats.<sup>19</sup> The main causes of IBO are probably achylia and hypochlorhydria, a decrease in the secretion of IgA and malnutrition caused by liver dysfunction and alcoholism. The IBO could increase the severity of the hepatopathy and also produce bacterial peritonitis.<sup>20</sup> Thus, impaired motility of the small intestine, facilitating bacterial overgrowth of the small intestine, may be one of the explanations for recurrent SBP in cirrhotic patients.

## INTESTINAL PERMEABILITY IN LIVER CIRRHOSIS

Increased intestinal permeability has been implicated as a possible contributory factor in the development of encephalopathy and SBP seen in patients with cirrho-

sis.<sup>21</sup> Intestinal permeability to phenolsulfthalein is increased in patients with liver cirrhosis,<sup>22</sup> especially in patients with severe infectious complications. The impairment of the intestinal function barrier may also contribute to severe septic complications in these patients.<sup>23</sup> When portal hypertension is present, permeability of the gut wall may be affected by edema of the splanchnic tissues because of venous and lymphatic congestion.<sup>24</sup> Chronic elevation in portal pressure also increases intestinal transcapillary water flux in the canine intestine.<sup>25</sup> Keshavarzian *et al.* have shown that alcoholics with chronic liver disease have increased intestinal permeability and this may be a necessary cofactor for the development of chronic liver injury in heavy drinkers.<sup>26</sup> Increased permeability of intestinal tight junctions, retention of endotoxin and increased apoptosis have also been implicated in the pathogenesis of primary biliary cirrhosis (PBC).<sup>27</sup>

## BACTERIAL TRANSLOCATION IN SBP

Translocation of gut bacteria is facilitated by a number of factors, one being the fact that humoral and cellular host defenses against infection are most frequently impaired in patients with alcoholic cirrhosis and fulminant hepatic failure.<sup>1</sup> Shunting of portal blood predisposes to bacteremia from enteric organisms and intra- as well as extrahepatic shunting may be important determinants predisposing to SBP.<sup>28</sup> Abnormal colonization of the small bowel by colonic bacteria occurs in patients with cirrhosis<sup>29</sup> and intestinal bacterial translocation is common in cirrhotic rats with SBP.<sup>30</sup> Gram-negative aerobic bacteria from the family Enterobacteriaceae and non-enterococcal *Streptococcus* sp. are the most common causative organisms;<sup>6</sup> *Escherichia coli*, *Klebsiella pneumoniae* and  $\alpha$ -hemolyzing *Streptococcus* also having been isolated from ascitic fluid in patients with spontaneous bacterial peritonitis.<sup>31,32</sup> Organisms such as *Listeria monocytogenes* have also been implicated in SBP in patients with liver cirrhosis<sup>33</sup> and infection with *Vibrio vulnificus* has been reported to cause septicemia, resulting in death in a cirrhotic patient.<sup>34</sup> The cirrhotic liver is also predisposed to bacterial infections and different species of bacteria including *E. coli*, *Enterobacter* and *Bacteroides fragilis* have been found to colonize thioacetamide-induced cirrhotic rat liver.<sup>35</sup> The same bacterial species has been isolated in both mesenteric lymph node and ascitic fluid<sup>36</sup> and Llovet *et al.* have used molecular epidemiology techniques to prove the origin of bacteria simultaneously isolated from ascites and the mesenteric lymph nodes and/or ileum in rats with ascitic cirrhosis.<sup>37</sup> Bacterial translocation also promoted vascular nitric oxide (NO) release in cirrhotic rats<sup>38</sup> and NO has been implicated in the regulation of gastrointestinal motility.<sup>39</sup> Histopathologic studies on the route of bacterial translocation show that translocation of bacteria such as *Candida albicans* occurs by direct penetration of enterocytes, associated with disruption of basal membrane. Translocation of *E. coli* and endotoxin also occurred directly through enterocytes

rather than between them.<sup>40</sup> Thus, translocation of intestinal bacteria to mesenteric lymph nodes probably plays a major role in development of SBP in cirrhosis.

