Liver function in septic shock

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SUMMARY   Serum liver function tests were estimated in 57 patients admitted to an Intensive Therapy Unit (ITU) with a diagnosis of septic shock. Following an initial biochemical disturbance, persisting hyperbilirubinaemia was associated with a poor prognosis. Post-mortem liver histology in 22 patients showed varying degrees of non-specific reactive change, venous congestion, ischaemic necrosis, fatty change and intrahepatic cholestasis in 16 cases. In the remaining six cases there was moderately severe cholestasis with inspissated bile in the cholangioles. The possible aetiology of the observed cholestasis is discussed.

Although multiple organ failure is a frequent cause of death in patients requiring management in intensive therapy units (ITU) overt hepatic failure is rare and therapeutic support is usually focused on other organs, lungs, kidneys and heart in particular. However, Ledingham and McArdle recorded a 23% incidence of jaundice in a consecutive series of 113 patients with septic shock.[1] In the present retrospective study we have further investigated the incidence of hepatic dysfunction in some of these patients, and have attempted to show relationships between the hepatic dysfunction and the duration of shock and the subsequent clinical course in these patients. In addition, in a number of necropsies, we have noted a distinctive pattern of intrahepatic cholestasis and attention is drawn to this morphological feature.

Patients and methods

In the period 1975–1978, 66 patients with a diagnosis of septic shock, as defined by Ledingham and McArdle,[1] were admitted to the ITU at the Western Infirmary, Glasgow. Of these, nine were found to have pre-existing hepatobiliary or pancreatic disease or to have "preshock" disturbances of routine liver function tests (LFTs), and they were excluded from this study. Of the 57 patients studied, 27 survived, comprising 16 men and 11 women with a mean age of 48 ± 20 (SD) yr, and a mean stay in the ITU of 22 ± 18 days; the 30 in the non-survivor group comprised 18 men and 12 women, mean age 59 ± 10 yr, and a mean stay in the ITU of 14 ± 12 days.

The duration of the shock episode was defined as the time in hours during which the systolic blood pressure (SBP) remained at or below 100 mm of mercury, excluding isolated readings above this level; this could be accurately assessed in 40 of the patients. The primary source of sepsis in the patients was as follows: upper gastrointestinal tract (19), small intestine (7), large bowel (13), appendix (7), female genital (4), soft tissue (4), and others (3). Perforation of viscera and postoperative anastomotic dehiscence were the most frequent factors precipitating the septic shock episode.

Serial estimations of serum bilirubin (µmol/l), alkaline phosphatase (King Armstrong Units (KAU)/100 ml), glutamic oxalacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) (IU/l), total protein (g/l), and albumin (g/l), were carried out using standard laboratory techniques.

The Limulus lysate test[2] to detect endotoxaemia was carried out in 31 patients. The test was regarded as positive if obvious gel formation occurred after incubation of the patient's serum with the lysate for 4 h at 37°C. Blood cultures were performed each time a sample was taken for the endotoxin assay. Additional blood cultures were performed where clinically indicated.

A post-mortem examination was performed in 22 of the 30 patients who died and sections of liver tissue were examined using routine staining methods.

Results

The mean duration of shock for survivors was 13 ± 8 h and for non-survivors 23 ± 16 h. Positive blood cultures were obtained in 26 (46%) patients with Gram-negative organisms being isolated in 17 of these; *Escherichia coli* (in 8 patients) was the most

commonly cultured organism. The Limulus lysate test was positive in all of the 31 patients in whom this assay was performed.

Clinical jaundice was present in 36 (63%) patients, 24 of the non-survivors as compared with 12 of the survivors, a statistically significant difference (p < 0·001 − X^2 test). The results of the LFTs carried out within 48 h of the onset of the shock episode are summarised in Table I. In 85% of the patients at least one of the indices measured was found to be abnormal. There were no statistical differences (Student's *t* test) between survivors and non-survivors for any of the LFT indices. When mean values for LFT indices were compared 2, 5 and 10 days after the onset of shock, there was a significantly higher mean bilirubin level (p < 0·05, Student's *t* test) on day 10 in the 16 non-survivors (110 ± 28 μmol/l) as compared with 12 survivors (30 ± 8 μmol/1); the other indices were not significantly different between these two groups.

Analysis of the LFTs in relation to the duration of the shock episode is shown in Table 2. While this shows a trend towards more deranged LFTs the more prolonged the shock episode the results do not attain statistical significance.

POST-MORTEM EXAMINATION OF LIVER

Macroscopically the livers showed no unusual features and in none of the 22 cases examined was there any evident large duct obstruction. Microscopically the livers in 16 cases showed a number of changes comprising varying degrees of non-specific reactive changes with focal liver cell necrosis, Kupffer cell hyperplasia and portal tract inflammation, venous congestion, ischaemic necrosis, fatty change and intrahepatic cholestasis.

