Infections

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Bacterial infections are responsible for serious and often fatal complications in patients with severe acute or chronic liver disease. The most common types of infection are bacteraemia, pneumonia, urinary tract infections, bacterial endocarditis, and spontaneous bacterial peritonitis. Defects of humoral and cellular defence mechanisms compromise the patient's ability to resist and overcome infection. The resulting infections spread rapidly to overwhelm the host or precipitate deterioration of renal function, hepatic encephalopathy or gastrointestinal haemorrhage. Unfortunately, patients often do not manifest the normal clinical features of infection – that is, rigors, fever, hypotension, and leucocytosis – and so the only clue may be more subtle changes in the clinical condition such as increase in plasma creatinine. Infection is a potentially curable complication, and is becoming an increasingly important challenge for clinicians and researchers. This article outlines the clinical problems and reasons for susceptibility to infection in patients with liver disease and the contribution made by the Liver Unit at King's College Hospital to this aspect of hepatology.

Fulminant hepatic failure

Severe damage to the liver renders the patient with fulminant hepatic failure at greatest risk of infection. An early post mortem study from the Liver Unit at King's College Hospital documented major sepsis, endocarditis, meningitis, peritonitis, and empyema which were considered to have contributed to death in 11% of 105 subjects.[11] A later prospective study of 103 patients observed bacteraemia in 23% and infection was thought to have had an adverse effect on outcome in 10% of patients.[2] Infection was unrelated to the aetiology of the hepatic necrosis, and caused by Gram positive organisms (61%) especially streptococci while *E coli* was isolated from 26% (Table I). A study of 15 children with fulminant hepatic failure managed at the same unit during the same period found bacteraemia in 40% and several cases also had infection with fungi.[3] Bacterial infection was also observed in 20% of 84 patients with presumed non-A:non-B fulminant viral hepatitis and was considered to have contributed to the morbidity and mortality.[4] A recent prospective survey of 50 consecutive patients documented 53 episodes of bacterial infection in 40 (80%) of the patients and was suspected clinically in a further five cases.[5] Infection was thought to have arisen from the respiratory tract in 37%, urinary tract in 23% and bacteraemias were present in 26% of these cases with infections. Gram positive organisms were responsible for 70% of infection with more frequent isolation of *Staph aureus* (36%) than in previous reports. Infection occurred in 28 of the 30 fatal cases and was often associated with renal failure. Infection with fungi, mainly candida was detected in 32% of patients in this study, usually in cases with concomitant bacterial infection. In seven of these fungal infection this was thought to have been a major cause of death.[6]

Chronic liver disease

Infection is mainly a problem for patients with cirrhosis, especially of the alcoholic type and was responsible for 7% of the deaths in patients with compensated cirrhosis.[7] A prospective study of patients admitted to hospital with cirrhosis, mainly alcoholic, reported infections in 40% with urinary tract infection, bacteraemia, pneumonia, and spontaneous bacterial peritonitis in 27, 14, 11, and 8% of cases respectively.[8] The types of organism isolated were similar to those found in fulminant hepatic failure (Table I). Patients with decompensated cirrhosis tended to suffer infection with Gram negative enteric organisms which presumably originated from the gastrointestinal tract and spread through portasystemic anastomoses. These cases had a worse prognosis than those with compensated liver disease in whom infection was generally with Gram positive organisms which resulted in an inhospital mortality of 30% compared with 70% for cases with decompensated liver disease.[9] In general, the mortality in alcoholic liver disease is related more to the severity of the liver disease than the alcoholism itself. There appears to be an association between infection and upper gastrointestinal bleeding.[10] Infection occurred within 48 hours of admission in 22% of 149 patients with cirrhosis who had been admitted with upper gastrointestinal haemorrhage.[11] Patients who developed infection were likely to have mucosal erosions and tended to have more severe liver disease and a worse prognosis. In-hospital mortality was 70% for those with, and 42% for those without, infection. One mechan-

TABLE I *Types of organisms responsible for bacteraemia in patients with liver disease*

