Liver Failure in Early Infancy: Aetiology, Presentation, and Outcome

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ABSTRACT

Objective: Acute liver failure (ALF) in early infancy is rare and challenging to recognize and manage. We aim to describe the presentation and outcome of infants with ALF according to their final aetiology to elucidate features to facilitate early recognition leading to prompt diagnosis and management.

Methods: All infants presenting within 120 days from birth with liver failure were included in a retrospective review over a 19-year period. The aetiology, clinical features, presenting investigations, and outcome were collected.

Results: Seventy-eight young infants presented with ALF. The aetiology was established in 94% and included metabolic disease (36%), hypoxic-ischaemic (HI) insult (19%), infection (17%), neonatal haemochromatosis (9%), and infiltrative disease (9%). Infections, infiltrative disease, and acute HI insult usually resulted in higher transaminases and international normalized ratio, whereas neonatal haemochromatosis and tyrosinaemia were characterized by lower or near normal transaminases. Overall jaundice was not visible in 24% of infants at presentation. Forty-five (58%) infants were alive at discharge from hospital. Survival at 1 year was 53% and survival with native liver 50%. Later deaths occurred in infants with mitochondrial disease. Six infants received a liver transplant and 4 subsequently died from their underlying disease.

Conclusion: ALF should be considered in any young infant with a coagulopathy as transaminases and/or bilirubin levels can be near normal at presentation. Better intensive care and the judicious use of liver transplantation may have contributed to the improved outcomes for this group compared with previous decades.

Key Words: herpes simplex virus, infantile acute liver failure, liver transplant, metabolic liver disease, neonatal haemochromatosis

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What Is Known

- Acute liver failure in early infancy is rare with high mortality.
- Recognition is delayed because of lack of specific features of liver disease.
- Liver failure should be considered in the differential diagnosis in any infant with a coagulopathy.

What Is New

- Recognition of acute liver failure in infancy remains challenging. This large, detailed study reinforces the need to consider liver failure in infants with no visible jaundice or only mildly abnormal liver function tests.
- Tyrosinaemia may present with apparently isolated coagulopathy.
- High levels of lactate and ferritin are nonspecific.
- Outcomes have improved compared with series from previous decades.

Acute liver failure (ALF) in early infancy is rare and detection may be difficult. Until recently it has invariably been associated with high mortality, approaching 80% to 100% in some series (1). With improved recognition and management, including appropriate use of liver transplantation, the outcome may be more favourable. The challenges of timely and accurate diagnosis, and defining precise aetiology, however, remain. They are the cornerstones for guiding appropriate management strategies.

We aim to describe the presentation, aetiology, and outcome of infants presenting with ALF within 120 days of birth, to elucidate the spectrum of disease and characterize the pattern of liver dysfunction according to aetiology, which may facilitate early recognition by clinicians leading to prompt diagnosis and management.

METHODS

All infants with ALF presenting to a single centre within 120 days of birth between 1993 and 2012 were included. Entry criteria were hepatic-based coagulopathy not corrected by vitamin K with *either* prothrombin time $\geq$15 seconds or international normalized ratio (INR) $\geq$1.5 in the presence of clinical hepatic encephalopathy (HE) *or* prothrombin time $\geq$20 seconds or INR $\geq$2.0 regardless of the presence or absence of clinical HE (2). HE is difficult to define in early infancy and was considered present when infants were inconsolably irritable or somnolent (3), even though in some cases this may have been related to their underlying aetiology of the liver failure. Infants with recognized liver disease who decompensated before 120 days of age were not included. Infants were identified from a prospective database, which noted clinical mode of presentation to the liver unit as ALF or neonatal liver failure. Further details were collected from the case notes retrospectively.

