The aetiology and outcome of children with acute liver failure admitted to Tygerberg Children's Hospital from January 2009 to December 2013.

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Declaration

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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Dedication

I am immensely grateful to my dear wife Sumaiya for her patience, sacrifices and for tirelessly encouraging me throughout my years of study and training to be a Paediatrician as well as through the process of writing.

I appreciate my children for bearing with me during the writing of this thesis. I am deeply thankful to my parents and siblings for their endless support and prayers.

I dedicate this work to all of them.

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Abstract

Background: Acute Liver Failure is a rapidly progressive and potentially life-threatening disease.

There is scarcity of data from SA regarding Paediatric ALF and therefore its incidence remains unknown.

Paediatric acute liver failure is defined according to the PALF study group definition.

Objective: to evaluate the aetiology and outcome of ALF in children in a tertiary healthcare facility in the Western Cape Province, SA.

Methods/Design: A retrospective review of the medical records of paediatric patients presented with ALF between January 2009 and December 2013. The demographics, aetiologies and outcomes were recorded and, based on the final outcome, patients were categorised as either survivors or non-survivors.

Setting: Paediatric Gastroenterology Unit, Tygerberg Hospital, SA.

Results: Nineteen children (12 boys), aged 5 weeks to 6 years (mean age 18 months), were identified with ALF during the 5-year study period. The ALF causes were: infective (68.4%), INH-related (10.5%) and indeterminate (10.5%). One child presented with toxin-induced ALF and an underlying metabolic cause was suspected in one infant.

Of the infective aetiologies, hepatitis A infection was the most common (10/19) and was found to be associated with the highest mortality. Other viral causes also had fatal outcomes.

The overall mortality was 52.9% and children with aetiologies other than acute viral hepatitis were more likely to recover spontaneously.

Conclusion: Our study demonstrated that Hepatitis A infection is the single most common cause of ALF in our small cohort of patients. Measuring the risk of HAV-associated morbidity and mortality as well as the cost of LT and its complications and the need for lifelong immunosuppression therapy against the cost-effectiveness and benefit of Hepatitis A vaccine favours the introduction of hepatitis A vaccine in the EPI in SA.

There is a need for larger, multicenter and prospective studies to better evaluate the aetiology and outcome of ALF in children, the results of which will surely contribute to the establishment of a national database to determine the number of children with ALF who potentially require LT in SA.

Introduction

Acute liver failure is a catastrophic disease in children. Regardless of the initial insult, progressive loss of liver function leads to severe metabolic derangements that in many cases will lead to death(1–7). As the largest gland in the body, liver plays a major role in metabolic homeostasis. Briefly, its major functions are:

a) Regulation of uptake and processing of nutrients from the intestine.
b) Synthesis, storage and degradation of carbohydrates, amino acids and lipids: liver accounts for 15% of the total body protein production and the majority these proteins are secreted as plasma proteins such as albumin and coagulation and fibrinolytic proteins, transport proteins and components of the complement system, amino acid degradation takes place in the liver, generating a highly toxic metabolite, ammonia, which readily crossed the blood brain barrier and is associated with hepatic encephalopathy.
c) Maintenance of blood glucose levels by gluconeogenesis and gluconeogenesis.
d) Production and excretion of bile which is required for the digestion of lipids and lipid-soluble vitamins and for the elimination of many toxic compounds and waste products.
e) Detoxification/metabolism of drugs.
f) Endocrine functions.
g) Immunological function: the liver is a lymphoid organ, contains approximately 10^{10} lymphocytes comprised of both innate and adaptive immune cells with 3 types of antigen-presenting cells (Kupffer cells, dendritic cells and liver sinusoidal endothelial cells) which play a key role in clearing toxins and microorganisms from the portal circulation and in initiating the immune response.

