INFECTION, COAGULATION, AND VARICEAL BLEEDING IN CIRRHOSIS

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SUMMARY

Bacterial infections in cirrhotic patients are common. There is a predisposition to intestinal bacterial overgrowth, intestinal dysmotility, and increased intestinal permeability, all leading to an increase in bacterial translocation. Bacterial translocation is the probable mechanism for some of the most common infections in cirrhosis, such as spontaneous bacterial peritonitis, but is also the source of bacterial byproducts such as endotoxin which can cause an increase in portal pressure, impairment of liver function, and worsening of haemostasis.

The effects of bacterial infection and bacterial products on portal and systemic haemodynamics in cirrhosis and clinical data on infection, from both retrospective and prospective studies of variceal bleeding and other settings, demonstrate the importance of infection in pathophysiological mechanisms in cirrhosis. This has been followed by recent clinical evidence that antibiotic therapy reverses systemic vasodilation and prevents early variceal rebleeding.

INTRODUCTION

In cirrhotic patients there is an increased susceptibility to bacterial infection, related to the degree of liver dysfunction[1] leading to several abnormalities of defence mechanisms, all of which increase the susceptibility to infection, including deficiency of bactericidal and opsonic activities, impaired monocyte function, depressed phagocytic activity of the reticuloendothelial system (RES), defective chemotaxis, and low levels of complement in serum.

A particularly important role is played by the reduced RES activity, due to the presence of extrahepatic and intrahepatic shunts through sinusoids without Kupffer cells, reduced number of Kupffer cells, and impaired Kupffer cell function. Thus cirrhotics with impaired RES phagocytic activity (as assessed by elimination of 99 m technetium-sulphur colloid) develop acute bacterial infections more frequently than cirrhotics with normal RES phagocytic activity.[2]

Both community and hospital acquired bacterial infections are frequently diagnosed in cirrhotics, most frequently spontaneous bacterial peritonitis (SBP), urinary tract infections, pneumonia, and skin infections.[3] Their incidence rises with worsening liver function.[3] Importantly, half of these episodes are asymptomatic.[1]

Recently, bacterial infections and/or endotoxaemia have been associated with failure to control variceal bleeding,[4] more early variceal rebleeding,[5] abnormalities in coagulation,[6 7] vasodilatation of the systemic vasculature,[8] and worsening liver function.[9] There has also been increased recognition that bacterial infections are involved in several pathophysiological abnormalities in cirrhosis. In this review we evaluate the potential mechanisms and clinical evidence illustrating the pivotal role of bacterial infection. This could lead to new treatment strategies.

ENDOTOXAEMIA IN CIRRHOSIS

Endotoxaemia in liver disease, first described in 1970 in patients with biliary obstruction, is frequently found in cirrhotics,[10] even in the absence of any signs of sepsis. Thus higher endotoxin concentrations are found in peripheral blood of cirrhotics than in normal subjects[10] with a statistically significant gradient between portal and peripheral blood,[11] highlighting the role of the bowel as the source of endotoxin. Both peripheral and portal levels of endotoxaemia are correlated with the severity of liver disease[10 11] which is a more important predictor of high plasma endotoxin concentrations than portosystemic shunting or portal hypertension.[10]

BACTERIAL OVERGROWTH, ALTERED INTESTINAL MOTILITY, AND INCREASED INTESTINAL PERMEABILITY

Altered small bowel motility, bacterial overgrowth in the small intestine, and increased intestinal permeability all lead to increased endotoxaemia, increased bacterial translocation, and ultimately

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the risk of bacterial infection in cirrhotics. In cirrhotic rats with ascites, bacterial overgrowth is promoted by intestinal hypomotility, and bacterial translocation only occurs in the presence of overgrowth and severe disruption of the gut barrier.[12] In humans with cirrhosis, bacterial overgrowth has been shown in one third of alcoholic cirrhotics, especially those with ascites and severe liver dysfunction,[13] and is associated with reduced small bowel motility, hypochlorhydria, decrease in intraluminal immunoglobulins, and reduced secretion of IgA.[14] There is also abnormal small bowel colonisation by colonic bacteria. The altered small bowel motility causes delayed intestinal transit which worsens with increasing severity of liver disease.[15] A coordinated bowel motor function is probably the most important mechanism for preventing bacterial overgrowth.[12]