The following data were collected: (1) clinical features: visible jaundice, encephalopathy, bleeding, hypoglycaemia, and

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TABLE 1. Patient demographics

	Total number	Preterm	SGA	M:F	Age (days) at presentation Median (range)
Neonatal haemachromatosis	7	5/7**	0/5	2:5	6 (1–11)
Galactosaemia	11	0/7	1/7	8:3	10 (5–85)
Mitochondrial	9	0/7	3/7	4:5	42 (5–120)
Tyrosinaemia	3	0/3	0/2	2:1	32 (19–63)
Other metabolic*	5	0/5	2/4	4:1	47 (2–119)
Infection†	13	4/10	1/8	9:4	10 (1–68)
Infiltrative‡	7	0/7	0/6	4:3	20 (1–57)
Hypopituitarism	3	1/3	1/2	1:2	3 (3–36)
Hypoxic/ischaemic	15	5/15	5/10	8:7	6 (1–60)
Unknown	5	0/5	1/2	4:1	7 (4–19)
Total	78	15/69 (22%)	14/52 (26%)	46:32	10 (1–120)

*Transaldolase deficiency 1, inborn error of bile salt metabolism 2, idiopathic chronic cholestatic liver disease 1, Donohue syndrome 1.
†Herpes simplex virus (HSV) 9, congenital cytomegalovirus infection 2, enterovirus 1, *E. coli* 1.
‡Haemophagocytic lymphohistiocytosis (HLH) 6, acute lymphoblastic leukaemia 1.SGA = small for gestational age.
**$P < 0.005$.

renal failure; (2) results of blood investigations at presentation: bilirubin, alanine transaminase (ALT), INR, albumin, ammonia, lactate, ferritin, and alpha-fetoprotein (AFP); (3) ultrasound scan findings including presence of hepatomegaly, abnormal liver echotexture, splenomegaly, and ascites; and (4) outcome including liver transplantation, death, or survival. Children were investigated and managed as described previously (4). Extrahepatic haemosiderosis, to confirm a diagnosis of neonatal haemochromatosis (NH), was sought by magnetic resonance imaging and biopsy of the salivary glands of the lip. In some infants the diagnosis was only made postmortem. Investigations for mitochondrial disorders included magnetic resonance imaging scan of the head, cerebrospinal fluid lactate, echocardiogram, analysis of respiratory chain enzymes in muscle, and mitochondrial copy number in liver and/or muscle.

Infants were considered for liver transplantation when the INR was >4 according to the criteria of NHS UK Blood and Transplant. Infants with infiltrative disorders (haemophagocytic lymphohistiocytosis [HLH] and leukaemia), or multisystem disease (generalized mitochondrial cytopathy, multiorgan failure) were not considered for transplantation. Between 1993 and 2000, infants requiring consideration for liver transplantation were referred to another centre, whereas those presenting since remained at our centre, which had been designated in 2000 as a supraregional liver service for children.

Ethics

This audit is registered with the Leeds Teaching Hospitals NHS Trust audit department.

Statistics

Categorical data were reported as percentages, or as a fraction of those with available data and compared using Fisher exact test. Numerical data were reported as median and range. Results in 1 diagnostic category were compared with the rest of the group using the Mann-Whitney test.

RESULTS

Whole Group

Seventy-eight infants with ALF within 120 days of birth were identified, of which 46 (59%) were boys. Overall 22% (15/69) of infants were preterm and 26% (14/52) were small for gestational age (Table 1). Sixty-two per cent presented within 2 weeks of birth (Table 1). Clinical features of liver disease were jaundice (76%), hypoglycaemia (54%), renal failure (33%), bleeding (28%), and encephalopathy (26%) (Table 2). The results of initial blood investigations on presentation demonstrated a wide range when all infants with liver failure were examined as 1 group; bilirubin 9 to 787 μmol/L (median 124, normal <20 μmol/L), ALT 10 to 2726 IU/L (median 176, normal 7–56 IU/L), albumin 11 to 39 g/L (median 27, normal 35–51 g/L), INR 1.5–>20 (median 2.9). In 20% of infants bilirubin was <60 μmol/L at presentation.

Results of ultrasound imaging were available for 70 infants. Ascites was detected in 46%, hepatomegaly in 34%, and splenomegaly in 16%. The liver echotexture was described as abnormal in 16%.