Overview of the definitions of acute liver failure in children

The term fulminant hepatic failure, which was first used in 1970(1,8–10), has ever since been used interchangeably with acute liver failure in the literature to describe a rare but potentially fatal medical condition caused by a wide spectrum of aetiologies(1,3,4,6,11,12).

It is characterised by rapid onset of severe hepatic dysfunction and coagulopathy, with or without hepatic encephalopathy in a previously healthy child with no history of pre-existing liver disease(1–4,6,9,12–14).

The definition developed by O'Grady and colleagues in 1993(1–3,15) is still used to describe the acute liver failure in adults but not in children.

The Pediatric Acute Liver Failure Study Group (PALFSG), which was formed in 1999, defined ALF in children as 1. Having no pre-existing liver disease 2. Biochemical evidence of acute hepatic

injury e.g raised plasma bilirubin and liver enzymes 3. Coagulopathy defined as prothrombin time (PT) $\geq$ 15 seconds or International normalised ration (INR) $\geq$ 1.5 not corrected by vitamin K, in the presence of hepatic encephalopathy (HE) , or PT $\geq$ 20 seconds or INR $\geq$ 2 regardless of the presence or absence of HE(4).

Another definition developed by Bhaduri and Vergani, which is also accepted for clinical and research studies, defined ALF in children as a rare multi-system disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis in a patient with no recognised underlying chronic liver disease(8,13).

Durand et al defined acute liver failure as prolonged prothrombin time $>$ 17 seconds and clotting factor V concentration $<$ 50% of normal(11).

There is a general consensus in the literature that encephalopathy is not essential in order to make a diagnosis of ALF in the paediatric age group as it can be, if it occurs, a very late manifestation in the course of the disease or it can also be very difficult to recognise particularly in the neonates and infants and where the signs of irritability and excessive crying cannot be ascribed solely to HE rather than the underlying aetiology of ALF per se(1,4–8,11,16–21).

In neonates, an international normalised ratio (INR) of 2 may still fall with the normal range and normal premature babies may have an INR of $\geq$ 2. So, it might be safe to reset to INR $\geq$ 3 in cases of ALF in the neonatal age group(18).

Early recognition and prompt identification of the aetiology of ALF, whenever possible, is paramount, as there are cause-specific interventions exist for certain underlying causes, and its early institution may limit the progression of hepatic injury to multi-organ failure and be life-saving, for instance galactose-free diet in Galactosemia, administration of N-acetyl cysteine in children with confirmed or suspected paracetamol overdose, administration of IV acyclovir in cases of HSV-related ALF and the use of antioxidant cocktail and exchange transfusion for Neonatal Haemochromatosis Gestational alloimmune liver disease (NH-GALD)

Early diagnosis and intervention not only influence the management of the baby, but it also has implications on the subsequent pregnancies. For example, in case of GALD, antenatal administration of IVIG 14 weeks, 16 weeks and weekly from week 18 of gestation has been shown to reduce severity of illness in the newborn in a series of 15 pregnant mother who previously had an affected baby(8,18,21,22).

Prompt initiation of disease-specific medical therapy should not preclude the ongoing and careful assessment of disease severity and its response to treatment. Continuous monitoring is essential in order to prevent any delays of successful emergent liver transplantation whenever available.

Liver transplantation has substantially improved the outcomes of children with ALF.

Despite advances in critical care and better understanding of the pathophysiology of ALF, management of children with ALF remains challenging in both developed and developing countries and the mortality rate is still high especially in countries lacking the liver transplantation facilities.

PALFSG results have laid the foundation for many subsequent studies evaluating the aetiologies and outcomes of ALF in children. The tremendous and continuously updated database has also been used to investigate the prognostic factors in PALF.

The true incidence of this clinical syndrome remains unknown in most developed and developing countries(5,7,18,19,23,24). However, some reports from the United States showed and overall incidence of between 1- 6 cases per million people every year(1).

There is scarcity of data from Africa regarding the outcomes of children with ALF compared to data from the remainder of both developing and developed world.

