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Bacterial infection in the pathogenesis of variceal bleeding. Is there any role for antibiotic prophylaxis in the cirrhotic patient?

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SUMMARY

Bacterial infections are frequent in cirrhotic patients particularly in those admitted to hospital. Several risk factors have been implicated to explain the propensity of cirrhotic patients to develop bacterial infections, such as iatrogenic factors that may disrupt the natural defense barriers, the occurrence of bacterial translocation from the intestinal lumen to extraintestinal sites, the depression of hepatic reticuloendothelial system function and the decreased opsonic activity of serum and ascitic fluid seen in cirrhosis. Particularly in cirrhotic patients with gastrointestinal hemorrhage, bacterial infections have an incidence of 35% to 66% and are closely related to the recurrence of hemorrhage and survival. Although gastrointestinal hemorrhage can predispose cirrhotic patients to bacteremia there is recent data that support the hypothesis that bacterial infection may initiate gastrointestinal hemorrhage, particularly variceal bleeding in cirrhosis. The strong association between bacterial infections and gastrointestinal hemorrhage in cirrhosis has led to the use of antibiotic prophylaxis in the setting of acute variceal bleeding. A recent meta-analysis demonstrated that antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding decreases the rate of bacterial infections and increases short-term survival. Spontaneous bacterial peritonitis (SBP) is the most characteristic infectious complication of cirrhotic patients and it is diagnosed according to certain diagnostic criteria. Third-generation cephalosporins are the first-choice antibiotic treatment in SBP, although selected patients with uncomplicated SBP may be treated with oral quinolones. Selective intestinal decontamination with norfloxacin is safe and effective in the primary and secondary prophylaxis of SBP.

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The incidence of bacterial infections in cirrhotic patients is high, particularly in patients admitted to hospital. According to several studies 30% - 50% of cirrhotic patients are diagnosed with bacterial infections at admission and between 15% and 35% developed this type of complication during hospitalization.[1,2] These data are in sharp contrast with the hospital-acquired infection rate in a general hospital patient population, which ranges between 5% and 7%. The most frequent types of infection in cirrhotic patients are urinary tract infections (12%-29%), spontaneous bacterial peritonitis (10%-30%), respiratory tract infections (6%-15%), and bacteremia (5%-10%).[2]

Two important clinical characteristics of bacterial infections in cirrhotic patients need to be underlined:

1) The atypical clinical presentation of bacterial infections in these patients, in whom the first sign of infection may be an abrupt deterioration of liver function or the development of unexplained renal dysfunction.

2) The absence of fever, even in cirrhotic patients with severe infections.[3]

PATHOPHYSIOLOGY OF BACTERIAL INFECTIONS IN CIRRHOSIS

Risk factors

Iatrogenic factors

Cirrhotic patients are frequently subjected to several invasive diagnostic and therapeutic procedures that may alter the natural defense barriers and therefore increase the risk of bacterial infections. In addition to procedures well known to predispose to infection, such as intravenous or urethral catheters, endoscopic sclerotherapy for bleeding oesophageal varices, the placement of transjug-

ular intrahepatic porosystemic shunts (TIPS) or peritoneovenous shunts (LeVeen shunts) may be associated with an increased incidence of bacteremia.[2] Endoscopic sclerotherapy and TIPS placement can cause transient bacteremia, but usually not clinically significant bacterial infections. However in several series the incidence of bacterial infections after the insertion of a LeVeen shunt for the treatment of ascites was approximately 20%.[4,5]

Changes in the intestinal flora and the intestinal barrier

Bacterial infections in cirrhotic patients are caused, predominantly, by enteric organisms. Whereas aerobic gram-negative bacilli are present in low numbers in the small bowel of normal subjects, these microorganisms have been reported significantly increased in the jejunal flora of many cirrhotic patients.[6] Experimental studies have shown that, in cirrhotic rats with ascites, there is an increased passage of bacteria normally colonizing the gastrointestinal tract from the intestinal lumen to extraintestinal sites, including mesenteric lymph nodes and the systemic circulation. This process has been called bacterial translocation.[7-9] The change in the intestinal flora caused by the abnormal small-bowel colonization in cirrhosis may increase the chance of aerobic gram-negative bacteria invading the systemic circulation and cause infections of enteric origin in cirrhotic patients.