Intestinal permeability is impaired by portal hypertension, particularly with severe liver disease,[16] especially if there is ongoing alcohol intake.[17] Gastrointestinal mucosal abnormalities (leading to increased permeability) due to portal hypertension[14] can be caused by overproduction of nitric oxide (NO), which leads to disruption of the integrity of the intestinal epithelium.[18] Intestinal permeability has been assessed in 80 cirrhotics (mostly alcoholic): an increase in permeability was correlated with the occurrence of septic complications.[16]

SBP is a haematogeneous infection localising in ascitic fluid, the source most likely being bacteria translocating from the gut. A history of SBP is associated with more severe intestinal dysmotility and more frequent bacterial overgrowth.[14] Bacterial overgrowth leads to bacterial translocation and together with increased intestinal permeability leads to an increased risk of SBP and worsening of hepatic encephalopathy.[19]

Cisapride and antibiotics (such as norfloxacin and neomycin) improve both small intestine dysmotility and bacterial overgrowth in cirrhosis.[20] Interestingly, propranolol, which lowers portal pressure, reduced the risk of post surgical infections from 42% to 15% in a cohort of 73 cirrhotics.[21] This protection is probably due to increasing bowel motility by its sympatholytic action, indirectly decreasing microbial translocation. A recent retrospective study of 139 patients suggested that propranolol may prevent SBP.[22] Given these data, propranolol may have another mode of action in reducing variceal bleeding by preventing or reducing bacterial translocation, thus reducing the frequency of infection which may be a trigger for bleeding.[23] At present, it is not known whether probiotics (a live microbial supplement which partially substitutes intestinal flora) alter bowel motility in cirrhotics (see box 1).

BACTERIAL TRANSLOCATION

The term bacterial translocation was first coined in 1979[18] and was later defined as the passage of both viable and nonviable microbes and microbial products, such as endotoxin, from the intestinal lumen through the epithelial mucosa into the mesenteric lymph nodes (MLNs) and possibly other organs.[18] There are multiple routes by which an organism could potentially translocate from the gut to extraintestinal sites[18] but in cirrhosis the intestinal macrophages play a key role by carrying bacteria from the gut to MLNs.[24] The principal factors that normally prevent bacterial translocation are the balance of intestinal bacterial populations (mainly controlled by peristalsis), the integrity of the intestinal barrier, and immunocompetence. In addition, decreased killing of bacteria, rather than an increase in transepithelial penetration, may increase colony forming units in the MLNs,[18] as most microbes breaching the epithelial barrier are killed. Thus for bacterial translocation to become clinically significant, failure of local and/or systemic immune defence, as is commonly present in cirrhotics, is also required.[18]

In animal cirrhotic models, bacterial translocation occurs with an incidence ranging from 37% to 83%.[18] Portal hypertension is one factor determining bacterial translocation; the latter increases in cirrhotic rats after the development of ascites[25] but other factors also have a role, such as reduced defences and bacterial overgrowth.[26] A reduced translocation rate is recorded in portal vein ligated rats with chronic prehepatic portal hypertension but without parenchymal liver damage, which also have milder histological changes in the bowel.[26] In human cirrhosis, the incidence of bacterial translocation is also related to the degree of portal hypertension and liver dysfunction, reported in approximately 30–40% of cirrhotics with ascites,[12 25 27] and more frequently in Child C than in Child A and B cirrhosis.[27]

Only a few types of intestinal bacteria are able to translocate into MLNs: *Escherichia coli*, *Klebsiella pneumoniae*, other Enterobacteriaceae, *Pseudomonas aeruginosa*, enterococci, and some streptococci. These constitute up to three quarters of microorganisms isolated in SBP.[28] In cirrhotic rats, there is frequent genotype identity between ileal flora and bacteria colonising MLNs.[29] In a recent study, seven of 17 advanced cirrhotics with culture negative non-neutrocytic ascites had the simultaneous presence of bacterial DNA in blood and ascitic fluid at admission to hospital, which persisted in blood for 24–72 hours.[30] Furthermore, nucleotide sequencing demonstrated that bacteria detected in the first sample were identical to those detected later, proving that bacterial translocation is a single species dynamic process.[30] Cirrhotics are also predisposed to other spontaneous infections in addition to SBP by intestinal bacteria as a consequence of bacterial translocation. Selective intestinal decontamination with antibiotics reduces bacterial translocation[27] and decreases the risk of infections, especially those due to Gram negative bacteria.[31] This again supports the role of intestinal bacteria as a major infective source in cirrhotics and may explain why prophylactic antibiotics both orally and intravenously are so effective in reducing infections during variceal bleeding.[31]

