**Progress report**

**Problems of bacterial infection in patients with liver disease**

Despite the widespread use of broad spectrum antibiotics, bacterial infection is responsible for up to a quarter of the deaths of patients with liver disease. The occurrence of bacterial infection in patients with different types of liver disease is difficult to ascertain from published reports, but the most susceptible seem to be those with alcoholic cirrhosis, especially when complicated by gastrointestinal haemorrhage. In a recent review of 187 patients admitted to hospital with alcoholic cirrhosis bacterial infection was present in 46% of cases, half of which were serious. In a four year follow up study of 37 patients with alcoholic cirrhosis the same authors found one or more episodes of bacterial infection in 38% of cases which proved fatal in nearly a third. In contrast, patients with chronic active hepatitis or primary biliary cirrhosis do not appear to be so susceptible to infection. 

Bacterial infection is extremely uncommon in patients with acute viral hepatitis or drug induced liver disease but may be responsible for up to 20% of deaths in the few cases which progress to fulminant hepatic failure or subacute hepatic necrosis.

Infection can prove fatal either directly or by precipitation of encephalopathy, gastrointestinal haemorrhage, or renal failure. Often recognition of infection is made more difficult by the absence of the normal clinical feature of infection — that is, fever, rigors, hypotension, and leucocytosis, in which case the only clues may be deterioration of hepatic precoma or coma or renal function.

Infection of the urinary tract, bacteraemia and pneumonia are the most common types of infection, although patients with ascites are particularly prone to spontaneous bacterial peritonitis. This article reviews progress in the diagnosis, treatment and understanding of susceptibility to bacterial infection of patients with liver disease.

**Bacteraemia**

The susceptibility to bacteraemia of patients with different types of liver disease is difficult to ascertain from the literature. In a study of patients with bacteraemia Javaloyes de Morlius et al, found that 11% had cirrhosis. Several reviews of bacteraemia caused by specific types of organism include patients who are described as ‘alcoholic’ or ‘cirrhotic’, but often histological evidence is lacking. Such cases tended to have a higher mortality, which the authors attributed to hepatic insufficiency rather than alcoholism per se.

There are few prospective surveys of the incidence of bacteraemia among patients with liver disease. Patients with chronic active hepatitis or primary biliary cirrhosis are rarely affected by bacteraemia. In contrast,
bacteraemia was documented in seven to 20% of patients admitted to hospital with cirrhosis.\textsuperscript{1,4,10-17,25,24} The mortality for bacteraemia in patients with decompensated alcoholic cirrhosis is about 70% compared with 30% for cases with compensated liver disease.\textsuperscript{16,25} Gram negative organisms are most frequently isolated from patients with decompensated cirrhosis (Table 1), while Gram positive organisms are more common in patients without hepatic decompensation.

Infection of the urinary or respiratory systems is responsible for half of the cases of bacteraemia, but a source of infection is found less often in patients with decompensated liver disease, in whom infection tends to be spontaneous.\textsuperscript{23} The frequent isolation of enteric organisms suggests that the gastrointestinal tract is an important source of infection.\textsuperscript{4,16,17} Further evidence comes from the reduction of bacteraemia with enteric organisms in patients with cirrhosis who are treated with gut sterilisation.\textsuperscript{21,22}

Bacteraemia occurs in up to 36% of patients in coma because of fulminant hepatic failure irrespective of the cause of hepatic necrosis.\textsuperscript{11,12,14,26,27} The likelihood of bacteraemia increases from the second day of coma. Infection may precipitate the initial encephalopathy or occur during the early phase of recovery with reoccurrence of encephalopathy.\textsuperscript{12,14} The main types of organism responsible (Table 1) are similar to those isolated from patients with chronic liver disease. The most common sources of bacteraemia are the respiratory or urinary tracts; infection from intravenous cannulae and arteriovenous shunts is rare unless vascular access is through the groins.\textsuperscript{13,14,27} Bacterial infection should be suspected if encephalopathy develops in the presence of mild liver damage, which would not be expected to account for the patients' deteriorating consciousness.

