Development of biliary sludge in patients on intensive care unit: results of a prospective ultrasonographic study

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Abstract
Biliary sludge may be a precursor of gall stones in man. The aim of this study was to determine the incidence of biliary sludge in a prospective study of 36 patients admitted to the intensive care unit for longer than two days. The presence of biliary sludge was determined by ultrasonography. Biliary sludge developed in 17 patients (47%), after a mean of 5-5 days in the intensive care unit. Patients who developed biliary sludge spent longer in the intensive care unit (14±2 d (1±3)), compared with patients who did not (8±3 d (1±4)); (p=0.003). Ten of the patients with biliary sludge had a recognised risk factor: total parenteral nutrition (five), abdominal surgery (two), or both (three). All neurosurgical patients (four) who required total parenteral nutrition developed biliary sludge. Seven patients with biliary sludge had no previously recognised risk factor, five of whom had severe head trauma or neurosurgery. In conclusion, biliary sludge develops frequently and rapidly in patients admitted to an intensive care unit. Neurosurgical procedures are associated with biliary sludge formation. (Sludge is commonly associated with the development of cholestatic liver biochemistry.)

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Biliary sludge is recognised ultrasonographically as echogenic material which layers in the most dependent portion of the gall bladder and does not produce acoustic shadowing.1 The major constituents are supersaturated bile, mucin glycoprotein in high concentrations and unconjugated bilirubin.2 A large body of experimental and clinical evidence suggests that biliary sludge is a precursor of gall stones in a large number of affected patients.3 Several risk factors have been identified. They include total parenteral nutrition,1 post bone marrow transplantation,1 pregnancy,1 AIDS,1 and after abdominal surgery.4 In many subjects, however, there is no clear risk factor.

Uncontrolled clinical impressions have led us to believe that biliary sludge frequently developed in subjects in the intensive care unit. The aim of the present study was to prospectively evaluate the incidence of biliary sludge in patients admitted to the intensive care unit for longer than two days, and to attempt to identify other risk factors for its development.

Methods

PATIENTS
Thirty six patients admitted to the intensive care unit at the University Hospital, Queens Medical Centre, Nottingham, for more than two days over an 11 week period were investigated. Biliary ultrasonography was performed by the same investigator (SJS), using an Aloka SSD-650 real time ultrasound machine with 5 mHz and 3.5 mHz curved linear array transducers. Biliary sludge was recognised as echogenic material which layered in the most dependent portion of the gall bladder without acoustic shadowing3 (Fig 1), but was also recognised as poorly defined globular masses of low echogenicity within the gall bladder (Fig 2). Initially these masses were not recognised as sludge, although they were of the same echogenicity. In these patients, however, subsequent scans always showed the typical layered appearance of biliary sludge. It is likely that in certain patients sludge initially forms as a globular mass which subsequently layers into the most dependent part of the gall bladder. Scans were done twice a week on average. Statistical analysis was performed using Student’s unpaired t test and Fisher’s exact test.

All patients except two were mechanically ventilated. The male to female ratio was 26:10 with an average age of 47 years (range 17–80). Underlying major illnesses included neurosurgery/severe head injury 19, multiple trauma six, abdominal surgery eight (vascular surgery five, gastrointestinal surgery three), others (Gram negative sepsis, epiglottitis, encephalitis/post cardiac arrest) three. Three patients had major bacterial sepsis on admission to the intensive care unit.

Ten patients received total parenteral nutrition early in their treatment in the intensive care unit, and three at a later stage. On average, total parenteral nutrition began 3±1 days after admission to the intensive care unit (range 0–7).

Results
Biliary sludge developed in 17 of 36 patients (47%), after mean 5±5 days (SEM 0.9). Three of these patients had sludge on their initial scan (one patient who had undergone aortic aneurysm repair five days previously; one had a subarachnoid haemorrhage and subsequent repair of intracranial aneurysm in the previous week; one had undergone intracranial haemorrhage three days before). Subjects who developed biliary sludge spent longer in the intensive care unit 14±2 (SEM 1±3) days, than those who did not 8±3 (SEM 1±4) days (p=0.003).