EFFECTS OF ENDOTOXAEMIA AND INFECTION

Chronic exposure to sublethal levels of endotoxin may prime liver parenchymal cells for producing NO when exposed to increased levels of endotoxin and/or tumour necrosis factor α

Box 1 Possible therapeutic approaches to reduce the infection related risk of bleeding in cirrhotics

► Prokinetics to reduce dysmotility and reduce bacterial translocation
► Probiotics to replace the bacterial population
► Antibiotics in acute variceal bleeding to prevent early rebleeding
► Reduction of portal pressure (non selective beta blockers) with long term antibiotics

(TNF-α).[32] NO itself may prime monocytes to endotoxin[33] and other biological mediators released by endothelial cells when these are exposed to biomechanical stimuli, such as shear stress in portal hypertension. In ascitic cirrhotics, monocytes are spontaneously activated by enteric bacterial products to produce TNF-α and contribute significantly to elevated serum TNF-α.[34] In cirrhosis, in response to endotoxin, there is increased release of TNF-α, interleukin (IL)-1, and IL-6 and increased expression of CD11b/CD18 on the surface of monocytes,[33] not only due to the preactivation status of monomacrophages but also to a reduced catabolism of cytokines associated with hepatic dysfunction. Cirrhotics with bacterial infection have very large concentrations of endotoxin in the systemic circulation and a marked and sustained increase in TNF-α and IL-6 concentrations.[35] These remain high for a longer time compared with non-infected decompensated cirrhotics and non-cirrhotic infected patients.[35] Treatment with norfloxacin in 60 alcoholic ascitic cirrhotics normalised the increased number of monocytes and reduced their activated phenotype and their ability to produce TNF-α.[34]

As endotoxin is primarily removed by Kupffer cells, the hepatic RES modulates most of the effects of endotoxin on the liver (such as an increase in ICAM-1 expression on hepatocytes, endothelial cells, and macrophages).[36] Clinically, increased endotoxin concentrations may lead to increased disturbance of the systemic and regional circulations, coagulopathy, and encephalopathy, resulting in both renal and hepatic failure and ultimately death, in both chronic and acute liver disease.[37][38]

INFLUENCE OF INFECTION ON HAEMODYNAMICS
Nitric oxide
Arterial vasodilation, particularly in the splanchnic circulation, is a major pathogenetic factor for the hyperdynamic circulatory syndrome in cirrhotics.[39] There is also impaired vascular contractility with hyporeactivity to vasoconstrictors[40] due to overproduction of NO[41] (its major source being endothelial nitric oxide synthase (NOS)[42]) as well as other mechanisms. Bacterial translocation, together with portosystemic shunting and reduced hepatic clearance, leads to bacteria, endotoxins, and cytokines in the systemic circulation,[8][18] thus enhancing NO production in cirrhotic animals[43] and humans.[44] The latter occurs via a direct stimulatory effect of endotoxin, and endotoxin induced secretion of cytokines such as TNF-α, and via GTP-cyclohydrolase I which increases tetrahydrobiopterin synthesis (an essential cofactor in the synthesis of NO).[45] This increase in NO further aggravates arterial vasodilation in cirrhosis.[8]