Type of organism	*Chronic liver disease*[9] %	*Fulminant hepatic failure*[2] %
Gram positive	58	61
Staphylococci	21	17
Streptococci		
Group B haemolytic	–	13
Pneumoniae	16	17
Viridans	5	4
Bacillus sp.	–	4
Clostridium welchii	–	4
Other gram-positive sp.	16	–
Gram negative	42	39
Escherichia coli	16	26
Pseudomonas aeruginosa	–	9
Klebsiella pneumoniae	5	4
Proteus sp.	5	–
Other gram negative sp.	16	–

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TABLE II *Relation of clinical signs and ascitic fluid content in patients with ascites*

	Clinical signs of peritonitis	Ascitic fluid analysis: PMN count	Gram stain	Culture
Normal/sterile	None	<250	–	Negative
'Bacteriascites'	None	<250	+/–	Positive
Culture negative neutrocytic or probable peritonitis	Yes	>500	–	Negative
'Silent' peritonitis	*Minimal	>500	+/–	Positive
Spontaneous bacterial peritonitis	Yes	>250	+/–	Positive

PMN = Polymorphonuclear leucocyte.
* = Some cases have fever or abdominal pain but without signs of peritonism.

ism may be systemic endotoxaemia which is well recognised in patients with alcoholic liver disease, and is known to be associated with mucosal erosions, renal impairment, and a worse prognosis.[12]

Infection is less common in patients with chronic active hepatitis and primary biliary cirrhosis, and tends to occur only in those cases with the most severely decompensated liver disease.

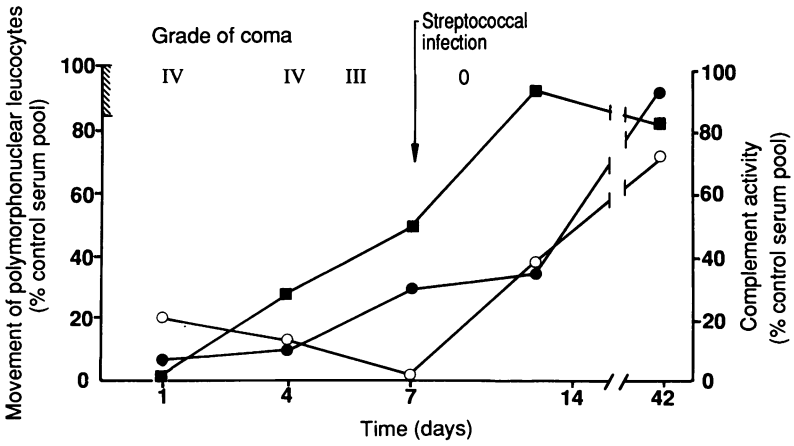
PNEUMONIA

This is mainly a problem for patients with alcoholic liver disease, especially those with hepatic decompensation, the presence of gross ascites and bleeding from oesophageal varices, particularly when managed with balloon tamponade are predisposing factors. Organisms responsible include pneumococci, *Haemophilus influenzae, Klebsiella pneumoniae* and Gram negative bacteria. Mortality tends to be highest in cases with leucopenia or hepatic insufficiency.[13] Alcoholism and concomitant treatment with immunosuppressive drugs are probably adverse risk factors for tuberculosis.

URINARY TRACT INFECTIONS

Infections of the urinary tract occurred over a two year period in 25% of patients with decompensated cirrhosis and were often caused by *E coli*.[8] Such infections occurred more often in hospitalised patients with alcoholic liver disease and formed a source for infection in 50% of bacteraemias and 20% of attacks of spontaneous bacterial peritonitis. In patients with alcoholic liver disease there is an increased concurrence of urinary tract infections and renal papillary necrosis and pyelonephritis.[14]

Asymptomatic bacteriuria has been observed twice as often in women with primary biliary cirrhosis (19%) as in women with other types of chronic liver disease or controls (7%).[15] These women are also more likely to experience recurrent attacks of bacteriuria, than controls. Reasons for this susceptibility are not understood.