### Pneumonia

Death from pneumonia is more common among alcoholics, than age and sex matched controls and mortality is higher for women and those with hepatomegaly.\textsuperscript{28,29} Alcoholics suffer more complications with prolonged

| Table 1 Types of organisms responsible for bacteraemia in patients with liver disease |
|---------------------------------|-----------------|-----------------|
| Type of organism                | Chronic liver disease* (%) | Fulminant hepatic failure† (%) |
| Gram positive                   | 58              | 61              |
| Staphylococci                   | 21              | 17              |
| Streptococci                    |                 |                 |
| Group B haemolytic              |                 |                 |
| Pneumoniae                      | 16              | 13              |
| Viridans                        | 5               | 4               |
| Bacillus sp.                    |                 |                 |
| Clostridium welchii             |                 |                 |
| 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              |                 |

Adapted from: *Jones et al (1967)* \textsuperscript{16} †Wyke et al (1982) \textsuperscript{14}. 
fever and consolidation, increased incidence of abscess formation, empyema and atelectasis. Respiratory infections, in particular pneumonia, were present on admission in up to 11% of patients with cirrhosis especially of the alcoholic type and were associated with a mortality of 30%.\(^9\) Pneumonia is responsible for 5% of deaths from primary biliary cirrhosis\(^8\) but no recent data are available for patients with chronic active hepatitis. Patients recumbent with ascites or bleeding from oesophageal varices, especially if managed with a Sengstaken Blakemore tube, are prone to develop chest infection. Several reviews of pneumonia due to a particular type of organism include patients who are described as alcoholic. Thus approximately half of the patients with primary klebsiella pneumonia, pneumonia due to Gram negative bacteria or pneumococci, or adults with pneumonia due to *Haemophilus influenzae* are alcoholics.\(^{30,31}\) The mortality is related to the presence of hepatic insufficiency or leucopenia or both rather than alcoholism itself.\(^{31,32,33}\)

Although patients with alcoholic liver disease seem to be most susceptible to pneumonia there is still a need for up to date data on the occurrence and outcome of pneumonia in different types of liver disease.

**Tuberculosis**

Despite the decline in the incidence of tuberculosis in the general population, studies from several countries, with similar life styles and incidences of tuberculosis, show increasing numbers of alcoholics among patients with tuberculosis.\(^{34,36}\) Alcoholics tend to have more advanced tuberculosis at the time of presentation, more adverse effects from chemotherapy, poorer compliance, and increased incidence of drug failure.\(^{34,35}\) Fortunately, when adequate therapy has been completed there is no significant difference in relapse rates between patients with and without a history of alcoholism.\(^37\) Recent reviews of abdominal tuberculosis make no mention of alcoholics or cirrhotics, and only sporadic cases are reported in series of patients with liver disease and spontaneous bacterial peritonitis.\(^{38,39}\) Immunosuppressive therapy administered to patients with liver disease may result in development of tuberculosis either *de novo* or by reactivation. Patients with liver disease, particularly those with evidence of past infection with tuberculosis, should be monitored regularly for evidence of reactivation especially while receiving immunosuppressive therapy.

**Urinary tract infections**

A recent report has shown that bacteriuria occurs more than twice as often among women with primary biliary cirrhosis (19%) compared with those with other types of chronic liver disease (7%) (including chronic cholestasis), chronic inflammatory conditions such as rheumatoid arthritis (8%), or age matched controls (6%).\(^40\) Half of the episodes were asymptomatic and during a two year follow up, half of the patients developed recurrent attacks which is double the expected rate even for women with recurrent bacteriuria. The types of organism(s) isolated were the same as for patients without liver disease, with *E coli* responsible for 70% of episodes. Bacteriuria was not related to the degree of cholestasis or abnormalities of the renal tract, and only two patients developed acute
pyelonephritis. The reasons for this susceptibility to bacteriuria of patients with primary biliary cirrhosis is not understood. Renal infections occur in up to 40% of patients admitted to hospital with cirrhosis irrespective of the cause. Unfortunately most series do not include patients with primary biliary cirrhosis.\textsuperscript{2,4} Urinary tract infections accounted for half of the infections occurring in a prospective study of patients with decompensated cirrhosis, especially those with impaired reticuloendothelial function.\textsuperscript{4} Urinary tract infection has been implicated as the source of bacteraemia in up to 50% of patients with cirrhosis, 20% of episodes of spontaneous bacterial peritonitis, and isolated cases of infective endocarditis.\textsuperscript{16 17 41 42}