In six cases, however, the livers showed an unusual pattern of cholestasis. In these there was moderately severe cholestasis, predominantly perivenular but in some extending to the periportal zone; intracellular bile retention and canalicular concretions were present and there was a related reactive inflammatory process with Kupffer cell hyperplasia and aggregates of ceroid-laden macrophages. In addition, however, at the portal/parenchymal interface the cholangioles (canals of Hering) were prominently dilated, their epithelium swollen, and many of them contained inspissated strongly PAS-positive bile concretions (Figure). Neutrophil polymorphs were conspicuous within the dilated cholangioles and also surrounding them and extending into the periportal parenchyma. The portal tracts showed some mild oedema, with a light mixed inflammatory cell infiltrate. The bile ducts appeared unremarkable. No bile concretions were noted within them and there was no evident acute cholangitis.

Table 1 *Liver function tests within 48 hours of septic shock episode*

	Survivors (n = 27) Mean ± SEM	Non-survivors (n = 30) Mean ± SEM
Bilirubin (μmol/l)	44 ± 9	81 ± 21
Alkaline Phosphatase (KAU/100 ml)	11 ± 1	14 ± 2
SGOT (IU/l)	110 ± 30	105 ± 26
SGPT (IU/1)	46 ± 10	74 ± 21
Albumin (g/l)	31 ± 1	28 ± 1
Total protein (g/l)	58 ± 2	55 ± 1

n = number of patients.

**Table 2** *Liver function tests (mean ± SEM) in 40 patients within 48 h of the onset of septic shock related to the duration of the shock episode*

	Duration of shock episode (h)			
	6 (n = 9)	6–12 (n = 8)	13–24 (n = 16)	>24 (n = 7)
Bilirubin (μmol/1)	44 ± 12	36 ± 9	70 ± 17	151 ± 71
Alkaline Phosphatase (KAU/100 ml)	13 ± 2	12 ± 1	10 ± 1	13 ± 4
SGOT (IU/l)	53 ± 16	88 ± 20	114 ± 36	176 ± 86
SGPT (IU/l)	29 ± 12	52 ± 12	42 ± 9	142 ± 65

n = number of patients.

Discussion

Cardiogenic shock, bacterial sepsis, septic/endotoxin shock and toxic shock are recognised causes of liver injury. In acute cardiogenic or hypovolaemic shock with inadequate hepatic perfusion, ischaemic liver cell necrosis may be extensive resulting in jaundice with biochemical features resembling those seen in acute hepatitis.[3-5] Jaundice associated with lobar pneumonia was first reported in 1836,[6] and a review of the syndrome as it occurred in Western countries was published by Zimmerman and Thomas in 1951;[7] in recent years the syndrome has been reported mainly from African countries.[8] The term cholangitis lenta was applied in 1939 to a syndrome in which jaundice occurred in association with streptococcal infection.[9] Infection by Gram-negative bacteria in particular has, however, been most commonly associated with clinical jaundice, although a variety of organisms have been incriminated. This is a well known and important cause of jaundice in the neonatal period and in infants,[10 11] but which may also affect adults.[12-14] These topics have been well reviewed by Zimmerman and his colleagues.[15] In the newly recognised toxic shock syndrome, associated with an exotoxin produced by *Staphylococcus aureus*, jaundice is a frequent feature[16] and in one series of 22 patients cholestasis was a feature in all.[17]
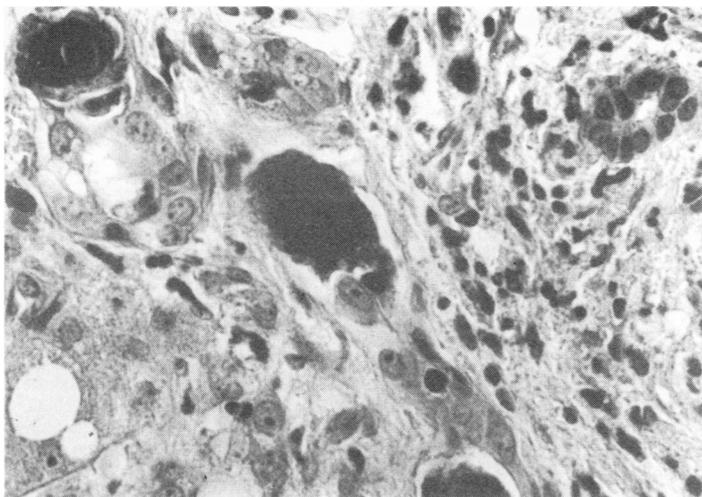
Post-mortem liver from a patient dying with septic shock following an antrectomy for a gastric carcinoma. There is a mild chronic inflammatory cell infiltrate in the portal tract, but note that the bile duct appears normal and there is no cholangitis. At the portal parenchymal junction a number of dilated cholangioles are seen containing bile concretions. The cholangiolar epithelium is swollen and shows some cytoplasmic vacuolation; a light neutrophil polymorph infiltrate is present around the dilated cholangioles. Haematoxylin & eosin × 490

