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Leading article

Spontaneous bacterial peritonitis

Infection of ascitic fluid without any apparent intra-abdominal foci of sepsis – spontaneous bacterial peritonitis (SBP) – is an often fatal complication of cirrhosis. Early publications emphasised the atypical features of such peritonitis and the frequency of misdiagnosis.[1–4] The 16 year review by Conn[4 5] in which the earlier prevalence of 8% in cirrhosis with ascites was reported to have risen to 18%, lend credence to the view that there has been a true increase in SBP, quite apart from enhanced clinical awareness. The latter has resulted in the detection of a large number of patients with minimally symptomatic infections, which is well illustrated in one recent study[6] embracing a five year period, which showed a 12-fold increase in the number of cases diagnosed with an atypical presentation of SBP compared with a four-fold rise in those with a more characteristic picture of peritonitis. Overall prevalence figures in more recently reported series approach 25%.[7 8]

This review addresses three questions: (1) What is the pathogenesis of this syndrome and can predisposing factors be identified? (2) When should it be suspected and what is the best means of diagnosis? (3) How can survival be improved?

Pathogenesis and predisposing factors

Infection with a single organism, usually enteric, is found in most cases.[5 6] Gram negative bacilli are present in about 70% of isolates and are principally *E coli*.[5 7 9] Gram positive cocci, particularly pneumococcus, comprise an additional 10–20% of cases[9–10] while anaerobes are found in 6–14%.[11] The latter require special conditions of culture and are most often isolated when multiple organisms are grown.[6]

The frequent isolation of enteric organisms suggest that the gut is the most likely source of infection. Studies in patients with cirrhosis have shown colonisation of the upper small bowel with colonic flora.[12] When portal hypertension is present permeability of the gut wall may be affected by oedema of the splanchnic tissues because of venous and lymphatic congestion. Organisms may be able to migrate across the gastrointestinal mucosa as the presence of hypertonic solutions in the peritoneal cavity of dogs results in the spread of *E coli* from the gut.[13] A similar explanation has been invoked to explain enteric bacterial peritonitis which sometimes occurs with peritoneal dialysis. If this was the mechanism, however, one would expect a larger proportion of ascitic infections to be due to anaerobes as they are a major constituent of the intestinal flora.[14] A small number of patients with infections of the respiratory, or urinary tract also develop SBP with the same organism,[6 7] which suggests that haematogenous spread occurs. Infection in the chest may also spread to the peritoneal cavity through transdiaphragmatic lymphatics. Bacteraemia caused by enteric organisms is a well recognised

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complication of patients with chronic liver disease.[1 3] Indeed in at least 50% of patients the same organism is simultaneously isolated from blood and ascites, whilst in others blood cultures are positive when ascitic fluid is sterile.[5 15] Clinical and experimental data suggest that impaired function of the reticulo endothelial system (RE), in particular the Kupffer cells of the liver, together with intrahepatic and portasystemic shunting of blood, is important in the genesis of bacteraemia and SBP.[16–19] Enteric bacteria normally removed by the hepatic RE system would then pass directly into the systemic circulation and could give rise to SBP. Against this hypothesis is the observation that several studies have failed to isolate organisms from the portal blood of cirrhotic patients.[20–21] Whether peritonitis is a primary factor, or a consequence of bacteraemia is thus unclear.

Irrespective of the route of infection, the persistence of bacteraemia and spread of infection will be enhanced by defects of host defences, which are well recognised in patients with severe liver disease. Defects of serum bactericidal function,[22] opsonisation,[23] chemoattraction,[24 25] low serum concentrations of fibronectin[26] and impaired function of polymorphonuclear leucocytes and monocytes[27] in such patients will compromise clearance of bacteria. Malnutrition and alcoholism which often coexist in these patients are also known to impair host defence mechanisms. Although normal peritoneal fluid has antimicrobial activity for a number of organisms, ascitic fluid from cirrhotics has been shown to have impaired, or deficient antimicrobial, or opsonic activity for *E coli*, streptococcus faecalis and pneumococci.[28–30] Interestingly, in those studies ascitic fluid was bacteriostatic for bacteroides, which may explain the uncommon isolation of these organisms.