The causes of bacterial translocation are a disruption of the intestinal permeability barrier, bacterial overgrowth and/or a decrease in host immune defenses. A recent study has shown that the marked oedema and inflammation of the submucosa of cirrhotic rats with ascites may predispose these animals to a rupture in the intestinal permeability barrier, and thus favor bacterial translocation.[9] Changed permeability of the intestinal mucosa has been seen in hemorrhagic shock due to variceal bleeding which is a frequent event in cirrhotic patients.[10]

Depression of activity of the reticuloendothelial system

The reticuloendothelial system of the liver, comprised mainly of Kupffer cells and endothelial sinusoidal cells, constitutes approximately 90% of the whole reticuloendothelial system throughout the body. Several studies have shown that many cirrhotic patients have marked depression of hepatic reticuloendothelial system function. In addition it has been shown that the risk of acquiring bacteremia and spontaneous bacterial peritonitis in cirrhosis is directly related to the degree of dysfunction of the reticuloendothelial system in these patients.[11,12]

The pathogenesis of the depression of phagocytic activity of the reticuloendothelial system in cirrhosis has not been clarified. Most studies suggest that this impairment could be attributed to the presence of anatomic or functional intrahepatic portosystemic shunts, which cause the escape of the blood from the phagocytic action of the reticuloendothelial Kupffer cells.[13] Several other mechanisms have also been proposed, including the reduction of the phagocytic activity of monocytes (which are considered as the Kupffer cells precursors) and an impaired function of macrophage Fc gamma receptors, which are important in the host defense, since they participate in the clearance of IgG-coated microorganisms.[14]

Decreased opsonic activity of serum and ascitic fluid

Serum opsonic activity is markedly reduced in cirrhotic patients, mainly due to the decreased levels of complement and fibronectin. These substances are necessary for the opsonization and phagocytosis of microorganisms. Moreover, the deficiency of serum complement and fibronectin levels can be aggravated in the setting of massive variceal hemorrhage, frequently seen in cirrhotic patients, when loss of opsonins in the shed blood is replaced by saline.[15]

Opsonic activity of ascitic fluid in cirrhosis is directly correlated with the concentration of defensive substances, such as immunoglobulins, complement, and fibronectin, and with the concentration of total protein in ascites.[16] Recent studies have demonstrated an inverse and statistically significant correlation between ascitic fluid opsonic activity, as represented by total protein concentration of ascitic fluid, and the risk of spontaneous bacterial peritonitis in cirrhotic patients with ascites. According to these studies, cirrhotic patients with ascites and protein concentration in ascitic fluid below 1 gr/dL develop statistically significantly more often spontaneous bacterial peritonitis during hospitalization or one-year follow-up, than patients with ascitic protein concentration over 1 gr/dL.[17] Moreover, protein concentration in ascitic fluid, together with serum bilirubin concentration, have been identified as the only prognostic factors for the first episode of spontaneous bacterial peritonitis.[18] The very low concentrations of total protein in ascitic fluid depend not only on the severity of liver failure but also on the volume of water diluting these ascitic fluid solutes. This last notion is supported by the finding that diuretic-induced reduction of water in ascitic fluid increases the total protein concentration and the antibacterial capacity of as-

cites, and by the common observation in clinical practice that spontaneous bacterial peritonitis occurs predominantly in cirrhotics with large-volume ascites.[2]

Neutrophil leucocyte dysfunction

The most frequent disorder of neutrophil leucocyte dysfunction in cirrhotic patients is a marked reduction of chemotaxis, probably caused by the presence of substances in the serum that inhibit granulocyte migration.[2] Furthermore reduced phagocytic and bacterial killing capacity of neutrophils has been reported in many cirrhotic patients.[19] However as the types of infection frequently developed by patients with congenital or acquired neutrophil function abnormalities (mainly chronic granulomatous diseases and recurrent staphylococcal and fungal infections) are very different from the infections developed by cirrhotic patients, it seems very unlikely that leucocyte dysfunction plays any major role in the susceptibility of cirrhosis to bacterial infection.

BACTERIAL INFECTIONS IN CIRRHOTIC PATIENTS WITH GASTROINTESTINAL HEMORRHAGE

Bacterial infections are frequently diagnosed in cirrhotic patients with gastrointestinal hemorrhage. Prospective studies have shown that bacterial infections are documented in 22% of such patients within the first 48 hours after admission.[20,21] Within 7 to 14 days after initial bleeding, the incidence of bacterial infections reaches 35% to 66%.[22-27] Moreover infections are closely related to prognosis in bleeding cirrhotic patients. We have shown in a previous study that proven bacterial infection or empirical antibiotic use started on admission or shortly afterwards, when the presence of fever (>38^{0}C), leucocytosis (>10 x 10^9/L with a shift to the left), or clinical signs of chest and urinary infection suggested bacterial infection, are independently associated with failure to control bleeding during the first 5 days after the episode of variceal bleeding.[22] The prognostic significance of bacterial infection resulting from this study shows that the occurrence of bacterial infection should be included in the analysis and planning of clinical trials for the treatment of bleeding in cirrhotic patients.