**Bacterial endocarditis**

Bacterial endocarditis is rare in patients with liver disease, affecting mainly those with alcoholic cirrhosis.\textsuperscript{43-47} When data from two retrospective necropsy surveys are combined there is no significant difference in the frequency of endocarditis among patients with and without cirrhosis (1.33 and 0.81% respectively).\textsuperscript{46 47} The frequency of endocarditis among patients admitted to hospital with cirrhosis was about 0.34% compared with 0.1% of patients without cirrhosis.\textsuperscript{48} Although the difference is significant (p<0.05), the frequency of endocarditis among patients without cirrhosis is low possibly because of the highly selected population of the Veterans Administration Hospitals. Non-rheumatic calcific aortic stenosis appears to be more common in patients with cirrhosis\textsuperscript{43 45 46} and may account for this valve being the most common site for infection. The types of organism responsible differ from those isolated from patients without cirrhosis, with more frequent isolation of enteric Gram-negative bacteria and pneumococci.\textsuperscript{45 46 48} Indeed pneumococcal endocarditis occurs almost exclusively in patients who are alcoholic or cirrhotic\textsuperscript{49 45} and may be accompanied by pneumococcal pneumonia or meningitis. The mortality from infective endocarditis is high and the diagnosis is easy to overlook in a patient with decompensated liver disease. Thus, it may be necessary to cover invasive practical procedures with prophylactic antibiotics especially in patients with prosthetic or congenital abnormalities of valves or with a particular predisposition to bacterial infection.\textsuperscript{49}

**Bacterial meningitis**

Bacterial meningitis is also rare in patients with liver disease, there being isolated reports of pneumococcal meningitis in patients with alcoholic cirrhosis and primary biliary cirrhosis.\textsuperscript{8 50} Reviews of patients with bacterial meningitis include patients who are described as alcoholic but histological evidence of liver disease is seldom presented. From these reviews alcoholism was present in 25% of patients with pneumococcal meningitis, 6% with meningococcal meningitis, 19% with meningitis due to Listeria monocytogenes, and 12% of cases of meningitis due to other types of organisms.\textsuperscript{45 51 55} The diagnosis can be readily overlooked especially in alcoholic patients who are confused or encephalopathic and prone to head injury, which predisposes to meningitis.\textsuperscript{51 56} Mortality of meningitis in patients with liver disease is difficult to ascertain from these reports but appears to be especially high for infection with pneumococci.\textsuperscript{19 45}
Spontaneous bacterial peritonitis

The syndrome of spontaneous bacterial peritonitis was brought into prominence between 1964 and 1975 by Conn and Colleagues. They defined it 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. Patients with alcoholic cirrhosis represented 98% of cases in early studies, mainly from Veterans Administration Hospitals, but increasingly the syndrome has been recognised in patients with ascites caused by other types of liver disease. In some recent reports from Europe less than 25% of patients have alcoholic cirrhosis with large numbers of cases of chronic active hepatitis. This may be a reflection of the frequency with which certain types of liver disease occur in the catchment population. A recent publication reports peritonitis in children with severe chronic liver disease and ascites. Even patients with ascites complicating acute liver diseases, such as subacute hepatic necrosis and Budd-Chiari syndrome, can develop bacterial peritonitis. Regardless of the aetiology all patients who develop spontaneous bacterial peritonitis have severe liver disease usually with evidence of portal hypertension.

Early mainly retrospective studies of spontaneous bacterial peritonitis found a prevalence of 4–6% in patients admitted with cirrhosis and 8% in those with ascites. Prospective studies have shown a genuine increase to around 20% in patients with cirrhosis and ascites. This increase may be because of greater familiarity with the condition and the recognition of less typical forms which can precede the development of the full blown syndrome. Indeed, ascites is no longer a prerequisite of spontaneous bacterial peritonitis as cases have been recognised in the absence of ascites. This has, however, usually accumulated soon after the diagnosis.