Relationship to invasive procedures

Invasive procedures such as fibreoptic endoscopy, sigmoidoscopy, balloon tamponade, or paracentesis are potential vehicles of infection.[31–35] In most series, however, no direct relation between SBP and such procedures has been found.[5 6 36] Experimental studies have shown, however, that gastrointestinal haemorrhage and acute hypovolaemia may increase intestinal permeability to enteric bacteria and impair hepatic RE function.[37 38] Indeed, it has recently been reported that the incidence of SBP is particularly high immediately after gastrointestinal bleeding and that prophylactic administration of non-absorbable antibiotics is effective in prevention.[39] Arteriography, especially when accompanied by injection of Vasopressin, has been implicated as a precipitant of SBP,[40] particularly involving anaerobic organisms. The accompanying vascular spasm and hypoxia may impair gastrointestinal mucosal nutrition and favour transmural spread of bacteria.[41–43]

Clinical and laboratory diagnosis

Although fever, abdominal pain or tenderness do occur in most patients, symptoms are often minimal and easily overlooked.[5–7 36 44 45] Nausea, vomiting, or diarrhoea are common. In one third or more of patients there are no symptoms, or signs directly referable to the abdomen.[5 7]

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Indirect features pointing to the presence of peritonitis comprise deterioration in hepatic or renal function. Increasing encephalopathy or ascites are particularly common. Such features could readily be attributed to spontaneous progression of liver disease, hence a high index of suspicion is needed. A recent study[6] has confirmed our experience that a rising creatinine, or temporary resistance to diuretics is often an early sign in such patients.

Diagnostic aspiration of 20 ml ascitic fluid is thus required in a patient with any of these features. In view of the high mortality (48–70%),[6 7 9 36] early diagnosis and treatment are imperative, but as the results of bacterial culture are not available for 24–48 hours reliance has to be placed on other characteristics of ascitic fluid infection. Cloudy fluid is present in more than three quarters of patients with SBP and in one third of those with sterile ascites.[10 36] Protein, lactic dehydrogenase concentration and glucose content, although of value in the diagnosis of infection within the pleural space, joint cavity or cerebro-spinal fluid (csf), are not very helpful in the diagnosis of bacterial peritonitis.[10 46 47] Normal values for protein fall within a range of 0·1–9·6 g/l (mean 2·0±0·1) compared to 0·5–4·7 g/l (mean 1·6±0·1) in SBP. The range of glucose concentrations is similarly wide and only 8% of patients with SBP have a low ascitic fluid glucose with respect to blood.[10] A gram stain of a centrifuged deposit of ascitic fluid should be examined, although organisms are only detected in one third of cases in which SBP is subsequently proven by bacterial culture.[5 6 36]

The commonest way in which diagnosis is established, or even considered is by measurement of the ascitic fluid white cell count. Sterile ascites normally contains less than 300 WBC/mm^3, most of which are lymphocytes and less than 25% polymorphs. Thus a diagnosis of SBP was considered probable when these values were exceeded,[5 9 10] although others have suggested that this cut off point is too low, because such numbers of white blood cells can be found in up to 50% of patients with sterile ascites.[44 48] Administration of diurectics, however, has now been shown to increase the ascitic fluid white cell count.[49] As the volume of ascites decreases, protein concentration and numbers of lymphocytes (which have a long life cycle) increase, while polymorphonuclear cells (which have a short lifespan) decrease in the absence of infection. This important observation suggests that the total WBC count should no longer be used as the criterion for the diagnosis of SBP. Instead the diagnosis must be based on the number of polymorphonuclear cells >250/mm^3, if there is any suspicion of infection.[50]