One obvious hypothesis that could explain this strong association between gastrointestinal hemorrhage and bacterial infections in cirrhotic patients is that gastrointestinal hemorrhage could predispose bleeding cirrhotic patients to bacteremia. Several risk factors for the development of bacterial infection, already mentioned, are present in these patients. First, cirrhotic patients with variceal bleeding are subjected to several invasive therapeutic procedures such as placement of intravenous and urethral catheters, endoscopic sclerotherapy and the placement of TIPS, which could break the natural defence barriers. The occurrence of hematemesis, performance of upper gastrointestinal endoscopy and sclerotherapy or variceal ligation, and the placing of a tamponade nasogastric tube may also induce aspiration pneumonia.[25] Moreover gastrointestinal hemorrhage and the resulting hypovolemia could also increase bacterial translocation and depress transiently the reticuloendothelial system function as well as decrease complement levels in ascitic fluid.[15,28]

However there are data that may support a different sequence of events, namely that it is bacterial infection that initiates gastrointestinal haemorrhage, particularly variceal bleeding in cirrhosis. It is well known that varices bleed unpredictably when there is a significant and probably abrupt rise in portal pressure.[29] We have recently published a hypothesis stating that bacterial infections in cirrhotic patients may be the critical factor that triggers variceal bleeding, mainly through the release of endotoxin.[30] In patients with chronic liver disease increased levels of endotoxin are detected in the portal and systemic circulation, resulting from the increased translocation of gut derived endotoxin as well as the impaired phagocytic function of the reticuloendothelial system and the presence of portosystemic shunts in cirrhotic patients.[31] Moreover, large quantities of endotoxin are released into the systemic circulation during episodes of bacterial infection.[32] In patients who already have large varices with a high wall tension, endotoxin causes a further increase in portal pressure, mainly through the synthesis of endothelin and nitric oxide. Endothelins (mostly endothelin–1) are the most potent mediators of stellate cell contraction and through this effect could induce an increase in portal pressure, as has been shown in experimental and clinical studies.[33] Endotoxin released during bacterial infection could also contribute to the initiation of variceal haemorrhage through the induction of cyclo-oxygenase products, such as thromboxane A_2 and prostaglandin F_{2a}.[34] Furthermore, endotoxin-induced nitric oxide and prostacyclin, together with prostacyclin induced by endothelin, could cause inhibition of platelet aggregation.[35] This process may result in a further deterioration of primary haemostasis at the level of varix. The combination of these dual effects, namely the increase of portal pressure (and subsequently variceal pressure) together with impairment of primary haemostasis could lead to the onset of variceal haemorrhage in cirrhotic patients (Fig 1).

PREVENTION OF BACTERIAL INFECTION IN PATIENTS WITH ACUTE VARICEAL BLEEDING

The strong association between bacterial infections and gastrointestinal haemorrhage in cirrhotic patients has rendered the use of short-term antibiotic prophylaxis a rational approach in the care of patients with variceal haemorrhage. A first randomized controlled trial in 1985 showed that selective intestinal decontamination with oral nonabsorbable antibiotics from admission up to 48 hours after cessation of haemorrhage significantly reduced the incidence of bacterial infections in bleeding cirrhotic patients from 35% in the control group to 16% in the treated group.[23] This was achieved mainly by a significant decrease in the incidence of bacterial infections caused by enteric bacteria, the most frequent and severe infections in cirrhotics. The regimen used in this landmark study consisted of gentamicin, vancomycin and nystatin or neomycin, colistin and nystatin. The combination of these antibiotics has some disadvantages, such as possible overgrowth of potentially pathogenic resistant bacteria and increase of side effects and cost.[24]

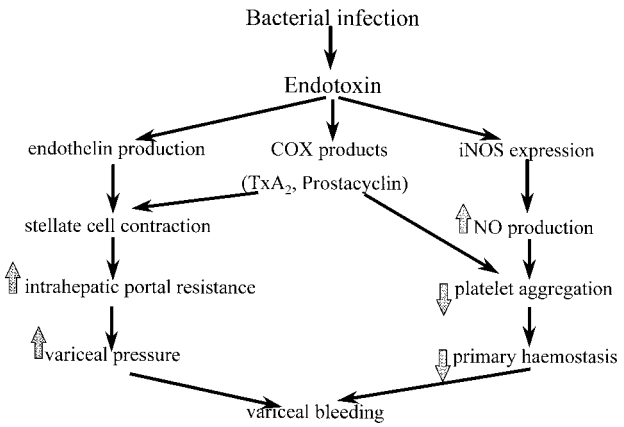

Figure 1. Proposed mechanism through which bacterial infection could trigger variceal bleeding in patients with cirrhosis.