## SPLANCHNIC CIRCULATION AND IMMUNE FUNCTION IN CIRRHOSIS

Considerable alterations in fluid and solute exchange in the hepatic and intestinal microcirculations are seen during cirrhosis, and lymph flow from the intestine and liver in cirrhotic animals is increased.<sup>41</sup> Splanchnic blood flow in liver cirrhosis is affected in patients with varicose veins of the esophagus and stomach.<sup>42</sup> Both mesenteric flow and portal flow are affected, the contribution of splanchnic blood flow to the portal flow being reduced.<sup>43</sup> Arterial vasodilation, particularly that occurring in the splanchnic circulation, is a major causative factor in the pathogenesis of the hyperdynamic circulatory syndrome that is known to occur in cirrhosis and portal hypertension.<sup>44</sup> Cirrhotic rats with ascites have a decreased systemic vascular resistance and high splanchnic endotoxin levels, suggesting that splanchnic endotoxemia may be involved in the development and/or maintenance of hyperdynamic circulation.<sup>45</sup> Splanchnic blood flow was found to be significantly increased in cirrhosis, accompanied by an increase in circulating levels of glucagon and vasoactive intestinal polypeptide. This increase in splanchnic blood flow may be partly responsible for elevated portal pressure, because there was also a strong correlation between portal pressure and glucagon levels.<sup>46</sup> There is greater impairment in vascular reactivity in cirrhotic rats with bacterial translocation and this is largely mediated by endothelial overproduction of NO. This was associated with a decrease in the pressure response to methoxamine in the superior mesenteric arterial bed.<sup>38</sup> Endothelin-1 is also implicated in the pathogenesis of portal hypertension and its plasma levels are increased; levels in both superior mesenteric and splenic venous blood being higher than in systemic blood in cirrhotic patients.<sup>47</sup> Moreover, in patients with chronic liver disease and in animal models of portal hypertension, elevated blood concentrations of tumor necrosis factor (TNF)- $\alpha$  have been reported compared with normal controls.<sup>48</sup> Increased levels of TNF- $\alpha$  are seen in mesenteric lymph nodes of cirrhotic rats with bacterial translocation and this probably contributes to the associated systemic levels.<sup>38</sup>

A variety of immunologic disturbances are seen in liver cirrhosis, including autoantibody production, decreased cellular immunity and decreased natural killer cell activity.<sup>49</sup> A high percentage of cellular immune reactions is seen in patients with cirrhosis of the liver, probably due to impairment of the physiologic elimination of antigens by the liver.<sup>50</sup> Gut-liver interactions have been implicated in lymphocyte migration as well as the modulation of IgA levels and, in cirrhotic patients, IgA concentrations are significantly higher than in control subjects.<sup>51</sup> It has been demonstrated that increased IgA synthesis in the intestinal mucosa may contribute to elevation of serum IgA levels in liver cir-

rhosis.<sup>52</sup> This is accompanied by changes in cellular immunity, with decreases in the number of T cells in the intestinal mucosa of cirrhotic rats.<sup>52</sup> The largest lymphoid organ in the body, the gut-associated lymphoid tissue (GALT), plays a role in diseases such as PBC<sup>53</sup> and the GALT has been shown to produce and release TNF- $\alpha$  in response to bacterial translocation, even in the absence of the portal or systemic spread of bacteria.<sup>54</sup> The changes in bile acid composition and bacterial flora probably induce a condition of chronic stimulation of the GALT.<sup>55</sup> In addition, the local immunologic changes in intestinal mucosa closely correlate to the lymphatic disturbances in liver cirrhosis.<sup>56</sup> There appears to be localized mucosal immunity in the secretory system of PBC<sup>57</sup> and antibodies to the endoplasmic reticulum protein calreticulin occur in PBC and yersiniosis as well as in alcoholic liver disease. This again probably reflects the reactivity of the gut-associated immune system.<sup>58</sup>  $\gamma$ -Interferon induced NO synthase more rapidly in macrophage cultures from cirrhotic livers and these macrophages also synthesized more NO when stimulated by lipopolysaccharide compared with controls.<sup>59</sup>

## BACTERIAL TRANSLOCATION AND OXYGEN FREE RADICALS

Bacterial translocation occurs in a variety of other clinical conditions, including sepsis, hemorrhagic shock, surgical stress and multiorgan failure. Similar to SBP, in these conditions Gram-negative bacteria<sup>60</sup> and their endotoxins<sup>61</sup> are mainly translocated. Hemorrhagic shock-induced bacterial translocation is prevented by the inhibition of the superoxide generating enzyme xanthine oxidase, implicating oxygen free radicals in this process.<sup>62</sup> It has also been shown that intestinal ischemia leads to bacterial translocation accompanied by oxygen free radical production.<sup>63</sup> The intestine has been shown to be susceptible to oxidative stress and we have earlier shown that enterocyte function is affected in this process.<sup>64</sup> Work from our laboratory has also shown that surgical stress induces oxidative stress in enterocytes, accompanied by widening of intercellular spaces, which may facilitate bacterial translocation.<sup>65</sup>