Aetiology:

The aetiology of paediatric acute liver failure varies considerably with age and geographical region.(1,3–5,11,12,14,17,25–28)

The most common ALF aetiologies include indeterminate, infective, drug-related, metabolic and auto-immune disorders.(1,4,11,12,14,17,25–27)

In developed countries, the causes were indeterminate in almost half of children(4) and the drug-induced liver injury (DILI) accounted for nearly 20% of all cases of paediatric acute liver failure(29). Studies from North America and the UK reported Paracetamol as the leading cause of acute liver failure in children, accounting for 14% of cases with 4% mortality(29,30). Paracetamol overdose secondary to medication error was found to be the single most commonly identified cause of ALF in children in Australia and New Zealand(30). Other aetiologies (metabolic, non-paracetamol drug-related, infections, auto-immune hepatitis and others) made up to 37%(4).

In much of the developing world, acute viral hepatitis remains the leading cause of ALF, with Hepatitis A being the most common in some regions, while hepatitis E predominates in others. And the mortality reported to be high(1,2,10,12,31–36).

In certain communities in developed countries, HAV-associated ALF had been the indication for liver transplantation in approximately 10% of cases(9).

The prevalence of HAV-related ALF and hence mortality have remarkably declined following improvement of the sanitation, provision of clean water and food and the implementation of cost-effective hepatitis A vaccination programmes in the endemic areas(33,37–41). These public health measures consequently reduced the need for liver transplantation for HAV-induced ALF and made more donor livers available for ALF caused by other aetiologies(34).

The aetiologies responsible for acute liver failure also vary with age.

In neonates, the leading causes are neonatal haemochromatosis- Gestational alloimmune liver disease (GALD-NH), viral infections, metabolic disorders, hemophagocytic lymphohistiocytosis and indeterminate(8,16,18,20,21,42).

GALD-NH is the single most commonly identified cause of ALF in neonates reported by Taylor et al(18), Durand et al(11), Shanmugam et al(21), Lee et al(43) and Sundaram et al(20). the mortality rate is very high without prompt identification and liver transplantation, and thus a high index of suspicion is required in order to diagnose a newborn with NH and initiate supportive treatment promptly awaiting liver transplantation when indicated(8,11,18,20–22).

Early recognition and management not only improve the outcomes of survival of the baby and decide whether or not a liver transplantation is indicated but to also manage any subsequent pregnancies because the recurrence rate of this medical condition is relatively high (approximately 80%)(8,21,22). Administration of IVIG to the pregnant mother, who had a previous baby with NH, has been shown to remarkably reduce the occurrence and severity of GALD(8,18,21,22).

Herpes simplex virus -1 is the most common viral cause of NALF, carries a high mortality and rarely present with skin lesions, Verma et al, reported 11 newborns with HSV-associated NALF, only 2 patients who received early parenteral acyclovir survived, hence again a clinical suspicion is required to make the diagnosis and initiate IV acyclovir(18,21,44).

Metabolic disorders are an important cause of NALF. The most common metabolic diseases to be considered are galactosemia, tyrosinemia type 1, hereditary fructose intolerance and mitochondrial respiratory chain disorders (MRCD). Within this category, galactosemia was the most common diagnosis in some studies followed by MRCD(8,11,16,42).

Galactosemia and tyrosinemia type 1 together comprised $>$ 50% of study cohort(16).

By contrast, Taylor et al reported in their review that metabolic hepatopathies are rare causes of NALF and of the 3 autosomal recessive inherited diseases (galactosemia, tyrosinemia type 1 and HFI), only galactosemia regularly presents within the first month of life after the introduction of milk feeds and that most cases of galactosemia in the United States are diagnosed with newborn screening and never present in liver failure(18).

Diagnostic clues can be obtained from the presence of family history of consanguinity, neonatal deaths/sudden infant death syndrome, deaths of unknown cause in siblings and similar history in family(16,45).

