Research Article

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Lessons from look-back in acute liver failure? A single centre experience of 3300 patients

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Background & Aims: Acute liver failure (ALF) is a rapidly progressive critical illness with high mortality. Complex intensive care unit (ICU) protocols and emergency liver transplantation (ELT) are now often available, but rarity and severity of illness have limited its study and evidence-base for care. We reviewed patients treated over a 35-year period at a specialist high-volume ICU, quantifying changes in disease aetiology, severity and evolution of ICU support and ELT use and outcome.

Methods: Review of adult patients admitted during the period 1973–2008, with acute liver dysfunction and coagulopathy with overt hepatic encephalopathy (ALF) and those without (acute liver injury; ALI).

Results: 3305 patients fulfilled inclusion criteria, 2095 with ALF. Overall hospital survival increased from 30% in 1973–78 to 76% in 2004–08; in ALF from 17% to 62% (both p <0.0001). In ALF patients treated without ELT, survival rose from 17% to 48% (p <0.0001); in those undergoing ELT (n = 387) from 56% in 1984–88 to 86% in 2004–08 (p <0.01). Coincident with drug sales-restriction, paracetamol-related admissions fell significantly. Viral admissions fell from 56% to 17% of non-paracetamol cases (p <0.0001). Admission markers of liver injury severity fell significantly and the proportion of patients with intracranial hypertension (ICH) fell from 76% in 1984–88 to 20% in 2004–08 (p <0.0001). In those with ICH, mortality fell from 95% to 55% (p <0.0001).

Conclusions: The nature and outcome of ALF have transformed over 35 years, with major improvements in survival and a fall in prevalence of cerebral oedema and ICH, likely consequent upon earlier illness recognition, improved ICU care, and use of ELT.

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Introduction

Acute liver failure (ALF) combines the clinical features of an acute severe insult to a previously normal liver, with the development of progressive hepatic encephalopathy (HE), coagulopathy, jaundice, and the potential to rapidly progress to multi-organ failure [1–3]. In those with severe HE, progression to cerebral oedema (CE) and intracranial hypertension (ICH) is a feared outcome, often with fatal consequences [4,5]. ALF is rare, with an incidence in the developed world of probably fewer than 5 cases per million population per year [6,7].

This disease rarity, severity and phenotypic heterogeneity combine, to result in a uniquely challenging illness, particularly in relation to its study and the development of effective treatments. Few specific interventions have been tested in controlled trials, with most supportive interventions and decision-making strategies evolving from analysis of natural history data with extrapolation from other critical illnesses [1,8,9].

Even with these limitations, the last four decades have seen major changes in approach to the care of patients with ALF. The most visible impact has come from emergency liver transplantation (ELT) with less tangible improvements from complex intensive care. The profile of ALF has also changed over time, influenced by public health initiatives reducing the incidence of acute viral hepatitis and by some restrictions of the availability of hepatotoxic medication – exemplified by the restriction of sales of paracetamol (acetaminophen) in the United Kingdom (UK) [10].

Since its opening in 1973, the Liver Intensive Therapy Unit (LITU) within the Institute of Liver Studies, Kings College Hospital, has maintained a specific interest in the care of patients with

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Abbreviations: ALF, acute liver failure; ICU, intensive care unit; ELT, emergency liver transplantation; ALI, acute liver injury; ICH, intracranial hypertension; CE, cerebral oedema; LITU, liver intensive therapy unit; HE, hepatic encephalopathy; ICP, intracranial pressure; KCC, Kings College Criteria; RRT, renal replacement therapy; AVHD, arterio-venous hemodialysis; CVVHF, continuous veno-venous hemofiltration; NAC, N-acetyl cysteine; DILI, drug-induced liver injury; INR, international normalised ratio; OTC, over the counter; CSF, cerebrospinal fluid.