Cirrhotics with bacterial translocation have haemodynamic derangement, with lower systemic vascular resistance (SVR) and higher cardiac output if endotoxaemia is present.[10] Moreau et al observed that cirrhotics with septic shock had lower vascular resistances than non cirrhotics with septic shock.[46] Concentrations of lipopolysaccharide binding protein (LBP), a surrogate marker of endotoxaemia, are increased in 40% of ascitic cirrhotics, but not in non-ascitic cirrhotics.[47] This suggests that the increased nitrate concentrations due to endotoxaemia and bacterial translocation may be related to worsening of portal hypertension and/or liver function. This is in agreement with the finding that serum nitrate levels not only correlate significantly with endotoxaemia but are also increased in cirrhotics with ascites or kidney failure and are associated with high plasma renin activity, aldosterone, and antidiuretic hormone levels and low urinary sodium.[48] Interestingly, selective intestinal decontamination can normalise LBP levels, reduce renin and nitrate levels, and increase SVR in cirrhotics, but not in those with normal LBP.[47] In another study, cirrhotics with high TNF-α concentrations in MLNs (suggesting bacterial translocation) had a higher cardiac index and higher portal pressure.[49] In rats with portal hypertension, inhibition of TNF-α production was accompanied by amelioration of the hyperdynamic syndrome and even a decrease in portal pressure.[50] These studies suggest that endotoxaemia and bacterial infection can exacerbate the haemodynamic alterations in cirrhosis, thus leading to further worsening of portal hypertension via activation of neurohumoral pathways and further fluid retention in response to systemic vasodilatation. The correlation between the presence of endotoxaemia or bacterial translocation and worsening of the haemodynamic status is confirmed by the fact that intestinal decontamination reduces nitrate and endotoxin levels and vasodilation, both in cirrhotic patients[48] and in a rat cirrhotic model,[51] in which intestinal decontamination reduced the development of ascites.[51] In cirrhotic patients, basal forearm blood flow and the vasoconstrictive effect of the NOS inhibitor N^G-mono-methyl-L-arginine was increased compared with controls but returned to normal in cirrhotics after selective intestinal decontamination with norfloxacin.[52] In a recent study in 14 alcoholic cirrhotics,[8] selective intestinal decontamination reduced serum endotoxin concentrations and partially reversed the chronic peripheral and systemic vasodilatation by increasing SVR and mean arterial pressure and decreasing cardiac output and forearm blood flow. Interestingly, hepatic venous pressure gradient (HVPG) was also decreased by a mean of 2.43 mm Hg,[8] further strengthening the hypothesis that bacterial products contribute to the hyperdynamic circulation and portal hypertension in cirrhosis.

Cytokines
In addition to the direct effects of the release of vasoactive mediators such as NO with regard to worsening of the haemodynamic derangement in infected cirrhotics, release of inflammatory mediators may also play a role. TNF-α is involved in the pathogenesis of the hyperdynamic syndrome in portal hypertension; the gut and its associated lymphoid tissue produce and release TNF-α in response to bacterial translocation even in the absence of portal or systemic spread of bacteria. Vascular reactivity in cirrhotic rats with bacterial translocation to the MLNs is more impaired than in those without translocation and is most likely due to an increase in endothelial NOS activity mediated by TNF-α.[43]

Renal failure in SBP occurs in the setting of an intense inflammatory response and is related to deteriorating circulatory dysfunction (as shown by higher aldosterone and norepinephrine levels and plasma renin activity)[53]; it is the result of combined circulatory dysfunction of cirrhosis, and of sepsis, leading to additional stimulation of the renin-angiotensin system. Cirrhotics with SBP who develop renal impairment have significantly higher ascitic fluid counts of neutrophils and higher plasma and ascitic fluid concentrations of TNF-α and IL-6, than those without renal impairment.[54] Hepatorenal syndrome (HRS), which is accompanied by the most extreme haemodynamic derangement in cirrhosis, is associated with increased concentrations of IL-6 and TNF-α compared with patients with liver failure and normal renal function.[55] After liver transplantation, IL-6 and

TNF-α levels return to near normal, concomitant with improving renal function, suggesting that IL-6 and TNF-α emanating from the liver play a role in HRS.[55] This could be either through TNF-α induced oxygen radical formation by mesangial cells or through a TNF-α related increase in NO by mesangial or endothelial cells.[55] A further link between inflammation and haemodynamic dysfunction is that cirrhotics with gross ascites have increased levels of C reactive protein[56] and that serum nitrate levels are correlated with orosomucoid concentrations (a protein synthesised by the liver in response to cytokines). Treatment with intravenous albumin in addition to antibiotics reduces the likelihood of renal impairment in SBP,[57] not only by expansion of the decreased plasma volume but possibly also by binding of cytokines or NO by albumin[58] or its antioxidant effect in sepsis.[58] Renal failure occurs frequently in patients with variceal bleeding so that bacterial infection may contribute directly to renal dysfunction over and above any hypotension which can lead to acute tubular necrosis.