These clues should lead to a thorough metabolic workup, as early recognition and dietary manipulation or disease-specific therapy may be life-saving and is associated with better long-term outcome(8,16,21,45).

Aetiology of ALF in infants and older children:

The causes of ALF in infants vary from those in older children and adolescents with metabolic disorders and infiltrative conditions (especially HLH) being the most common in infants and young children, whereas infectious, toxin/drug-related, autoimmune hepatitis and metabolic (most frequently Wilson's disease) causes were reported to be the commonest in older children(3,4,6,7,28,43,46).

Indeterminate aetiologies accounted for 30- 50% in some series(4–6,17,19,47). However, a proportion of infants labelled as having indeterminate aetiology may actually have had incomplete workup or may include undiagnosed metabolic disorder.

According to the PALF study group, around 25-30% of cases of PALF are infants(4).

Duran et al, in a review of 80 infants, found that the main causes associated with ALF were metabolic disorders which constituted 42.5% of the cases, of these the most common was mitochondrial respiratory chain disorders followed by tyrosinemia type 1(11).

In the same review, AVH was reported in 12 patients, half of them were due to acute hepatitis B infection, however, not a single case of hepatitis A infection was reported in this 14-year experience review (1986-2000)(11). By contrast, Debray et al, in a retrospective review from France, found that hepatitis A infection was the most common cause of ALF and accounted for 10% of liver transplants, but it was noted that the majority of the 24children that were included in the study were either of North African origins, returned from areas endemic for HAV or had a family contact with hepatitis A virus(9).

Hegarty et al, in a review of 127 children aged < 5 years, found that indeterminate causes accounted for almost a third of ALF cases, followed by inherited metabolic disorders and infectious cause. Of the metabolic, galactosemia was diagnosed in 17 children and mitochondrial respiratory chain disorders in 7 children, whereas drug toxicity was reported in only 4% of patients(16).

Alam et al, in a study conducted in a specialised paediatric liver centre in India, found that metabolic liver diseases (MLD) and haemophagocytic lymphohistiocytosis (HLH) together accounted for 50% of ALF case in children aged < 3 years. AVH was reported in 5 of the 30 children included in the study and the diagnosis remained indeterminate in 10% of children(45).

It was noted that children with DILI and AVH had better survival outcome than those with MLD and HLH(45).

DRUG-INDUCED LIVER INJURY:

In this study, in keeping with the international usage, we will use the term “drug” rather than “medicine” when referring to drug-induced liver injury.

One of the key functions of the liver is the biotransformation of medications (Over-the-counter and prescription), herbals and dietary supplements into more safely metabolised and readily excreted compounds. There have been over a thousand medications, herbal and dietary supplements (HDS) associated with the development of DILI(29).

The metabolism of medications as well as herbals and dietary supplements occurs through the 3 phases of hepatic drug metabolism, namely phase 1: activation, phase 2: detoxification and phase 3: excretion. Drug- induced hepatotoxicity is most often caused by accumulation of Phase 1 metabolites, following one of two patterns: intrinsic hepatotoxicity and idiosyncratic hepatotoxicity. Or a combination of the two patterns (synergistic effect)(29)(48).

Although drugs with the idiosyncratic pattern of hepatotoxicity constitute the majority of drugs causing DILI, only few drugs with the intrinsic pattern of hepatotoxicity cause DILI and paracetamol is the most common and well documented example of them(29).

Acetaminophen causes hepatic injury in a predictable and dose-dependent manner(49). In large doses, it is converted to the toxic metabolite N-acetyl-p benzoquinone imine (NAPQI) which is normally neutralised by the glutathione, however, excessive production of NAPQI in cases of acetaminophen overdose, depletes the hepatic stores of glutathione and causes hepatocyte injury. Glutathione stores can be replenished with N-acetyl cysteine (NAC), Which was first used to treat patients with paracetamol poisoning in 1979 and is currently being used to also treat non-paracetamol ALF in adults and paediatric patients(30)(48).