Serial values of serum stimulatory activity (movement of normal PMNs towards patients' serum) and complement levels in a patient with paracetamol overdose while in grade IV encephalopathy and during the acute stages of recovery. (○=serum stimulatory activity; ●=complement factor C3; ■=complement factor C5; shaded area represents normal range). Note serum defect still present during early recovery and development of infection at this time.

INFECTIVE ENDOCARDITIS

Bacterial endocarditis occurs in less than 1·5% of patients with cirrhosis and is probably more common than in patients without cirrhosis.[16,17] Infection tends to affect previously normal heart valves, especially the aortic or mitral. The common isolation of *Strep pneumoniae* and enteric organisms differ from the usual pattern of infection responsible for infective endocarditis in patients without cirrhosis. Mortality is higher for cirrhotics than controls (38% and 28% respectively), possibly the result of the underlying liver disease, but also because of delayed or missed diagnoses. Antibiotic therapy must be chosen to treat the previously noted organisms and should be started early. Alcoholism appears to be an important risk factor for pneumococcal bacteraemia, endocarditis, pneumonia, and meningitis.[18]

SPONTANEOUS BACTERIAL PERITONITIS

More papers have been published on spontaneous bacterial peritonitis than any of the other types of infections which complicate patients with liver disease.[19] The syndrome of an abrupt onset of acute bacterial peritonitis without an apparent intra-abdominal source of infection in patients with ascites and liver disease, is well described.[20] More recent reports draw attention to the silent presentation of peritonitis in 7–30% of cases.[21] The only indication is often of an insidious deterioration in renal function, encephalopathy or onset of gastrointestinal haemorrhage. Spontaneous bacterial peritonitis has been reported in children and adults with ascites due to a wide variety of liver disease, but the most common associations in the United Kingdom are with alcoholic liver disease and chronic active hepatitis.[20-22] Prospective surveys report spontaneous bacterial peritonitis in up to 20% of patients with ascites as a result of alcoholic liver disease. The diagnosis is confirmed by isolation of bacteria from cultures of the ascitic fluid, best obtained by direct inoculation of the fluid into culture media – that is, blood culture bottles – at the bedside.[19] Early indication of infection is provided by analysis of the ascitic fluid, polymorphonuclear leucocyte content and presence of organisms on a Gram stain of the centrifuge pellet. Despite many studies of other parameters

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for early and rapid diagnosis of spontaneous bacterial peritonitis, such as ascitic fluid pH and lactate concentration, the polymorphonuclear leucocyte count still represents the most readily available, sensitive and specific screening test. On the basis of the content of the ascitic fluid different clinical categories have been recognised ranging from an asymptomatic bacteria ascites to the full blown syndrome (Table II).

E coli and Gram negative enteric organisms are responsible for 70% of culture proven cases of spontaneous bacterial peritonitis in adults while pneumococci are responsible for most attacks in children and 20% in adults.[22] Bacteraemia with the same organism occurs in 40% of patients.

Antibiotic treatment should be started at once, but despite this, inhospital mortality is high, generally more than 50% with 40% of cases dying in the first week.[21] Survivors have a high probability of recurrent attacks of spontaneous bacterial peritonitis which has been suggested as an indication for liver transplantation.[24]

MECHANISMS FOR SUSCEPTIBILITY TO BACTERIAL INFECTION

Patients with liver disease are often in poor physical condition, malnourished, and have to undergo invasive investigations and treatments, all of which may predispose to infection. The frequent occurrence of bacteraemia, especially with enteric organisms, is probably related to reduced clearance of bacteria from the portal circulation, caused by portasystemic anastomoses and impaired Kupffer cell function. *In vivo* studies of reticuloendothelial phagocytic function show severe impairment in most cases of fulminant hepatic failure and in 40% of cases of alcoholic liver disease.[23 26] A contributory factor is deficiency of the opsonic glycoprotein fibronectin, necessary for Kupffer cell phagocytosis. Concentrations of plasma fibronectin are severely reduced in cases of fulminant hepatic failure and in alcoholic liver disease are associated with a poor prognosis.[8 27 28]