Four other randomized controlled trials (RCTs) of prophylactic antibiotic treatment in patients with cirrhosis and gastrointestinal bleeding have been published during the last decade[24-27] (Table 1). In one RCT only patients considered to be at high risk of infection (Child-Pugh's class C or rebleeding) were included.[26] The regimens used in these studies consisted of quinolones alone [norfloxacin (24) or ciprofloxacin (27)] or quinolones [ofloxacin (25 or ciprofloxacin (26)] in association with amoxycillin + clavulanic acid. In most cases, administration of the antibiotic by mouth or through a nasogastric tube was preferred.[24,27] In cases in which this was not possible, antibiotics were administered intravenously initially, followed by oral administration.[25,26] No differences were found between orally-administered versus intravenously-administered antibiotics.[36] The duration of treatment was 4 to 10 days. A recently published meta-analysis[36] of all these 5 studies demonstrated that antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding not only decreased the rate of bacterial infections (32% mean improvement rate, 95% CI: 22-42, $p<0.001$) but also increased short-term survival (9.1% mean improvement rate, 95% CI: 2.9-15.3, $p=0.004$). Therefore the use of antibiotic prophylaxis in the setting of acute variceal bleeding is mandatory. The antibiotic of choice according to a recent consensus document[37] is norfloxacin at a dose of 400mg/12h (*per os* or through a nasogastric tube), due to its simpler administration and lower cost. This prophylaxis should be administered over

Table 1. Randomized controlled trials of antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding

First author	Treatment Ab/C	No of patients Ab/C	Child-Pugh score A(%)	B(%)	C(%)	Patients with no infection Ab/C	Survival Ab/C
Rimola 1985	GYN/NCN, PO	68/72	ND	ND	ND	57/47	61/55
Soriano 1992	Norfloxacin 800 mg/d, PO	60/59	32/36	50/42	18/22	54/37	56/52
Blaise 1994	Ofloxacin 400 mg/d, IV then PO plus amoxycillin-clavulanic acid 1g before endoscopy	46/45	0/0	24/20	76/80	37/15	35/29
Pawels 1996	Ciprofloxacin 400 mg/d + amoxicillin-clavulanic acid 3g/d, IV then PO	30/34	7/0	10/29	83/71	26/16	26/26
Hsieh 1998	Ciprofloxacin 1000 mg/d, PO	60/60	8/10	55/52	37/38	54/33	47/42

Ab: antibiotic prophylaxis group; C: control group; GVN (Gentamycin 200mg + vancomycin 500mg + nystatin 1M)/6h; NCN: (neomycin 1g + colistin 1.5M + nystatin 1M)/6h; PO: per os; IV: intravenous; ND: not determined

a minimum period of 7 days. Since most cirrhotic patients are infected at the time of the bleeding episode, as we have shown in our study, the possible existence of any infection should be appropriately excluded before starting prophylactic antibiotic treatment.

SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis (SBP) is the infection of a previously sterile ascitic fluid, with no apparent intra-abdominal source of infection. This type of infection is the most characteristic infective complication of cirrhotic patients. The incidence of SBP in cirrhotic patients with ascites admitted to hospital has been estimated to range between 7% and 23%.[38] Therefore a diagnostic paracentesis should be performed on hospital admission in all cirrhotic patients with ascites, to investigate the presence of SBP, even in patients admitted for reasons other than ascites.[37]

A diagnostic tap should also be performed in hospitalized patients with ascites if and when they develop any of the following:[37]

a) local symptoms or signs suggestive of peritoneal infection, such as abdominal pain, rebound tenderness or clinically relevant alterations of gastrointestinal motility (i.e. vomiting, diarrhea, ileus);

b) systemic signs of infection such as fever, leukocytosis or septic shock and

c) hepatic encephalopathy or rapid impairment in renal function without any clear precipitating factor

d) evidence of gastrointestinal hemorrhage prior to the onset of antibiotic treatment