The clinical features of the classic ‘full blown’ syndrome are increasing hepatic decompensation with fever or rigors, nausea, diarrhoea and abdominal pain which is often generalised and colicky. Signs of peritonism are absent ‘silent’ peritonitis in up to 30% of cases and the only indication may be general deterioration with onset of encephalopathy, gastrointestinal haemorrhage or deterioration in renal function.

Laboratory features of spontaneous bacterial peritonitis

Confirmation of the diagnosis still rests on isolation or identification of the organism(s) from an aliquot of the ascitic fluid. The yield of positive cultures can be doubled, by inoculation of ascitic fluid into blood culture bottles at the bedside, but this is at the risk of an increased yield of contaminants. A Gram’s stain of the centrifuge pellet from the ascitic fluid is positive in only a third of cases and may be misleading in a third, possibly because the organisms are not viable. The appearance, protein content and lactate dehydrogenase and glucose concentrations of the ascitic fluid are unreliable for distinguishing between infected and sterile samples.

For some years bacterial peritonitis has been suspected when the ascitic fluid contained more than 300 white cells/cu mm, more than 25% of which are polymorphonuclear leucocytes: however, there is some overlap between patients with and those without evidence of infection. The observation in 1981 that diuretic treatment could increase the total white cell
concentration up to 2000/cu mm necessitated a change to the measurement of the actual number of polymorphonuclear leucocytes in the ascitic fluid.8

The search for a rapid marker of infection has focused recently on the changes in pH and lactate concentration which accompany infection in other serous spaces.7 In 1982 ascitic fluid concentrations of lactate were reported to be raised in patients with spontaneous bacterial peritonitis, and an ascitic fluid pH of less than 7-3 was found in six patients with peritonitis compared with values of more than 7-39 for samples from 50 patients without infection.8-11 A low pH also occur in patients with peritoneal malignancy or peripheral blood acidosis.62-63 Although measurement of the gradient of pH between samples of ascitic fluid and arterial blood was reported to overcome the problem of systemic acidosis,62 the specificity of a pH of less than 7-35 was low and was no better than a polymorphonuclear leucocyte count of more than 500 cells/cu mm. Other studies have found that less than 30% of cases with infected ascitic fluid have a pH of less than 7-31 and even if the threshold is increased to 7-41 only 75% of cases are detected.65-83,88 The combination of an ascitic fluid polymorphonuclear leucocyte count of more than 500/cu mm and/or an arterial ascitic fluid pH gradient of more than 0-1 are thought to be diagnostic of peritonitis but require further validation.82 In view of the uncertainty of the value of pH estimation, patients should be treated if there is a clinical picture of bacterial peritonitis and the ascitic fluid contains more than 250 polymorphonuclear leucocytes/cu mm or more than 500 cells/cu mm in the absence of clinical features of peritonism.86

Variants of spontaneous bacterial peritonitis

Increased understanding of the natural history of spontaneous bacterial peritonitis has come from prospective surveys of the relation between the content of the ascitic fluid and clinical features of peritonitis (Table 2).60,64 Thus asymptomatic ‘bacteriascites’, a condition analogous to bacteriuria, has been found in 4% of patients with cirrhosis and ascites.66 Cases of ‘culture negative neutrocytic ascites’64 constitute up to 50% of episodes in prospective surveys75,87 and almost half of these episodes are associated with bacteraemia or urinary tract infection. The clinical signs of peritonitis and ascitic fluid neutrocytosis resolve after treatment with antibiotics. Both culture negative neutrocytic ascites and bacteriascites should be treated with antibiotics as both can progress to the ‘full blown’ syndrome.

Table 2 Relation of clinical signs and ascitic fluid content in patients with ascites

<table>
<thead>
<tr>
<th>Clinical signs of peritonitis</th>
<th>Ascitic fluid analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PMN count</td>
</tr>
<tr>
<td>Normal/sterile</td>
<td>None</td>
</tr>
<tr>
<td>‘Bacteriascites’</td>
<td>None</td>
</tr>
<tr>
<td>Culture negative neutrocytic or probable peritonitis</td>
<td>Yes</td>
</tr>
<tr>
<td>‘Silent’ peritonitis</td>
<td>*Minimal</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

PMN=Polymorphonuclear leucocyte; *=Some cases have fever or abdominal pain but without signs of peritonism.
Problems of bacterial infection in patients with liver disease