The predominance of infection with encapsulated organisms suggest defects of humoral and polymorphonuclear leucocyte function which have been studied in some detail. Although serum immunoglobulins are usually present in normal or increased concentrations in patients with liver disease, impaired bactericidal function of IgM has been reported in 80% of patients with cirrhosis.[29]

Complement factors are synthesised in the liver and tend to be reduced in proportion to the severity of the liver disease. Patients with fulminant hepatic failure have very severe (less than 20% of activity of normal) deficiencies of serum complement factors of the classical and alternative pathways which cause correspondingly severe defects of *in vitro* tests of opsonisation and phagocytosis of *E coli* and yeasts by polymorphonuclear leucocytes.[3 30] Complement deficiency also causes severe impairment of serum chemoattractant activity for polymorphonuclear leucocytes (Figure).[31] All these serum functions can be improved by transfusion of fresh frozen plasma and return to normal after recovery from liver failure. In the early stages of recovery, however, such defects of host defence still render the patient at increased risk of infection which may result in recurrence of encephalopathy.

In the case of patients with chronic liver disease complement deficiency occurs in 25–40% of patients with alcoholic cirrhosis and chronic active hepatitis, but for some reason, is less common in patients with primary biliary cirrhosis who also tend to be less susceptible to bacterial infection.[32] Similarly, serum opsonisation and chemoattractant activity are both less often and less severely impaired than in patients with fulminant hepatic failure. Unlike patients with fulminant hepatic failure, there is no clear relationship between complement levels and these serum functions. Nevertheless, even these milder defects of host defences increase the risk of infection in individual cases.

Studies *in vitro* of the function of polymorphonuclear leucocytes from patients with liver disease have shown a number of defects. Adherence to nylon wool of neutrophils from patients with fulminant hepatic failure is reduced, normal in chronic active hepatitis and primary biliary cirrhosis but results are conflicting in alcoholic cirrhosis.[33] Such differences are probably a reflection of difference in duration of exposure to split products of complement. Polymorphonuclear leucocytes from 50% of patients with severe alcoholic liver disease have reduced chemotaxis and aggregation possibly because of impaired cellular response to C5a complement component and/or the presence of serum antagonists closely related to IgA.[34 35] Polymorphonuclear leucocytes from patients with alcoholic liver disease show reduced phagocytosis and intracellular killing possibly because of the adverse influence of factors in the patient's serum but also depletion of intracellular glutathione and granule enzymes. The action of an inhibitory factor in serum from patients with primary biliary cirrhosis is thought to be responsible for reduced phagocytosis by these patient's polymorphonuclear leucocytes. These *in vitro* techniques have been applied to monocytes from patients with liver disease. Serum from patients with cirrhosis contains either an inhibitor or antagonist of chemotactic factors. Monocytes from patients with cirrhosis have reduced spreading bactericidal activity, phagocytosis, and intracellular killing.[36] Application of these *in vitro* studies to ascitic fluid from patients with cirrhosis has shown impaired bactericidal, bacteriostatic and opsonic activity for organisms which commonly cause spontaneous bacterial peritonitis.[22 37] Ascitic fluid also has impaired chemoattractant activity for polymorphonuclear leucocytes which may account for the low numbers of these cells found in ascitic fluid, even in the presence of serious infection.[38] The main reason for these defects in function of ascitic fluid is inadequate levels of complement, in part as a result of dilution by the large volume of ascites.[39] Indeed, patients with low (<1·0 g/l) concentration of total protein in the ascitic fluid have an increased risk of developing spontaneous bacterial peritonitis and diuresis increases concentration of proteins in the ascitic fluid and reduces the risk of peritonitis.[40 41]

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The future

Future progress will come from the identification of patients with an increased susceptibility to infection and methods of reducing this risk. Patients with cirrhosis, complicated by ascites and/or upper gastrointestinal haemorrhage are a high risk group as are the generally less common cases with fulminant hepatic failure. The use of prophylactic antibiotics and gut sterilisation on these patients warrants further investigation in controlled clinical studies.

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