The diagnosis of SBP is established on the basis of a polymorphonuclear (PMN) cell count in ascitic fluid higher than 250 cells/mm^3. It is confirmed by a positive ascitic fluid culture in approximately 70% of the cases. However patients with increased PMN count ascites and negative ascitic fluid cultures should be considered as having SBP similar to other types of infections with negative cultures such as pneumonia, arthritis and meningitis.[37]

TREATMENT OF SBP

Antibiotic therapy must be empirically initiated in cirrhotic patients with an ascitic fluid PMN cell count >250/mm^3. The initial empirical antibiotic treatment should cover Gram-negative aerobic bacteria from the family of Enterobacteriaceae and non enterococcal Streptococcus spp., because these are the most common causative organisms. Several antibiotics have been tested for this empirical antibiotic treatment. The optimal dosage has only been investigated for cefotaxime. For this antibiotic a minimum dose of 2g/12h should be administered for 5 days.[39] Other antibiotics that have been used are several cephalosporins (cefonicid, ceftriaxone, ceftizoxime and ceftazidime), or amoxycyllin-clavulanic acid.[37] For these antibiotics standard doses for severe infections are recommended.

Patients with uncomplicated SBP, namely those with normal renal function and without hepatic encephalopathy, shock, or gastrointestinal bleeding, as well as those not receiving prophylaxis with quinolones can be treated orally with ofloxacin, at a minimum dose of 400mg/12h.[40] Conversely, for patients developing SBP while under quinolone prophylaxis, cefotaxime administration is the most adequate antibiotic regimen.

A recently published multicenter randomized controlled study showed the usefulness of intravenous albumin as an adjunct to antibiotic therapy in the treatment of patients with spontaneous bacterial peritonitis.[41] The authors randomly assigned 126 patients with spontaneous bacterial peritonitis to receive treatment with either cefotaxime alone, or cefotaxime plus an intravenous infusion of albumin given at a dose of 1.5 g/kg of body weight during the first six hours after randomization, with the infusion repeated at a dose of 1g/kg three days later. Patients receiving the combined regimen had significantly better outcomes. Renal impairment developed in 33% of patients in the cefotaxime group but in only 10% of those in the cefotaxime plus albumin group. Mortality during hospitalization were 28% and 6% respectively. The latter rate is the lowest mortality rate reported ever in patients with spontaneous bacterial peritonitis.

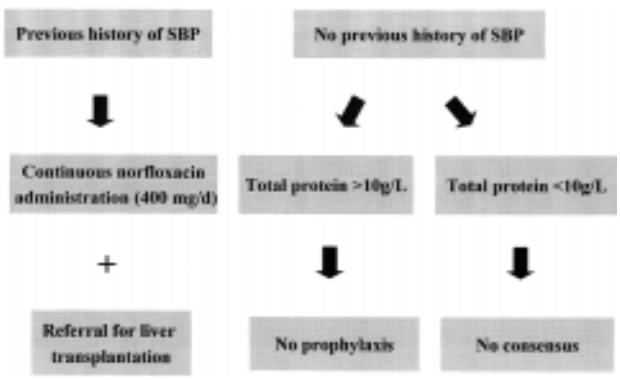

Figure 2. Antibiotic prophylaxis for spontaneous bacterial peritonitis.

PROPHYLAXIS OF SBP

Continuous oral administration of norfloxacin, 400 mg/d, is recommended in cirrhotic patients recovering from an episode of SBP. The prognosis after an episode of SBP is poor. One-year and two-year survival probability after the first episode of SBP has been reported to be 30%-50% and 25%-30% respectively.[42,43] Since liver transplantation currently offers a much better survival rate, patients recovering from an episode of SBP should be considered as potential candidates for liver transplantation.

In cirrhotic patients without a past history of SBP and with a high ascites protein count (i.e. > 10 g/l), long-term prophylactic administration of antibiotics is not necessary since the risk of SBP in these patients is negligible provided adequate prophylaxis is given if and when gastrointestinal hemorrhage develops in the course of the disease.[37]

Finally there is no consensus on the use of antibiotic prophylaxis in cirrhotic patients without a prior history of SBP and low ascitic fluid protein concentration (<10g/L). The main reason for this is that there is increased concern that prolonged antibiotic prophylaxis will lead to selection of antibiotic-resistant bacteria that can be disseminated within the general community and in the particular hospital environment. The first relevant reports have recently appeared in the literature.[44]

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