Bacteriology
Cultures of the ascitic fluid yield organism(s) in 50–70% of cases with isolation of a single type of organism in 90%. The types of organism isolated are similar to those responsible for bacteraemia in patients with liver disease. There is a predominance of enteric organisms, in particular E. coli, but pneumococci are isolated from nearly a quarter of episodes occurring in adults and most episodes in children. Infection with anaerobic bacteria is becoming more common but they are still isolated from less than 20% of episodes, usually as part of a polymicrobial infection. Why anaerobes are not isolated more often is unclear. No relation has been found between the type of organism isolated and clinical or laboratory features of infection. Synchronous bacteraemia occurs in 40% of cases especially those infected with E. coli or enteric organisms but is rare with anaerobes. The same organism is isolated in 20% of cases from the respiratory or urinary tracts and occasionally from the female genital tract.

Distinction of primary and secondary peritonitis
Acute abdominal emergencies occur in 3% of patients with cirrhosis, are associated with a mortality of 85% and may be difficult to distinguish from primary peritonitis. The distinction is vital as surgical intervention in patients with severe liver disease has a high morbidity and mortality. Neither symptoms nor signs including the presence of a pneumoperitoneum on radiograph film can distinguish primary from secondary peritonitis. The ascitic fluid total white cell count and concentrations of protein tend to be higher in patients with secondary peritonitis but with poor discrimination in the individual case. There are no distinguishing microbiological features, although isolation of Candida albicans in the absence of systemic candidiasis or a recent intra-abdominal procedure is said to be suggestive of gut perforation. The value of laparoscopy in elucidating the cause of peritonitis is not established and could be hazardous in such gravely ill patients.

Treatment and outcome
The choice of antibiotic may be influenced by the Gram’s stain of the ascitic fluid or presence of infection at other sites. If a ‘best guess’ regimen is necessary current practice favours cefotaxime which is superior to ampicillin and tobramycin in the treatment of severe infections in patients with cirrhosis. Cefotaxime has the advantage of high tissue concentrations with a wide therapeutic/toxic range and less risk of causing renal impairment than aminoglycosides. Metronidazole can be included for action against anaerobes but has a prolonged half life in patients with severe liver disease.

A further approach is to reduce the spread of enteric organisms from the bowel by gut sterilisation. The addition of oral non-absorbable antibiotics (colistin, neomycin, and nystatin) to conventional parenteral antibiotic therapy has been found to improve resolution of attacks from 27–53% and reduce mortality from 86–58%. These results are encouraging and require validation in larger randomised studies. Gut sterilisation may also reduce systemic endotoxaemia, which can cause gastrointestinal bleeding and renal failure. Another approach may be the use of human antiserum to endotoxin core glycolipid, which can reverse established shock in Gram negative septicaemia and warrants evaluation in patients with liver disease.
About 40% of patients die within the first week of peritonitis. They tend to have the most severe liver disease complicated by renal impairment and features of systemic infection. Hospital mortality is lower for patients with bacteriascites but not for sterile neutrocytic cases or those with simultaneous bacteraemia. Recurrent attacks of spontaneous bacterial peritonitis or another type of infection, usually with the same type of organism, occur in up to 40% of survivors and have an equally bad prognosis as the initial attack.

**Reasons for development of bacterial infection**

The development of bacterial infection is often preceded by certain events, the most common of which is gastrointestinal haemorrhage especially from oesophageal varices. A major source of infection is the gut and a recent study has shown that the frequency of infection after gastrointestinal haemorrhage can be reduced by prophylactic gut sterilisation. The control of variceal bleeding by balloon tamponade or endoscopic injection sclerotherapy can result in bacteraemia and pneumonia. Bacteraemia associated with sclerotherapy is usually transient, occurring at the time of injection of the varix. Other risk factors are the use of long needles for injection and the presence of severe hepatic decompensation.

Although fibreoptic endoscopy can cause transient bacteraemia whether this is more common or more sustained in patients with liver disease is not known. A quarter of attacks of spontaneous bacterial peritonitis are preceded by abdominal paracentesis, but it is difficult to establish whether the procedure is responsible.