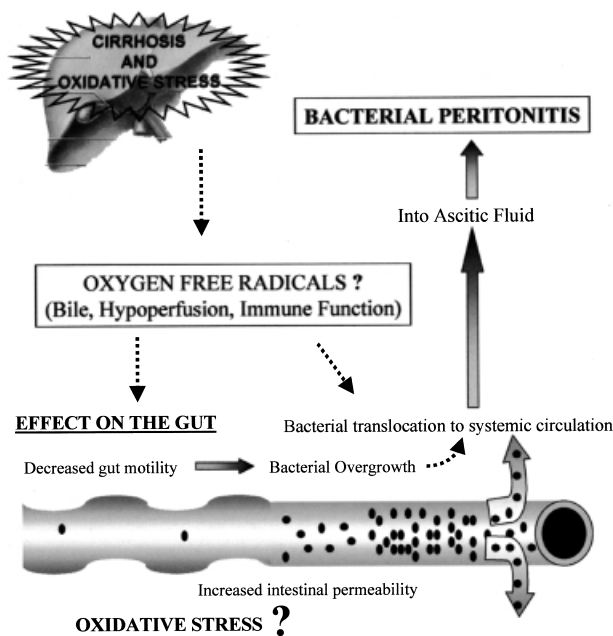
Oxidative stress plays an important role in the pathogenesis of toxic liver diseases and of other hepatic alterations.<sup>66</sup> A significant decrease in the plasma ascorbate level is evident after the onset of hepatitis, the subsequent cirrhosis and liver cancer.<sup>67</sup> A significant increase in plasma lipid peroxide and ascorbic acid and a significant decrease in reduced glutathione and superoxide dismutase activity in hemolysate were also observed in cirrhotic patients.<sup>68</sup> Oxidative stress has also been implicated in the process of fibrogenesis and many etiologic agents of fibrogenesis stimulate free radical reactions either directly or through inflammatory stimuli.<sup>69</sup> Protein oxidation may play a role in the pathogenesis of carbon tetrachloride-induced liver injury<sup>70</sup> and administration of anti-oxidants, such as selenium and vitamin E, also decreases the amount of hepatic fibrosis in carbon tetrachloride-induced cirrhosis.<sup>71</sup> Lipid peroxi-

dation increased in both liver homogenates and hepatic mitochondria of bile duct-ligated rats. This was accompanied by decreased glutathione peroxidase activity and glutathione levels. Glutathione peroxidase, as well as glutathione transferase, activity was also decreased.<sup>72</sup> Thus, it is possible that free radical generation in the liver could spill over to other organ systems.

Free radicals have been identified in the bile of rats treated chronically with alcohol<sup>73</sup> and it has been shown that the major part of the Electron Spin Resonance free radical signal arises from protein-bound bilirubin.<sup>74</sup> Deoxycholate has also been shown to stimulate superoxide production in colonic mucosal scrapings or crypt epithelium.<sup>75</sup> Endotoxin, along with ethanol treatment, induces a three-fold increase in radical adducts in the bile.<sup>76</sup> Intraperitoneal bile has been shown to increase bacterial growth and mortality in *E. coli* peritonitis in the rat, cholic and deoxycholic acid enhancing the release of endotoxin in this situation.<sup>77</sup> Bile salts can also activate stress response genes in *E. coli*, which may promote interaction of *E. coli* with cells of the colonic epithelium.<sup>78</sup> Preliminary work from our laboratory has shown evidence of oxidative stress in the intestine from cirrhotic rats, with increases in superoxide generation accompanied by conjugated diene and malondialdehyde production (A Ramachandran and KA Balasubramanian, unpubl. data, 2000). Tan *et al.* have shown

that the superoxide-generating enzyme xanthine oxidase can gain access to the circulation following ischemia, where it binds to vascular endothelial cells to produce site-specific oxidant injury to organs remote from the site of xanthine oxidase release.<sup>79</sup> Hence, the consequences of damaged liver function in cirrhosis could spill over to the gut due to a variety of changes, because free radicals could be transferred through the bile or altered gut perfusion could facilitate oxidative stress in the small intestine.

In conclusion, it seems that the translocation of intestinal-derived bacteria into the systemic circulation in cirrhosis is an important etiologic factor for the development of complications such as SBP. The decrease in intestinal motility associated with cirrhosis facilitates the overgrowth of bacteria in the gut lumen. An increase in bacteria coupled with an increased intestinal permeability caused by a loss of gut barrier function could then result in bacterial translocation. Oxidative stress in the intestine also probably plays a role (Fig. 1), although studies on this aspect of SBP are scarce. However, this is an important area that requires further study, because it is evident that the intestine plays a major role in the etiology of complications such as SBP. Identifying the molecular mechanisms that render the enterocyte susceptible to damage and lead to bacterial translocation would help in formulating therapeutic strategies to prevent such complications.



**Figure 1** Probable effect of liver cirrhosis on the intestine, facilitating development of spontaneous bacterial peritonitis (SBP). Decreased gut motility in cirrhosis would facilitate bacterial overgrowth and this, in turn, could lead to bacterial translocation and peritonitis. Oxidative stress induced in the liver by cirrhosis could spill over to the intestine through the bile, splanchnic hypoperfusion or by dysregulated immune function and these oxygen free radicals could mediate intestinal damage, thus facilitating increased intestinal permeability and bacterial translocation.

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