Before this observation the lack of specificity of the ascitic white blood cell count as an accurate marker of infection prompted investigation of other means of diagnosis. Much interest followed reports that the pH of cerebrospinal fluid, pleural and joint fluid produced good discrimination between sterile and infected exudates.[51–53] Gitlin subsequently reported that an ascitic fluid pH of 7·31 accurately identified all five of 56 patients with SBP.[54] Several short reports[8 55–57] together with the paper by Scemama-Clerque and colleagues[58] in this issue have not confirmed this intial experience. In Kao and Reynolds[55] study none of their five patients with SBP had a pH below 7·31. Similarly Martin and Galambos[56] studying 45 ascitic fluid specimens found that although ascitic fluid pH of patients

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with SBP was lower than the sterile group (pH 7·31±0·13 *vs* 7·39±0·11 $p<0·05$), the data were so widely scattered that pH could not reliably identify patients with SBP. Garcia-Tsao and Conn[57] found measurement of pH to be far less sensitive than the ascitic cell count, although it did add to the specificity. Stassen *et al*[59] in a study of only five patients with SBP found little difference between the tests. As might be expected, similar results are to be found by measurement of the ascitic fluid lactate levels.[56 57 59 60] The weight of evidence therefore, suggests that an ascitic fluid polymorphonuclear cell count of $>250/mm^3$ remains the best index for the diagnosis of SBP before the results of bacterial culture are available.

How can survival be improved

The high prevalence of SBP dictates that ascites should be treated promptly. Further prospective studies need to be undertaken to determine the importance of predisposing factors and the risk of infection with invasive procedures. Prophylaxis with antibiotics may be appropriate in certain patients. The value of gut sterilisation to prevent SBP in patients with upper gastrointestinal bleeding, a proposed high risk group,[39] merits further study. As host defence mechanisms are impaired intercurrent infections should be treated energetically. Continued awareness of the syndrome, examination of ascitic fluid at the first sign of clinical deterioration and immediate intravenous antibiotics if infection is confirmed, are vital. Early effective antibiotic therapy is an important correlate of survival and rational use of antibiotics is imperative. A cephalosporin, or ampicillin plus an aminoglycoside and metronidazole have been suggested as an appropriate antibiotic regimen for patients with SBP,[61] as nearly 90% of isolated organisms would be susceptible *in vitro* to these agents. The efficacy *in vitro* may be much lower,[61 62] however, and Felisant and his colleagues[62] have shown in a randomised controlled study that cefotaxine is more effective than a combination of ampicillin and tobramycin in cirrhotic patients with severe infections, despite similar *in vitro* antibacterial activity. This difference in efficacy may be a function of the wide therapeutic/toxic ratio of the cephalosporins, such that high dosages with resultant maximal tissue levels can be achieved without adverse effects.[63 64] In contrast, aminoglycosides have a narrow therapeutic band above which nephrotoxicity occurs. Within this range antibiotic concentrations may be close to the minimum inhibitory concentration of the infecting organisms.[65 66] Indeed it has been suggested that this fact may be of critical importance in patients with impaired host defence mechanisms.[67] Also in favour of the use of a cephalosporin rather than an aminoglycoside in cirrhotic patients is the suggestion that such patients are predisposed to develop aminoglycoside nephrotoxicity,[61 68] which may be responsible for a number of late deaths.[6]

Nutritional support is a further area of potential importance. The high incidence of immuno-incompetence may underlie the frequent occurrence of spontaneous infections. The close association of malnutrition and anergy,[69] so common in patients with decompensated chronic liver disease, suggests a potentially reversible component to this abnormality.

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Where malnutrition alone is the cause of anergy, refeeding can restore immune competence,[70] and it is possible that host defences in patients with cirrhosis might be improved by more attention to nutritional therapy. Nevertheless, the severity of the underlying liver disease remains the most important determinant of survival.

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