The aetiology of the liver failure was established in 94% of infants and is illustrated in Table 1. Metabolic disease was diagnosed in 28 of 78 (36%). In the mitochondrial group, only 2 infants had recognized pathogenic mutations in the *POLG1* gene, 2 had low levels of complex IV in respiratory chain enzyme analysis from muscle and liver, 1 had low mitochondrial DNA copy number in liver, and in the remaining 4 infants the diagnosis was based on multisystem disease, high blood or CSF lactate, neurological features, and suggestive abnormalities in liver or muscle biopsy material. HI liver injury included acute perinatal insults such as birth asphyxia and congenital heart disease, and those with chronic intrauterine hypoxia and was the primary cause of ALF in 15 of 78 (19%).

Differences According to Aetiology

Infants with NH were more likely to be preterm than those with other diagnoses (71% vs 16%, $P < 0.005$). Weight for gestational age did not distinguish between the groups, although birth weight was only available in 52 sets of notes. Although 28% of infants presented with bleeding, this was evident in 2 of the 3 with tyrosinaemia (Table 2). Encephalopathy was present in 67% of those with infiltrative conditions compared with 23% of other diagnoses ($P < 0.05$). Infants with HI injury were significantly more likely to have renal failure (73% vs 25%, $P < 0.005$). All children with panhypopituitarism had jaundice and hypoglycaemia, features which were variable with all other aetiologies.

Figure 1A–H demonstrates the results of initial investigations on presentation. The initial bilirubin was significantly

TABLE 2. Presenting features of liver disease

Diagnosis	Bleeding, %	Visible jaundice, %	Encephalopathy, %	Hypoglycaemia, %	Renal failure, %
Haemochromatosis (n = 7)	29	86	0	71	29
Galactosaemia (n = 11)	0	91	18	27	0
Mitochondrial (n = 9)	25*†	89	37*†	62*†	11
Tyrosinaemia (n = 3)	67	67	0	33	0
Other metabolic (n = 5)	0	80	20	40	20
Infection (n = 13)	46	54	46	54	46
Infiltrative (n = 7)	33*†	86	67*,†	71	28
Hypopituitarism (n = 3)	33	100	0	100	33
Hypoxic ischaemic (n = 15)	36*†	60	20	43*†	73**
Unknown (n = 5)	20	80	20	80	40
Total (n = 78)	28	76	26	54	33

†Data missing for 1 patient.
*$P < 0.05$.
**$P < 0.005$.

higher in the galactosaemia group ($P < 0.005$). Initial ALT was highest in infection, infiltrative, and panhypopituitarism groups and was normal in the 3 children with tyrosinaemia. INR was raised, by definition, with a wide range across all groups, but the infants with infection had the most deranged clotting at presentation ($P < 0.005$). Most patients had low albumin levels and only 7 patients had an albumin level >36 g/L. Lactate was highest in the infiltrative group ($P < 0.05$) but high levels were also encountered in infants with mitochondrial disease, infection, and HI insult. There was a wide range of AFP, but children with tyrosinaemia had significantly higher levels than the rest of the groups ($P < 0.05$). AFP was, however, only available in 31 children at presentation. The median ferritin was highest in the infiltrative group and was never <550 μg/L in infants with NH. It was, however, in the normal range (<300 μg/L) in only 5 children out of 53 in whom results were available.

Overall ultrasound features were not statistically discriminating between the groups. Hepatomegaly was most frequent in patients with infiltrative aetiology (67%) but only 2 of the 6 (33%) had splenomegaly at presentation. Splenomegaly was also seen in NH and mitochondrial disease. Most infants with NH had ascites at presentation (71%). Abnormal echotexture of the liver was most commented upon in those with NH (57%) and tyrosinaemia (100%).

Outcome

Forty-five (58%) infants were alive on discharge from hospital; however, 4 died during the succeeding 12 months so at 1 year survival was 53% (Table 3) and survival with native liver was 50%. Seven infants were listed for a liver transplant but 1 (with NH) died on the waiting list. Six infants underwent liver transplantation (4 at our unit, 2 elsewhere). Aetiology of ALF in these was NH (2), herpes simplex virus infection (2), and mitochondrial disease (2). Four died after transplant from intraventricular haemorrhage day 4 (1 infant with NH), renal failure day 81 (1 infant with herpes simplex), and 2 from complications of mitochondrial disease (fits and lactic acidosis day 45 and primary pulmonary hypertension at 10 months after transplant). In 3 infants graft function was normal at the time of death.