Endotoxin also stimulates the synthesis of endothelin, renal production of thromboxane A2, and increases plasma levels of leukotrienes, all of which act as renal vasoconstrictors.[59] This release of vasodilators and renal vasoconstrictors due to infection may be another factor contributing to the development of renal impairment in SBP.[59]

Systemic and portal haemodynamics

The most consistent clinical data on the influence of bacterial infection on systemic haemodynamics in cirrhotic patients has been reported in the setting of SBP: renal impairment develops in one third of patients,[59] especially in those with the most severe inflammation, as expressed by higher concentrations of cytokines in plasma and ascites.[53 54] SBP is associated with worsening of haemodynamic status, as shown by activation of the renin-angiotensin system[54] caused by the decrease in effective arterial blood volume as a result of infection.[54 59] Treatment with cefotaxime and albumin compared with cefotaxime alone, leads to less renal impairment and lower mortality, and lower levels of plasma renin activity.[57] Thus in SBP circulatory dysfunction develops which may be prevented by albumin treatment. Recently, in another study,[53] wedged hepatic venous pressure and HVPG increased (from 19.0 (2.6) to 23.6 (2.6) mm Hg; p<0.025) in eight cirrhotic patients with SBP and renal failure despite a decrease in effective arterial blood volume and systemic vasodilatation. This emphasises the differential effect that the same stimulus can have on the systemic and splanchnic circulations. When SBP is associated with systemic circulatory dysfunction there is an increase in HVPG, which is thought to be secondary to the action of endogenous vasoconstrictors on vascular smooth muscle cells in small venules and on activated hepatic stellate cells (myofibroblasts). In the setting of portal hypertension there is a relative deficiency in NO in the intrahepatic circulation, thus increasing the susceptibility to vasoconstriction.[60]

Endothelin and other vasoconstrictors

Endothelin 1 (ET-1) is the most potent mediator of stellate cell contraction and in the liver ET-1 receptors predominate in hepatic stellate cells, which have an important role in the regulation of intrahepatic portal hypertension in cirrhosis.[61] Both endotoxin itself and cytokines released in response to it, are potent stimuli for the production of ET-1,[23] which may act in combination with cyclooxygenase products to increase portal venous resistance during endotoxaemia.[62] In the cirrhotic liver there is greater induction of vasoconstrictor (ET-1) over vasodilatory (NO, carbon monoxide) forces after lipopolysaccharide (LPS) injection.[63] There is a compromised ability to upregulate sufficient vasodilatory forces to counterbalance the constrictive effect of ET-1 following increases in endotoxaemia, thus leading to increased intrahepatic resistance. This would result in an acute increase in portal pressure. Other vasoconstrictors such as angiotensin II and norepinephrine lead to an increase in intrahepatic resistance in rats and in in vitro models,[64] leading to increased portal pressure.[53] These mediators are increased in cirrhosis and are further augmented in response to the systemic vasodilatation occurring in bacterial infection.

Thus if infection has a causal role in precipitating variceal bleeding, then it could be acting via an increase in portal and/or variceal pressure secondary to a rise in intrahepatic resistance, as we have previously outlined as part of our hypothesis suggesting infection could trigger variceal bleeding.[4]

INFLUENCE OF INFECTION ON COAGULATION

Using thromboelastography (TEG), 20 cirrhotic patients who had bled from varices and then suffered early rebleeding were found to have a worse TEG trace on the day before rebleeding compared with those who did not rebleed.[65] TEG parameters were also found to worsen in 84 decompensated cirrhotic patients in the presence of bacterial infection.[66] A recent study found heparin activity in blood using heparinase I modified TEG in 28 of 30 patients with bacterial infection, but not in non-infected patients, and this effect disappeared after resolution of infection; other coagulation parameters were not modified significantly.[6] This heparin activity was subsequently found to be associated with anti-Xa concentrations in many, although not all, patients, suggesting that the heparinase effect is due to an endogenous low molecular weight heparin.[7] Moreover, a heparin effect was reported immediately after acute variceal bleeding in cirrhotics and thus could contribute to failure to control acute bleeding and early rebleeding.[67]