It had been shown that the use of NAC was associated with a shorter hospital stay and improved post-transplantation survival in paediatric patients with non-paracetamol ALF(50)

Unlike adults, the paediatric incidence of DILI is not known and it is because it is both, in many cases, not reported and under-recognised. But it is thought to be lower in children for so many reasons, most importantly, the fewer medication they take and the less likelihood of alcohol consumption and cigarettes smoking by children(29).

Severe DILI cases in children account for almost 20% of all cases of paediatric acute liver failure, paracetamol toxicity alone contributes to 14%(4) of them and antibiotics and central nervous system medications account for the remaining of cases, and is a major indication for liver transplantation in the USA(29).

The agents implicated in DILI vary with geographic location, HDS-associated DILI is more common in Asia(29). In a retrospective series of 69 children from China, Zhu et al reported that Chinese herbal medicine (CHM) and combination of drugs (including CHM) accounted for 21.7% of DILI cases each, whereas antibiotics followed by antineoplastic and antipyretic medications collectively accounted for 56% of cases. It had been noted that CHM-related DILI was associated with poorer outcome compared with other medications(51).

In South Africa, a considerable percentage of the population resort to using herbal medicines and despite the fact that the potential acute and chronic toxicities of these herbal remedies is well documented, there is scarcity of data reporting DILI in SA and especially so in the paediatric population. However, Steenkamp V et al demonstrated the presence of toxic pyrrolizidine alkaloids in traditional medicines in SA and established its association with hepatotoxicity and hepatic veno-occlusive disease(52).

The onset of DILI can occur weeks after cessation of the offending drug, and the time to recovery can vary considerably from days to months, but most cases eventually resolve(29).

Antituberculosis drugs:

TB is the leading infectious disease globally and represents a large disease burden in many countries where it is endemic, for example, the number of patients with TB in India accounts for one fifth of the world TB population(53,54), India and China together account for approximately 40% of the world's TB cases(55). The Drakenstein Child Health Study, conducted in a periurban area in South Africa, found that the burden of childhood TB was among the highest reported worldwide with an estimated 2900 cases per 100 000 children(56)

In 2013, there were nearly 9 million incident cases and 1.1 million deaths reported from TB(53,57,58).
Management of the active disease and the potential adverse effects of the antituberculosis treatment (ATT) poses an enormous challenge, especially in those patients with ATT-induced ALF requiring liver transplantation and a prolonged period of immunosuppressive therapy thereafter(53,54).

The spectrum of clinical presentation vary from asymptomatic liver injury with mild elevation of liver transaminases to the more severe picture of ALF(53,54,59).
In adult studies, anti-TB drugs are the leading cause of drug-induced liver injury and drug-induced acute liver failure. In India, anti-TB medications represent 58% of DILI and 5 – 22% of drug-induced ALF, compared to more developed countries where acetaminophen, antibiotics and CNS medications predominate the drugs causing liver injury. In contrast to results from the US in 1993 when O'Grady found that the single largest cause of idiosyncratic drug-induced ALF was anti-TB medications(53).

Anti-TB dug-related liver injury occurs throughout the course of treatment(53,54), although 76.8% of cases occurred in the first 2 months as reported by Devarbhari et al, Similarly Bankatte et al reported that the median duration of ATT intake prior to the development of jaundice was 2 months.

Antituberculosis drug-related hepatotoxicity carries a high morbidity and mortality, the mortality rate from anti-TB DILI is higher than that from paracetamol-induced acute liver failure, both in adults and children. Although the majority tolerate the medications, the outcome may be devastating in a small minority of patients who progress from mild DILI to severe ALF, particularly in areas where LT facilities are lacking(53,54).