In the present retrospective study we have found that in a series of 57 patients with septic shock jaundice was a feature in 63%, and in 85% of patients one or more abnormality of the standard LFTs was found within 48 h of the shock episode. In addition we have found that the severity of the hepatic biochemical dysfunction showed a relationship to the duration of the shock episode and that, in those patients with a fatal outcome, there was continued and progressive hepatic dysfunction during their management in the ITU. In none of the patients, however, did overt hepatic failure develop, and it is difficult, particularly in such a retrospective survey, to assess the contribution, if any, which impaired liver function made to the fatal outcome in some patients. The pattern of the liver function tests comprised hyperbilirubinaemia, mild to moderate increase in the alkaline phosphatase, and moderate increase in the SGOT with the SGPT showing abnormal activities only in more severely ill patients and those with a prolonged shock episode. This is a pattern similar to that which has been noted in other studies.[15]

In the patients we have investigated it must be freely admitted that disturbances of liver function are very likely to be multifactorial. Many of the patients had had surgery, a variety of anaesthetic agents and other drugs. Most patients received intravenous hyperalimentation, some had received blood transfusions and some had haematomas with extravascular haemolysis. All of these factors may have contributed to the abnormalities in LFTs, and it has not been possible for us to assess separately the contributory role of inadequate haemoperfusion, sepsis or endotoxaemia, or a combination of any two, or all of these.

The histological appearances which we found at post-mortem in the majority of the livers were essentially non-specific—intrahepatic cholestasis, focal liver cell necrosis, Kupffer cell hyperplasia, mild fatty change and portal tract inflammation—and were similar to the findings reported by others.[12–15] In six cases, however, we noted a pattern of bile retention in which, in addition to hepatocyte and canalicular cholestasis, bile retention was also evident at the cholangiolar level with abnormalities of the cholangiolar epithelium, conspicuous inspissated concretions within the dilated cholangioles and a related acute cholangiolitis. This pattern of bile retention has been noted before in the bacterial-associated jaundice in the neonate and young child and has been referred to as the "inspissated bile syndrome." In prospective studies which we have undertaken since the present work was completed we have seen this same pattern of bile retention in liver biopsies from patients with septic/endotoxin shock and a full description of this will be the subject of a further report (MacSween *et al*, in preparation). It is worth emphasising, however, that while these histological changes could be mistaken for large duct obstruction the features are those of a cholangiolitis without a cholangitis. We think that this, together with the presence of the cholangiolar concretions, represents a morphologically distinct lesion which

may sometimes be the basis for the cholestasis occurring in septic/endotoxin shock. Ishak and Rogers,[18] in a report of eight cases of cryptogenic acute cholangitis noted that six of these patients had toxic shock syndrome, the systemic complications of which were thought to be due to an exotoxin produced by *Staphylococcus aureus*. Ishak and Rogers suggested that the bile ducts may also be injured by the circulating toxin. In these cases cholangiolitis was not a feature and the principal differential diagnosis to be considered was that of large duct obstruction.

The precise mechanisms which produce the cholangiolar lesions which we noted in six cases are not clear. The organisms isolated from these six patients were similar to those found in the others. It is known that the canalicular bile exchanges water and electrolytes at the cholangiolar and duct level. Interference with this mechanism, producing a more concentrated bile, might result in cholangiolar plugging, with resulting cholestasis and pericholangiolitis. Endotoxaemia may also have a contributory role; on the basis of the Limulus lysate test all our patients had endotoxaemia. Utili and his colleagues[19][20] in in vitro studies with isolated perfused rat liver, have demonstrated an endotoxin-induced dose-dependent decrease in bile flow which may be the result of a selective decrease in the bile-salt independent fraction of bile. It is possible, however, that endotoxin may exert direct damage at the cholangiolar level. A further possibility is that, as a result of the shock episode, there is interference with blood flow through the peribiliary vascular plexus causing ischaemic damage to the cholangioles. In both septic/endotoxin shock and in the toxic shock syndrome therefore, further prospective studies are indicated to try and elucidate the pathogenetic mechanisms which produce the acute cholangiolitis and acute cholangitis seen respectively in these two conditions.

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