In a single study, plasma heparan sulphate concentrations were significantly raised in patients with recent variceal bleeding compared with those without bleeding or non-cirrhotic patients.[68] Endotoxin or cytokines could release heparinoids from endothelium in a dose dependent manner[6] and mast cell activation due to bacterial infection could also release heparin. Mast cells and activated endothelial cells are also able to release tissue plasminogen activator, which induces fibrinolysis.[6]

Sepsis causes defects in platelet aggregation,[69] and this may constitute another reason for impairment of the haemostatic process in cirrhotics, either via a decrease in platelet aggregation due to NO or due to the fact that endotoxin and ET-1 can impair platelet aggregation through release of prostacyclin.

Production of cytokines in the presence of bacterial infection can lead to activation of clotting factors and fibrinolysis.[70] In 30% of patients with advanced liver disease, accelerated intravascular coagulation and fibrinolysis has been shown, and these patients are prone to develop disseminated vascular coagulation (DIC) if sepsis occurs.[71] Hyperfibrinolysis was directly associated with gastrointestinal haemorrhage in cirrhotic patients[71]; unfortunately, the presence of infection was not documented in these studies.

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Bleeding from oesophageal varices has some correlation with the circadian rhythm of fibrinolysis in cirrhotics.[71] Features of DIC have been reported in cirrhotic patients with variceal haemorrhage, especially in those who die of continued bleeding,[72] where multiple transfusions may be a confounding factor. However, there is little evidence for DIC occurring as a primary event in cirrhosis.[73] In 41 cirrhotics, a study found a strong association between endotoxaemia and high plasma levels of prothrombin fragment F1+2 and D-dimer (a pattern suggestive of secondary fibrinolysis) which interestingly then returned to normal after administration of non-absorbable antibiotics.[74] A recent report showed a lower protein C activity in cirrhotics with severe sepsis compared with those with non-severe sepsis or without sepsis; this deficiency in protein C activity is associated with a significant inflammatory response and DIC.[75]

INFLUENCE OF INFECTION ON LIVER DAMAGE

Normal liver microcirculatory function is maintained by a balance of vasoconstrictors (ET-1) and vasodilators (NO, carbon monoxide).[63] Both endotoxaemia and cytokines such as TNF-α and IL-1 cause hepatic necrosis by disruption of the microcirculation, the alteration in the microcirculation due to endotoxin being mediated via Kupffer cells[76] in several experimental models of liver failure via infiltration of leucocytes. These are a source of reactive oxygen species as well as nitrogen species,[77] leading to lipid peroxidation in the liver and secondary damage to hepatocytes. Kupffer cells play a pivotal role in endotoxin induced hepatic injury. LPS triggers production of IL-1β, TNF-α, IL-12, and IL-18 from Kupffer cells, IFN-γ from hepatic lymphocytes, and induces Fas-Ligand on the surface of NK cells, all leading to acute hepatic injury. TNF-α is hepatotoxic in itself, inducing the apoptosis of hepatocytes. LPS induced liver failure in mice is prevented by inhibition of nuclear factor κB, thereby decreasing cytokine production.[78] In addition, hepatocytes have membrane receptors for both endotoxin and the lipid A component of LPS, thus offering another possible pathway for liver injury.[79]

Antibiotic treatment prevents early liver injury caused by ethanol in rats[80] and both cisapride and antibiotics improve liver function in cirrhotic patients,[20] strongly suggesting that bacterial products via translocation can worsen liver function. Other clinical evidence also suggests that liver function may be worsened by bacterial infections. Indeed, infections can aggravate liver dysfunction in patients with cirrhosis,[9 81] and severe liver failure occurs in most patients with cirrhosis and septic shock.[46] Thus sepsis may affect liver function independent of its haemodynamic effects.