Infection has been associated with mesenteric angiography, especially when accompanied by infusion of vasopressin. The resulting mesenteric vasospasm may impair gastrointestinal mucosal nutrition, and thus favour spread of infection. Liver biopsy even in patients with sterile liver tissue can result in transient bacteraemia in up to 30% of cases and may be higher for patients with infections of the liver. Poor dentition has been implicated as a source of bacteraemia, infective endocarditis, and spontaneous bacterial peritonitis in patients with cirrhosis or severe liver disease and emphasises the need for regular dental surveillance.

The formation of a peritoneovenous (‘le Veen’) shunt is complicated by major sepsis in 20% of patients. Wound infections occur in 10% of patients and bacterial peritonitis in 14%, which usually necessitates removal of the shunt. The clinical features of peritonitis are the same as those seen with spontaneous bacterial peritonitis but the organisms responsible include equal numbers of *Staphylococcus aureus* and Gram negative enteric organisms. Although this type of peritonitis is similar clinically and microbiologically to that associated with chronic ambulatory peritoneal dialysis, the mortality (25%) is higher probably because of the patient’s poorer general physical condition and underlying liver disease.

**Defects of host defences against bacterial infection**

The predisposition of patients with liver disease to infections with encapsulated organisms points to defects in humoral and polymorphonuclear leucocyte function rather than the function of macrophages. The interaction of these host defences against bacterial infection are shown in the
Problems of bacterial infection in patients with liver disease

Figure. Circulating host defence mechanisms against bacteria. Dotted line represents sequence of events for killing of serum sensitive bacteria.

Figure. Several of these humoral and cellular host defences have been studied, mostly in vitro, in patients with liver disease especially those with alcoholic cirrhosis.

Humoral defences

1 Antibody
Concentrations of immunoglobulins are generally increased in patients with acute and chronic liver disease, especially those with portal hypertension. Yet bactericidal function of serum IgM for certain types of E coli is impaired in 80% of patients with cirrhosis. Susceptibility to pneumococcal infection does not appear to be related to either deficiency or failure to produce specific antibody to pneumococci.

2 Complement
Deficiency is most severe in patients with severe acute liver disease especially those cases who develop fulminant hepatic failure (Table 3). Deficiencies tend to be less frequent and less severe among patients with chronic liver disease occurring mainly in those with active liver damage and/or cirrhosis (Table 3). But concentrations of complement tend to be normal in patients with primary biliary cirrhosis, who also suffer fewer problems with infection.

3 Opsonisation
This depends on complement function and hence tends to be normal in patients with acute viral hepatitis and drug induced liver disease unless
hepatic failure has developed (Table 4). The severe deficiency of complement in the hepatic failure patients results in impaired opsonisation which can be improved by transfusion of fresh frozen plasma and usually returns to normal within a week of recovery from coma. Defects of opsonisation are both less common and less severe in patients with chronic liver disease especially those with primary biliary cirrhosis (Table 4). Levels of complement factors, although decreased in some of these patients with chronic liver disease do not correlate with the defect of opsonisation. In contrast, serum bactericidal activity which is impaired in some patients with post-necrotic cirrhosis is correlated with deficiency of complement. Defects of complement and yeast opsonisation occur in children with chronic liver diseases and impaired opsonisation of pneumococci may predispose such children to pneumococcal peritonitis.

4 CHEMOATTRACTANT ACTIVITY
The ability of serum to stimulate the movement of normal polymorphs is reduced in most patients with fulminant hepatic failure, in 60% of patients with alcoholic liver disease, and less than a third of cases of chronic active

<table>
<thead>
<tr>
<th>Type of liver disease</th>
<th>Finding</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Acute viral hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Fulminant hepatic failure</td>
<td>Deficiency of classical pathway factors, especially in acute stage and with serum sickness</td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Alcoholic cirrhosis and/or hepatitis</td>
<td>Generally minor deficiencies of classical and alternate pathways. Most severe if liver disease decompensated. Unrelated to HBsAg status</td>
<td></td>
</tr>
<tr>
<td>(b) Chronic active hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Cryptogenic cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Primary biliary cirrhosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4  Studies of serum opsonisation in liver disease