In one adult series, almost a quarter of patients with ATT-related hepatotoxicity developed ALF 22.7% of them died. 9% of patients in this series were under the age of 18 years. And HIV infection was present in 7.8% of the study population. The reason for the association of hepatotoxicity with ATT in patients coinfected with HIV is not completely understood(53). However, it may be secondary to excessive immune activation leading to less efficient handling of oxidative stress and detoxification of drug metabolism(58).

Bavikatte et al reported on 7 patients who developed ATT-ALF requiring liver transplantation, three of them were under the age of 17 years and 2 died 25 and 30 days post transplantation(54).

The mortality was noted to be higher in patients with jaundice, encephalopathy or ascites(53). Longer duration of treatment was also associated with higher mortality(53,54).
Other factors that may contribute to the higher mortality with anti-TB DILI are 1. The severe disease at presentation 2. The higher proportion of patients who develop ALF and 3. The combination of 2 or 3 hepatotoxic agents in the TB treatment regimen(53).

The higher morbidity and mortality associated with ATT-DILI necessitates vigilant clinical monitoring throughout the duration of treatment, but this alone is not sufficient, parents and caregivers need to be educated about the potential adverse effects and what symptoms to look for and what to do if symptoms develop. However routine follow-up and performance of liver functions is debatable, as some patients can still develop ALF despite regular monitoring and there is no convincing evidence linking outcome to liver enzymes level monitoring(53).

Some of the issues that compound the management of ATT-related acute liver failure:
1. Worsening of TB upon cessation of treatment 2. Increased risk of ATT resistance 3. Prolonged duration of treatment 4. Liver transplantation in the sitting of an infectious disease in considered a contraindication 5. Post-transplantation immunosuppression(54).

Risk factors that may contribute to the development of anti-TB drug-induced hepatotoxicity have been studied, according to the national institute of nutrition, malnutrition was suggested as a risk factor and this could be ascribed to the depletion of glutathione reserves, in

malnourished patients, making them vulnerable to oxidative stress which is a mediator of hepatotoxicity(59,60).

Possuelo et al found that HIV positive status and slow acetylation profile were independent risk factors for hepatotoxicity and that HIV positive patients that have are slow acetylation profile to be at a remarkably higher risk of developing hepatotoxicity from ATT(61).

Multiple adult studies demonstrated that alcohol consumption is one of the most common risk factors that have been found to be associated with anti-TB DIH(59,60).

Isoniazid-induced hepatotoxicity and ALF:

With INH being the main drug to induce hepatotoxicity, it is worth some mention.

Since 1952, INH has remarkably decreased mortality from mycobacterium TB infection, but there has been a concern of the potential hepatotoxicity and the devastating outcome of ALF in a minority of patients(62,63).
Isoniazid preventive therapy (IPT) has been the standard of care for TB prophylaxis(64).
Following the administration of INH, derangement of liver function occurs in 10% - 20% of patients and symptomatic hepatitis develops in 1% - 2% of them(65,66).
The severity of presentation varies from acute hepatitis that responds to the discontinuation of INH to ALF that require LT(66).
IPT-induced liver failure is rare(62), and most children develop subclinical hepatitis and recover fully. However, some patients may develop clinically overt hepatitis and progress to liver failure requiring liver transplantation(62,66).

The first reported childhood mortality from INH-induced hepatotoxicity was in 1976(62).
INH-related liver failure accounts for 0.2% of all paediatric orthotopic liver transplantation (OLT)(62).

INH-related hepatotoxicity is believed to be mediated by monoacetylhydrazine, an intermediate product of the metabolism of the INH by N-acetyltransferase 2 (NAT2), which is further metabolised and by the cytochrome P450 2E1 (CYP2E1) enzyme system, the activities of NAT2 and CYP2E1 are affected by genetic variability and polymorphism. For example, a combination of slow acetylator status and CYP2E1 genetic polymorphism is known to be a risk for INH-associated hepatic injury. Similarly, coadministration of rifampicin, a CYP450 inducer, can augment the risk of liver injury due to INH(61,64).

The reason for severity of INH-induced liver injury and its pathogenesis remains elusive(64).