CLINICAL EVIDENCE LINKING BACTERIAL INFECTION TO VARICEAL HAEMORRHAGE

Bacterial infections are frequently associated with upper gastrointestinal bleeding in cirrhotic patients,[4 31] developing in up to 66% (20% within the first 48 hours, 35–66% within two weeks).[4] About two thirds of these infections are present at hospital admission while the remaining third develop during admission.[1] Moreover, bacterial infections are more common in cirrhotic patients with acute variceal bleeding than in those admitted to hospital with other forms of decompensation, such as encephalopathy (see box 2).[1]

Our group showed that proven bacterial infection, or a surrogate of its presence (use of antibiotics), had the strongest independent association with failure to control

> **Box 2 Clinical evidence linking infection to variceal bleeding in cirrhotics**
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> ► Bacterial infections are common in cirrhotic patients with variceal haemorrhage
> ► Infection is independently associated with gastrointestinal haemorrhage in cirrhotics
> ► Infection is associated with failure to control variceal bleeding and early variceal rebleeding in these patients
> ► Prophylactic antibiotics prevent early rebleeding after acute variceal haemorrhage

bleeding in cirrhotic patients with variceal bleeding, even stronger than active bleeding at endoscopy and severity of liver disease.[4] Recently, a prospective survey of 1037 cirrhotics reported that the 297 patients with proven infection had a fourfold increase in the incidence of gastrointestinal bleeding (8% v 2%; p<0.001) compared with 346 known not to have bacterial infection, and that infection was independently associated with the occurrence of gastrointestinal haemorrhage.[82] The strong association between infection and variceal bleeding in cirrhotics has been confirmed in several studies: association with failure to control bleeding,[4 83] early rebleeding,[4] and mortality.[83] A recent meta-analysis confirmed that antibiotic prophylaxis prevented infections in cirrhotic patients with gastrointestinal bleeding and significantly increased the short term survival rate.[31] The improvement in mortality was equivalent to that seen with terlipressin. In a very recent randomised study of 120 patients, prophylactic ofloxacin compared with on demand antibiotics was shown to prevent early rebleeding (24% v 64%; p<0.01) and to decrease the amount of blood transfused (1.40 (0.89) v 2.81 (2.29) units; p<0.05), in addition to preventing bacterial infections.[5] Therefore, since our hypothesis was published,[23] there are now a number of publications strongly suggesting a causal link between the presence of an infection and initiation of acute variceal bleeding and its associated early rebleeding, supporting our hypothesis.

Worsening of liver function is a recognised risk factor for first variceal bleeding[84] so that infection may contribute to this risk, or indeed be a trigger for variceal haemorrhage, particularly as the liver damage occurring in sepsis may itself contribute to an acute increase in portal hypertension. The risk of portal hypertensive related bleeding in cirrhotic patients is related to the degree of portal hypertension, liver dysfunction, and to the size and endoscopic appearance of varices.[84] However, trigger factors are not known. In the
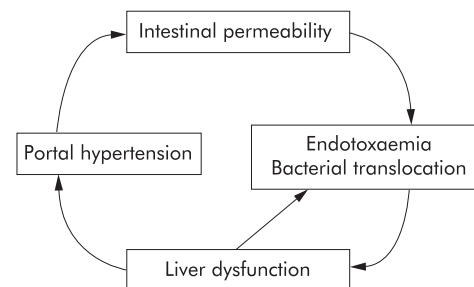

Figure 1 Damage to the intestinal barrier leads to bacterial translocation and endotoxaemia and thus to impairment of liver function and increase in portal pressure, possibly causing further damage to the gut: a vicious circle.
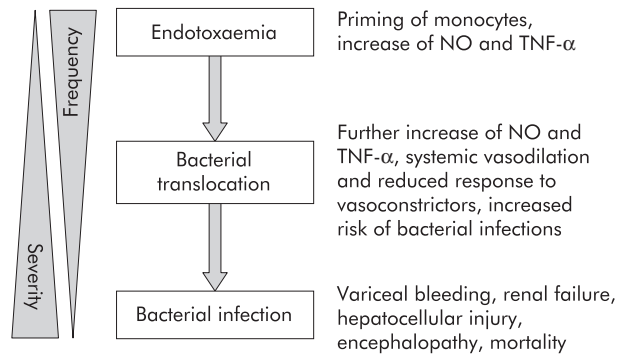
Figure 2 Endotoxaemia, bacterial translocation, and bacterial infection may be different expressions of the same process at different degrees of severity, and are associated with increasingly severe complications. NO, nitric oxide; TNF-α, tumour necrosis factor α.