In seven biliary sludge forming patients, there was no previously recognised risk factor. Of those seven, five had undergone neurosurgery or had received a severe head injury (having
Figure 1: Ultrasonographic appearance of biliary sludge showing echogenic shadowing which layers in the most dependent portion of the gall bladder, without acoustic shadowing.

Figure 2: Ultrasonographic appearance of biliary sludge showing echogenic shadowing in the most dependent portion of the gall bladder, without acoustic shadowing, but with a globular appearance to the superior surface.
received enteral nutrition but no total parenteral nutrition), one had multiple trauma, and one Gram negative septicemia. Ten of the biliary sludge forming patients had a previously recognised risk factor: total parenteral nutrition (five), abdominal surgery (two) or both abdominal surgery and total parenteral nutrition (three). Thus, five of eight subjects who underwent abdominal surgery developed sludge, as did eight of 10 subjects receiving total parenteral nutrition. All neurosurgical patients who received total parenteral nutrition (four) developed biliary sludge. This made of 19 patients who underwent neurosurgery or had a severe head injury developed biliary sludge. The development of biliary sludge in patients receiving total parenteral nutrition was more rapid than previously recognised in patients receiving total parenteral nutrition outside the intensive care unit (mean 3·1 days). The frequency of development of biliary sludge in the different patient groups is shown in the Table.

Liver biochemistry was performed regularly in 33 of 36 patients. Cholestasis developed in five of 16 non-sludge forming subjects and in 13 of 17 sludge forming subjects; this difference is statistically significant (p = 0·01). None of the patients in this series developed evidence of acute acalculous cholecystitis, and thus the development of abnormal liver biochemistry does not appear to relate to the development of this complication.

APACHE scores, an index of illness severity and prognosis widely used in patients on the intensive care unit, were obtained on admission to the intensive care unit in all subjects except two, and were similar in the non-sludge and sludge forming groups: non-sludge forming mean APACHE score 11·8 (SEM 1·9), sludge forming 14·1 (SEM 1·7); p = 0·38.

Discussion
The aim of this study was to evaluate the incidence of biliary sludge in critically ill patients admitted to the intensive care unit for more than two days. The major findings of this study are that biliary sludge develops frequently and rapidly in intensive care patients, and that the spectrum of patients who develop sludge is wider than previously recognised. In particular, we recognise major neurosurgical procedures and severe head injury as a risk factor for biliary sludge development, developing in nine of 19 subjects.

The classic ultrasonographic appearance of biliary sludge is that of echogenic material which layers in the most dependent portion of the gall bladder.1 In some of our subjects, however, a globular mass was initially seen in the gall bladder (Fig 2). We did not initially recognise this as biliary sludge, but believe that it represents an alternative appearance of biliary sludge, reflecting the high mucin glycoprotein content and thus high viscosity of biliary sludge2 and is analogous to the globular appearance noted by Lee et al in the in vitro sheep model of biliary sludge.2

Because gall stone formation is a frequent result of biliary sludge formation in all groups previously examined, this study may have potential therapeutic implications. Further research may focus on the subsequent incidence of gall stones and on developing a regime to prevent or clear biliary sludge in at risk patients. Potential candidates for such research include daily intravenous infusions of CCK-OP (cholecystokinin).3 CCK-OP has been shown to reduce biliary sludge formation in patients receiving total parenteral nutrition.4 Other potential therapeutic regimes which inhibit prostaglandin synthesis, because prostaglandins may be important in mediating secretion of gall bladder mucin glycoprotein, an essential component of biliary sludge and subsequent gall stone formation.5 Finally rapid intermittent intravenous amino acid infusions have recently been shown to stimulate gall bladder contractility, and may provide an acceptable method of preventing biliary sludge in patients receiving total parenteral nutrition.6

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