<table>
<thead>
<tr>
<th>Type of liver disease</th>
<th>Finding</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Acute viral hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Fulminant hepatic failure</td>
<td>Deficit for <em>S. aureus</em> in severe hepatitis with encephalopathy Severe defect for <em>E. coli</em> and yeasts in most cases. Unrelated to aetiology of hepatic necrosis</td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Alcoholic cirrhosis and hepatitis</td>
<td>Impaired opsonisation of <em>E. coli</em> and yeasts in 25–60% of patients. Generally those with most severe liver disease Isolated cases have defect only for yeasts</td>
<td></td>
</tr>
<tr>
<td>(b) Chronic active hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Cryptogenic cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Primary biliary cirrhosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of liver disease</th>
<th>Finding</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Acute viral hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Fulminant hepatic failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Alcoholic cirrhosis and hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Chronic active hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Cryptogenic cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Primary biliary cirrhosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

? Cell-directed antagonist in patient's serum
Serum deficiency probably complement
Deficiency of heat-labile opsonin not correlated with complement levels
? Defect of the alternate pathway but levels are normal
hepatitis or cryptogenic cirrhosis. In common with other serum defects in fulminant hepatic failure, complement deficiency seems to be the prime reason. But the defect in serum from patients with alcoholic liver disease is caused by the presence of inhibitors or antagonists of the normal chemotactic factors, substances with anticomplementary activity or proteases have been postulated.

**CELLULAR ACTIVITY**

Studies of patients’ polymorphonuclear leucocytes include: (1) Neutrophil adherence which is increased in patients with alcoholic cirrhosis, normal in chronic active hepatitis and primary biliary cirrhosis, and reduced in cases of fulminant hepatic failure. (2) Stimulated movement of polymorphonuclear leucocytes has been found to be reduced in children and adults with acute or chronic liver disease. In adults with severe alcoholic liver disease an abnormal cellular response to C5a complement component has been postulated. (3) Phagocytosis and intracellular killing of bacteria opsonised in normal serum have shown conflicting results in patients with liver disease. Cells from children who are carriers of hepatitis B surface antigen have impaired bactericidal activity, but whether this is primary or secondary to the carrier state is not known. Although studies of adults with acute or chronic liver disease have usually shown normal cellular function, recent work has shown defects of cells from patients with alcoholic cirrhosis and hepatitis because of depletion of intracellular glutathione and granule enzymes.

**RETICULOENDOTHELIAL SYSTEM**

The Kupffer cells, which form a vital defence against infection, are reduced in number in liver biopsies from patients with chronic active hepatitis, primary biliary cirrhosis and other types of cirrhosis. Kupffer cell function, assessed in vivo, is normal in patients with acute or chronic hepatitis without cirrhosis, but is impaired in 40% of patients with cirrhosis and in most patients in coma from fulminant hepatic failure.

Impaired Kupffer cell phagocytic functions have recently been associated with a bad prognosis and increased susceptibility to infection in patients with decompensated alcoholic cirrhosis. In this study, half of the episodes of bacteraemia were preceded by gastrointestinal haemorrhage, which can depress transiently reticuloendothelial function and thus result in spread of infection. Plasma fibronectin, an opsonin for Kupffer cells, is often deficient in patients with liver disease.

Monocytes have several roles in defence against infection including chemotaxis, phagocytosis, intracellular killing, and secretory functions which include the production of complement factors. Monocyte function in patients with liver disease has been reviewed recently and hence will not be discussed in detail here. Briefly, patients with liver disease especially those with cirrhosis have impairment of chemotaxis caused by circulating serum inhibitors, phagocytosis, and intracellular killing and spreading.

**HOST DEFENCE OF ASCITIC FLUID**

Normal peritoneal fluid has antimicrobial activity for a number of organisms. In contrast, ascitic fluid from patients with cirrhosis has impaired antimicrobial or opsonic activity for *E coli, Streptococcus faecalis*, and pneumo-
coccii, organisms which commonly cause spontaneous bacterial peritonitis, but is bacteriostatic towards bacteroides, which is an uncommon cause of infection. These defects are related to deficiency of immunoglobulin and complement, especially of the alternate pathway, probably because of dilution by the large volume of fluid. In the presence of these hormonal defects, killing of bacteria depends on contact between leucocytes and organisms as a result of random collision. The low concentration of white cells in the ascitic fluid from some patients, perhaps because of impaired chemotaxis, will reduce the chance of contact with bacteria.