ALF. Operating as a high-volume centre for the care of patients with liver disease, it has developed a multi-disciplinary approach to care of these patients and as such has a unique opportunity to evaluate the evolution of care and changes in the nature and outcome of the illness over time. In this study, we analysed data of the 3305 patients with acute liver disease admitted to the LITU over the period 1973–2008, seeking to evaluate and quantify the effects of intensive care support and the introduction and refinement of ELT. We sought also to delineate the changes in disease etiology and severity that had occurred over time, and how these related to the clinical complications and outcomes observed.

Patients and methods

Patients and dataset

The analysis is based on all patients aged ⩾16 years admitted to the LITU between 1973 and 2008, with a diagnosis of acute liver injury (ALI) or ALF. Inclusion criteria for ALI included: (1) an INR of ⩾1.5; (2) absence of a previous history and clinical/radiologic findings of liver disease; and (3) illness ⩽26 weeks of duration. Those who had or developed overt encephalopathy (HE grade ⩾2) [11] at any time during their hospital stay were classified as having ALF [12]. Transfer to the LITU was considered in all patients referred with ALF and in those with ALI, if there were features raising prognostic concern, including hypoglycaemia, extrahepatic organ failure or progressive coagulopathy with an INR >2 or PT >30 s. All patients with subacute disease and any coagulopathy or evidence of falling liver volume were considered for transfer [13].

Patients were identified through the admission diaries of the LITU which form a continuous record since the unit first opened. Clinical data was derived from archived records (1973–99) and after 1999 from the prospective LITU electronic database.

The dataset collected comprised patient age, gender, contemporaneous etiology, and laboratory test results (INR, bilirubin, creatinine and sodium) on admission to the LITU. Over the study period, changes in laboratory methods were unlikely to have impacted upon these values. Etiology was classified into paracetamol and non-paracetamol, and the latter subclassified into viral, non-paracetamol drug-induced, pregnancy-related and 'other' etiologies. The latter group included cases resulting from autoimmune disease, Budd-Chiari syndrome, malignancy, ischemia, *Amantia* fungi, Wilson's disease, and specific hepatotoxins. Cases were classed as indeterminate if none of these causative factors were present. Patients with liver dysfunction from primary systemic sepsis or following hepatectomy were not included in this analysis.

The presence or absence of overt encephalopathy and the requirement for intubation and ventilation were documented as was placement of intracranial pressure (ICP) monitors. Patients were classified as having ICH if in their clinical course they developed pupillary abnormalities (dilated (>6 mm) and sluggishly reactive to light), a sustained ICP of ⩾25 mmHg (in those with ICP monitoring), requirement for therapeutic intervention or at autopsy had evidence of gross CE. Clinical records did not permit collection of comprehensive data in respect of infection incidence or antibiotic administration, those who fulfilled poor prognostic KCC criteria but were not listed for ELT, or whether ALF patients were free of HE on admission.

Evolution of care

The evolution of medical supportive care in the LITU is illustrated schematically in Fig. 1. In brief, for renal replacement therapy (RRT), intermittent arterio-venous hemodialysis (AVHD) was the initial technique applied, being replaced by slow continuous AVHD and subsequently continuous veno-venous hemofiltration (CVVHF). Thresholds for its use progressively fell over time with latter indications including not only those standard for patients with acute kidney injury with anuria, but also for relative oliguria, metabolic stabilization and control of acidosis and hyperammonaemia.

Invasive hemodynamic monitoring with pulmonary artery catheterisation and cardiac output determination was in use from the early 1980s and became standard of care until replaced by Pulse Contour (Pulsion Medical Systems SE, Munich Germany) analysis-derived monitoring from 1995 onwards. Thresholds for insertion of such monitoring fell progressively with time, eventually being used in all patients requiring mechanical ventilation, inotropic or vasopressor therapy. Norepinephrine was the primary vasopressor used and dobutamine the primary ionotropic agent with adjunctive use of intravenous low-dose hydrocortisone and vasopressin.