One child with NH survived with antioxidant and supportive therapy and remains well with a follow-up of 10 years. The other surviving child with NH died at the age of 22 years from transplant complications. All infants with galactosaemia, tyrosinaemia, and panhypopituitarism responded to appropriate therapy and remain alive and well at a median of 12 years of age (5–19 years). None of the infants in the infiltrative group survived despite chemotherapy; 4 died within a few days of presentation. There was only 1 long-term survivor in the mitochondrial group, who is now 7 years old with neurological features. The other 3 who left hospital alive subsequently died by 2 years of age. We are not aware of any late deaths in the other survivors (other metabolic, infection, HI, and unknown) with a median hospital follow-up of 3 years (1–16 years), but there is no long-term data on 4 children from the HI group and 2 in the infection group.

Finally, 3 mothers, who had given birth to 4 of the infants with NH in this series, were treated with immunoglobulin transfusions during their next pregnancy and all were delivered of healthy neonates.

DISCUSSION

ALF in early infancy is rare and can be difficult to recognize and define. In older children and adults the presence of encephalopathy is a cornerstone of the definition (5) but in infants encephalopathy is difficult to determine and often occurs late in the illness. Most paediatric hepatologists suspect infantile liver failure in the presence of coagulopathy unresponsive to parenteral vitamin K (6,7). Other causes of coagulopathy such as disseminated intravascular coagulation need to be considered and sometimes it is necessary to seek advice from haematological colleagues if the overall clinical picture is not clear (8). Thus we adopted the same inclusion criteria of coagulopathy for the present study as the pediatric acute liver failure (PALF) study (2).

ALF in early infancy has different aetiologies to that in older children with a greater contribution from metabolic disorders, NH, haematological malignancies, and hypoxia (4). In this series 28 infants (36%) had a metabolic disorder responsible for their liver failure; similar to the study by Durand et al (7) but more than that in the infantile PALF study (6). The differences in the relative spectrum of causes of liver failure between the published series are probably related to different referral patterns and also the age range of children included but overall the main groups in each series include NH, metabolic, and infectious aetiologies. Only 6.4% of infants were categorized as indeterminate aetiology in this study which is lower than other single-centre series: 9% (9), 16.2% (7), 13% (10). In the infantile PALF study (6) the indeterminate group accounted for 37.8% of infants but this was a multicentre study with prospectively collected data and only a short follow-up period. It is unclear whether subsequent diagnoses elicited several months later