setting of portal vein thrombosis in non-cirrhotic patients, where often there are oesophageal varices of the largest size with red signs, the incidence of bleeding is much lower than in cirrhotics with similar varices. Thus the bleeding rate in portal vein thrombosis has been documented as 12.5 episodes per 100 patient years[85] whereas the risk of first bleeding with Child grade A cirrhotics with large varices and moderate red signs is 24% in one year and in Child grade C with small varices and no red signs, 20%.[84] The difference probably lies in the presence of liver disease (although the thrombophilic conditions often associated with portal vein thrombosis cannot be discounted). Cirrhosis predisposes to risk of infection which is not reported in non-cirrhotic portal hypertension.

This increased release of endotoxin and viable bacteria into the portal and systemic circulation is closely related to liver cirrhosis, with portal hypertension and liver dysfunction influencing increased intestinal permeability and altered small bowel motility on the one hand and bacterial overgrowth on the other (fig 1). Low grade endotoxaemia leads to priming of monomacrophages and an increase in NO and TNF-α. Bacterial translocation causes a further increase in NO and TNF-α, a reduced response to vasoconstrictors, and an increased risk of bacterial infection, with the associated risk of variceal bleeding, renal failure, hepatocellular injury, hepatic encephalopathy, and mortality (fig 2).

The possible causative role of bacterial infection in variceal haemorrhage is less easily understood but nevertheless is most intriguing.[23] Indeed, the known risk factors for variceal
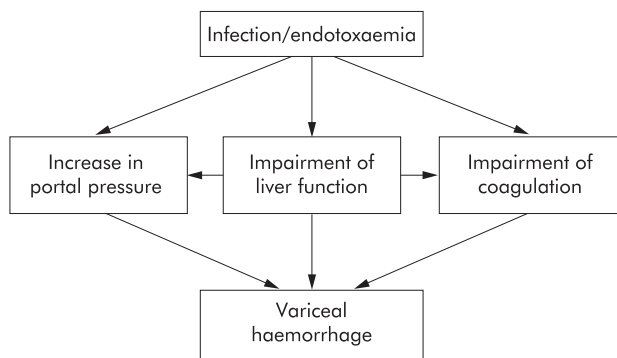

Figure 3 Possible pathophysiological pathways through which bacterial infection can trigger variceal haemorrhage.

Summary

► Endotoxaemia and infections are common in cirrhotic patients
► Endotoxaemia and infections derange systemic and splanchnic haemodynamics in cirrhotics
► Infections impair coagulation in cirrhotics
► Infections worsen liver function in cirrhotics
► Infections may trigger variceal bleeding
► Infections are a causative factor in early variceal rebleeding

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bleeding (HVPG, liver function, size of varices, and presence of red signs) do not readily explain why bleeding and early rebleeding occur unpredictably in patients with cirrhosis. Portal pressure rises significantly with daily meals as well as exercise, yet despite these marked daily changes, bleeding episodes are relatively infrequent. Thus a merely mechanical understanding of variceal bleeding as a consequence of portal pressure and tension on the variceal wall does not in our view explain the pattern of variceal bleeding. Endotoxaemia secondary to bacterial infection may indeed be the critical trigger for variceal haemorrhage[23] as it produces a wide series of effects that may predispose the cirrhotic patient to bleeding: impairment of primary and secondary haemostasis, increase in portal pressure, and worsening of liver function (fig 3).

CONCLUSION

Understanding of the consequences of bacterial infection and bacterial products in the portal and systemic haemodynamics of cirrhosis and the extensive amount of clinical data on infection gathered both from retrospective and prospective studies, in variceal bleeding and other settings, have been followed by recent clinical evidence of the efficacy of antibiotic treatment in reversing systemic vasodilation[8 52] and the prevention of early variceal rebleeding.[5]

We believe the evidence presented in this review justifies randomised studies of prokinetics and probiotic therapy in decompensated cirrhotics with infection, as well as in preventative studies. In particular, a randomised trial should be undertaken of long term antibiotics or selective gut decontamination together with propranolol in the primary or secondary prevention of variceal bleeding.

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