EFFECT OF ALCOHOL ON HOST DEFENCES

Studies of animals intoxicated with alcohol have shown impairment of glotic closure, alveolar macrophage migration, mobilisation of white cells into the peritoneum, leucocyte phagocytosis, and killing of bacteria. Infusion of alcohol to human volunteers has resulted in a reversible depression of serum bactericidal activity for some strains of *E coli* and *Haemophilus influenzae*, possibly because of impaired synthesis of complement. Acute alcohol abuse can have a direct toxic effect on the bone marrow resulting in granulocytopenia, while malnutrition among chronic alcoholics results in cutaneous anergy.

Conclusions

There is good evidence that patients with decompensated alcoholic cirrhosis, especially those with impaired reticuloendothelial phagocytic function and/or gastrointestinal haemorrhage, are at greatest risk of infection, and this often proves fatal. Infection rarely occurs in patients with acute liver disease, chronic active hepatitis or primary biliary cirrhosis unless these are complicated by hepatic decompensation. Patients with primary biliary cirrhosis, however, are susceptible to bacteriuria. The reasons for this are not understood. The most common problems are bacteraemia, pneumonia, urinary tract infection, and, in patients with ascites, spontaneous bacterial peritonitis. The only indication of infection may be increasing encephalopathy or deterioration of renal function.

Infection is usually due to Gram negative enteric organisms, especially *E coli*, and streptococci, in particular the pneumococcus. Infection with anaerobes is unusual. Patients with alcoholic liver disease are susceptible to pneumococcal endocarditis and meningitis. The syndrome of spontaneous bacterial peritonitis is now recognised in patients with ascites due to most types of liver disease. Analysis of the white cell content of the ascitic fluid still provides the best early indicator of peritonitis and has led to recognition of early less florid cases.

Reasons for susceptibility to infection have been discussed and attention is drawn to the potential hazards of invasive practical procedures. Humoral and cellular host defences against infection are most frequently impaired in patients with alcoholic cirrhosis and fulminant hepatic failure. Patients with defective reticuloendothelial phagocytic function and decompensated liver disease have a high risk of infection and a worse prognosis. Patients with decompensated liver disease also have impaired complement function which results in defects of serum and ascitic fluid antibacterial activity. Impaired antibacterial activity of patients' polymorphonuclear leucocytes and mono-
cytes appears to be due to the influence of serum factors rather than a primary cellular defect. The reasons for patients with primary biliary cirrhosis having less bacterial infections and fewer defects of host defence is not clear.

If the occurrence and mortality of bacterial infection is to be reduced then effective prevention, early diagnosis, and treatment are essential. High risk patients must be identified and rigorous microbiological screening undertaken. Such patients probably should have prophylactic antibiotics during invasive practical procedures. Parenteral broad spectrum antibiotics should be commenced when infection is suspected. Gut sterilisation with non-absorbable antibiotics shows promise in both prevention and treatment of infection and warrant further evaluation.

R J WYKE

Walsgrave Hospital,
Coventry
CV2 2DX

References


Problems of bacterial infection in patients with liver disease

638

Wyke

Problems of bacterial infection in patients with liver disease


108 Conn HO. Bacterial peritonitis; Spontaneous or paracentetic? Gastroenterology 1979; 77: 1145–6.


124 Thomas HC, Potter BJ, Elias E, Sherlock W. Metabolism of the third component of complement in acute type B hepatitis, HBs Antigen positive glomerulonephritis, polyarteritis nodosum, and HBs antigen positive and negative chronic active liver disease. Gastroenterology 1979; 76: 673–9.


Problem of bacterial infection in patients with liver disease


Problems of bacterial infection in patients with liver disease.

R J Wyke

*Gut* 1987 28: 623-641
doi: 10.1136/gut.28.5.623

Updated information and services can be found at:
http://gut.bmj.com/content/28/5/623.citation

**Email alerting service**

*These include:*

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections
- Pancreas and biliary tract (1949)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/