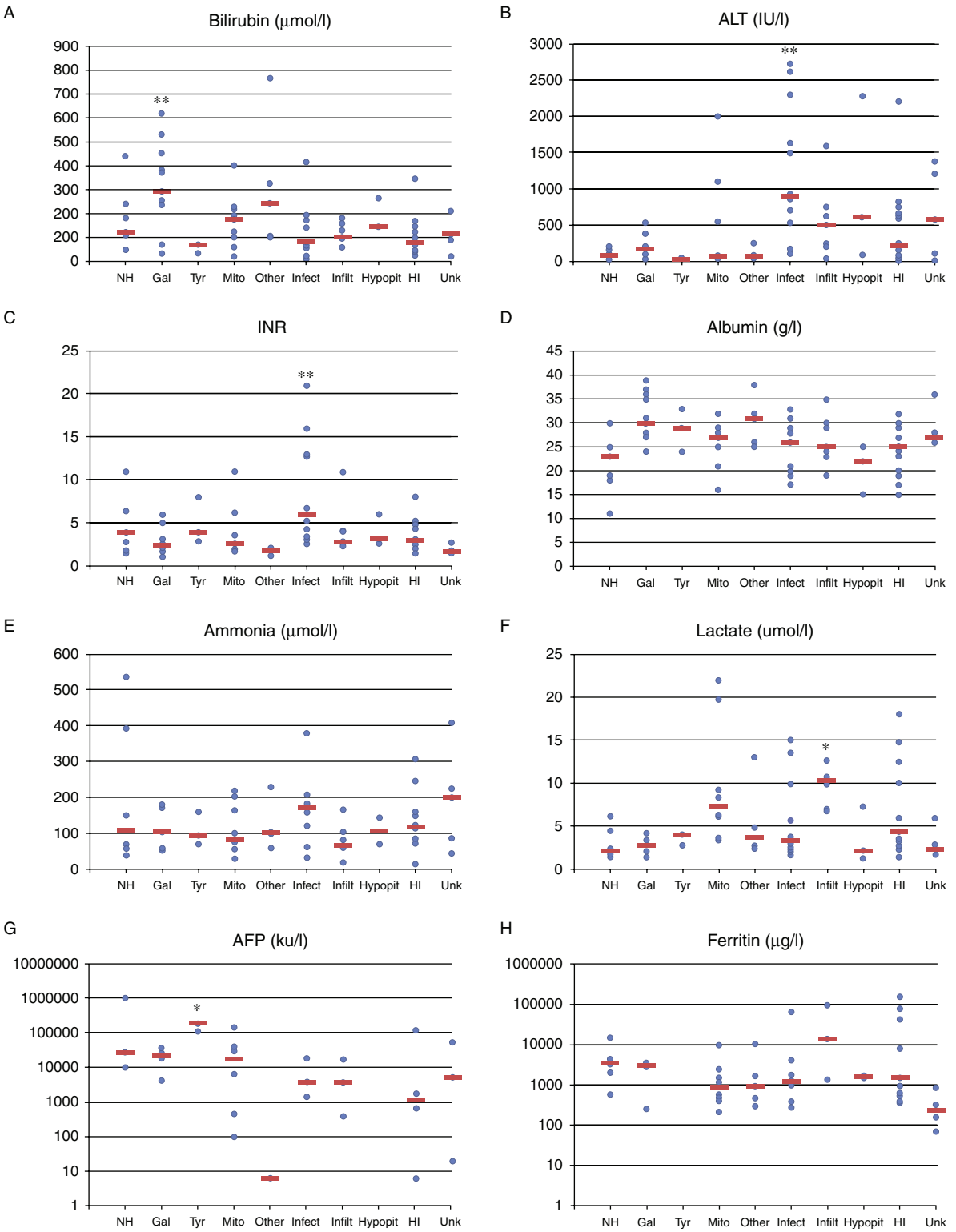

FIGURE 1. Results of investigations at presentation (median, range). A, Bilirubin, B, alanine transaminase, C, INR, D, albumin, E, ammonia, F, lactate, G, alpha fetoprotein, H, ferritin. NH = neonatal haemochromatosis; Gal = galactosaemia; Tyr = tyrosinaemia; Mito, = mitochondrial; Infect = infection; Infilt = infiltrative; Hypopit = hypopituitarism; HI = hypoxic ischaemic; Unk = unknown. $^{*}P < 0.05$, $^{**}P < 0.005$.

TABLE 3. Outcome at 1 year from presentation

Diagnosis	Total	Alive with native liver	Number transplanted	Died post-transplant
Haemochromatosis	7	1	2	1 (4 days)
Galactosaemia	11	11	0	0
Mitochondrial	9	4	2	2 (45 days, 10 mo)
Tyrosinaemia	3	3	0	0
Other metabolic	5	2	0	0
Infection	13	4	2	1 (3 mo)
Infiltrative	7	0	0	0
Hypopituitarism	3	3	0	0
Hypoxic ischaemic	15	9	0	0
Unknown	5	2	0	0
Total	78	39 (50%)	5	3

were then added to the enrolled subjects. In our series some metabolic diagnosis were made months and even years after the initial presentation.

Although the presentation and initial investigations are not exclusive to any group, certain patterns became evident. As expected preterm birth was more common in NH (11). Two of the 3 infants with tyrosinaemia presented with bleeding, while appearing otherwise quite well with only minimal derangements of other liver function tests. This highlights the need to look specifically for tyrosinaemia in infants with an apparently isolated coagulation defect (12). Our study reinforces the need to consider liver failure in infants with no visible jaundice: 20% of infants had a bilirubin <60 μmol/L at presentation of liver failure.