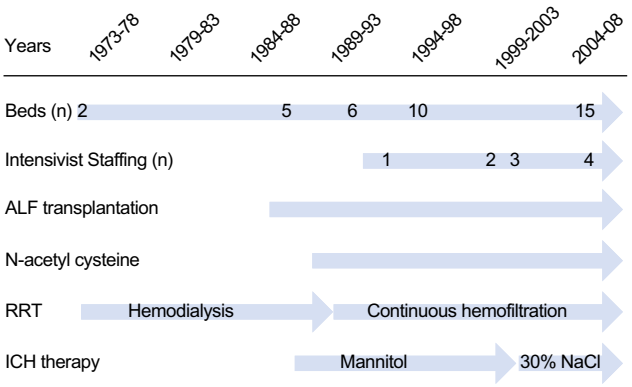

Fig. 1. Schematic evolution of care for patients with ALI/ALF at the Liver Intensive Therapy Unit, Kings College Hospital. ALF; acute liver failure, RRT; renal replacement therapy, ICH; intracranial hypertension.

All patients developing ALF with overt HE with agitation or coma were intubated, sedated, and mechanically ventilated. Sedation was initially with morphine and midazolam and with routine use of paralysing agents, with evolution to use of fentanyl and propofol infusions with rare use of paralysis. In these cases, monitoring for ICH utilized regular clinical assessment and non-invasive techniques, with direct ICP monitors first selectively used in 1977. In 2008, 13 of 42 (31%) patients ventilated with overt HE had ICP monitors inserted.

Treatment for ICH crises was initially with bolus intravenous mannitol and increased sedation with use of thiopentone in refractory cases. Continuous intravenous infusion of hypertonic saline (30%) was introduced for all ALF patients in 2001 and also used as bolus therapy for ICH, with mannitol and indomethacin for second-line use. Active temperature management was introduced in patients with severe HE in 1999, with a target of 36 °C and greater degrees of hypothermia reserved for those with ICH refractory to medical agents [8,14].

Intravenous N-acetyl cysteine (NAC) was administered to all patients after 1989. If they had not received a loading bolus dose prior to LITU admission, patients were initially administered 150 mg/kg over 15 min and all received an infusion of 100 mg/kg/24 h for a maximum of 5 days or until the INR was <2.

Initially, intravenous antibiotics were administered to all patients after admission, but use was reduced over time with current restriction to patients with established HE or other organ dysfunction, those fulfilling or likely to fulfil transplant criteria and to those without HE but with clinical signs of significant systemic inflammation in the absence of confirmed sepsis [8,15].

Liver transplantation

The first liver transplant for ALF was undertaken in 1984, and a total of 387 were performed over the study period. After 1990, all cases were selected using nationally adopted criteria based upon the Kings College Criteria (KCC) [16,17]. Contraindications to ELT included evidence of irreversible brain-stem dysfunction and fixed dilated pupils, refractory escalating vasopressor requirement or hypoxemia, or systemic sepsis with refractory deteriorating clinical status despite antimicrobial therapy. The decision to accept an allocated organ and the details of the operation were made by the duty transplant surgeon. ABO blood group compatibility was standard practice, and where possible, the organ was matched in size. Immunosuppression over the period 1984–94 consisted of a triple therapy regimen of corticosteroids, azathioprine, and cyclosporine, and, from 1994, a tacrolimus and low-dose corticosteroid regimen [18].

Statistical methods

The primary survival outcome measure was survival to leave hospital, with and without the use of ELT. Data are presented as median (inter-quartile range) or numbers (percent). To assess trends over time, annual admissions were analysed with year both as a continuous variable and in 5-year blocks. Univariate analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, USA) and utilized Chi-square and Fisher's exact tests for categorical, and Mann-Whitney *U* and Kruskall-Wallis tests for continuous data. Correlation between variables was assessed using Spearman's correlation. Multivariable analysis utilized multiple logistic

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