The ''acute'' presentations included infections, infiltrative disease, and acute HI insult. These presented with higher INR, ALT, and were more likely to have renal failure. The ''chronic'' presentations behaved like decompensated end-stage liver disease with mildly raised ALT and bilirubin, low albumin, and hypoglycaemia. This pattern of presentation was seen in those who had in utero liver disease, NH, chronic intrauterine hypoxia, and some mitochondrial disorders. This distinction is recognized by paediatric hepatologists and guides our investigations; however, the range of values within each diagnostic category in this study reminds us to be wary (13). Young infants with galactosaemia were mostly jaundiced (median bilirubin 292 [32–620]) and rarely presented with acidosis. The 24-hour turn around for measurement of galactose 1 phosphate uridyl transferase in our laboratory meant these infants were diagnosed promptly after referral.

Contrary to our expectations other investigations were not as diagnostic as we might have hoped; however, a limitation of this retrospective study is that not all infants had all investigations performed. Raised lactate is typically associated with mitochondrial disease and is expected in infants with overwhelming sepsis or ischaemic injury but, as our study demonstrates, lactate can be high in HLH (14). This was present even without evidence of hypotension or renal failure and may reflect the severity of the liver dysfunction in this group. It is important that the high lactate does not dissuade clinicians from pursuing the diagnosis of HLH. As described by previous authors raised ferritin did not discriminate children with NH and was normal in only 5 patients (15). The highest levels were found in infants with HLH.

Imaging by ultrasound, although not statistically discriminating is obviously important. Hepatosplenomegaly was most often seen in patients with infiltrative disease, but the lack of splenomegaly at presentation in this group does not exclude the diagnosis. Abnormal liver echotexture without hepatomegaly but with ascites was more suggestive of NH.

Fifty-eight per cent of infants were alive when discharged from hospital. This is similar to the survival at 3 weeks after recruitment recently reported in infants <90 days of age at presentation of ALF (6). In our study the overall survival after 1 year was 53% and survival with native liver at 1 year was 50%. The latter is considerably higher than the 24% previously reported in children younger than 1 year (7). This probably reflects an era effect in intensive care management of these infants. In those not transplanted, infants with infiltrative disease had the poorest outcome with 100% mortality and, as would be expected, infants with tyrosinaemia, galactosemia, and panhypopituitarism had the best survival rate (100% survival). For those infants who survive the episode of ALF the longer-term outcome is good. Late deaths, however, occurred in those with mitochondrial disorders.

The indications for liver transplantation in this age group are few, and include NH and some infections (4). Usually mitochondrial disorders are multisystem diseases and not considered for liver transplantation; however, as in our case, investigations may not detect extrahepatic disease before transplantation (16). Only 2 children with NH received a transplant and 1 died while on the transplant waiting list; 1 infant improved with antioxidant and supportive treatment but 3 deteriorated rapidly and died within 12 days of presentation. There were fewer children with NH in this series as the unit was not a referral centre for liver transplantation for the first 8 years of this series. Early detection and treatment with immunoglobulins in the affected infant and as a preventative measure in future pregnancies should make NH a less frequent indication for liver transplantation in the future (17,18).

The 1 year post-transplant survival in this series is only 33% compared to 52% to 69% in similar series (6,7). Even better results for post-transplant survival in this age group have been reported, although not all of the infants were transplanted for ALF (19). In our series the number transplanted was small and it could be argued, in retrospect, that 3 of them were not good transplant candidates; however, clinicians are making decisions on these infants in emergency situations without the benefit of hindsight.

We conclude that ALF in early infancy necessitates referral to a specialized paediatric liver centre with facilities for liver transplantation (20). Sometimes recognition of ALF in infancy is, however, delayed because of lack of specific features of liver disease such as jaundice and abnormal transaminases. Therefore liver failure should be considered in the differential diagnosis in any infant with a coagulopathy. Careful attention to the presenting features and associated biochemical abnormalities can help in determining the aetiology of ALF and therefore target further more invasive investigations and treatment decisions. The aetiology of ALF could be determined in up to 94% of patients and the overall survival has improved since earlier reports. Identifying those with excellent prognosis without transplantation is clearly important. In others liver transplantation, however, remains the definitive treatment and may contribute to further improvement in survival.

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