INH-related ALF was one of the indications for LT as reported by Wu et al in a 10-year survey of 84 centres performing paediatric liver transplantation in the US, the purpose of the survey was to estimate the incidence of paediatric referrals for INH-associated ALF and to describe the characteristics and outcome of 20 patients enrolled in the survey. The estimated incidence of

IPT-associated liver failure was up to 3.2/100,000. Four out of 20 patients recovered spontaneously, 10 underwent LT (2 died post transplantation) while 6 died awaiting LT. Notably, 5 patients seen for symptoms of hepatitis were initially advised not to stop treatment by their treating clinician, 4 of them were on INH monotherapy and developed irreversible liver injury, 2 had OLT and 2 demised(62).

Reports have shown that continued administration of INH beyond the onset of hepatitis symptoms is the most likely reason for severe DILI and deaths, and discontinuation of treatment at the onset of symptoms does not ensure recovery(64,65). Therefore, current recommendations by the Public Health Agency of Canada and the American Thoracic Society (ATS) are that INH should be withheld immediately at the appearance of any symptoms suggestive of liver dysfunction(62,65).

Due to the controversy that exist about the optimal monitoring strategy for patients taking INH and the lack of any sensitive and specific predictors of hepatotoxicity, studies to determine predictors of hepatotoxicity to guide clinical interventions aimed at the prevention or timely identification are needed(65).

Acute viral hepatitis:

Viral hepatitis is a serious public health concern and, although rare, is a well-documented cause of fulminant hepatic failure(1,35).

Of the hepatotropic aetiologies of acute viral hepatitis, hepatitis A virus is the leading cause of acute viral hepatitis in most of the developing world(1–3,10,12,26,28,31–36,47,67–70). It has a worldwide distribution and causes an estimated 1.5 million clinical cases annually(1,33,35,71). However, it is highly endemic in Asia, Africa and South America where the majority of population acquire a lifelong immunity through asymptomatic infection early in childhood(71).

Acute hepatitis A infection accounted for 50 – 60% of all cases of acute viral hepatitis in children in Pakistan(31,32,34).

Hepatitis A is an acute, vaccine-preventable and usually self-limiting infection, but can cause a high morbidity and mortality(1,33,35,36).

The clinically inapparent nature of HAV infection makes it very difficult to determine the exact prevalence of HAV-associated acute liver failure, however some studies found that the percentage of patients who develop ALF secondary to hepatitis A infection is < 1%(1,33,35).

Humans are the only known reservoir of the virus and its mode of transmission is closely related to the low socioeconomic circumstances including poor sanitation and lack of access to safe drinking water(1,31,32,40).

The virus sheds in the stool of the infected patients, whether symptomatic or asymptomatic, for prolonged periods and can survive in the environment for months(37).

The average incubation period of Hepatitis A virus infection is 28 days (range 15 – 50 days), and it is usually asymptomatic in children aged ≤ 5 years, clinically apparent cases were reported mainly in older children (5 – 10 years of age)(2,33,35), and the most common presenting symptoms were jaundice, which is by far the commonest clinical feature and was reported to occur in 100% of patients in some studies(9,31,35), followed by fever. Other less common symptoms with variable frequencies were nausea, vomiting, abdominal pain, anorexia, dark urine and mucosal bleeding.

The most common clinical manifestations were hepatomegaly, splenomegaly and hepatic encephalopathy with variable percentages among studies(9,31,34,35).

Kumar KJ et al reported that the most common complications caused by HAV infection were ascites, gall bladder wall thickening, INR > 1.5, pleural effusion, thrombocytopenia and ARF, 1.3% of children in this study had ALF with a reported mortality of 1.3%(35).

Several studies reported that HAV infection was the main cause of ALF that often required liver transplantation(9,12,26,31,32,34,36,47,67,69,72–74).

Is hepatitis A infection a relapsing disease?

Debray et al.(9) and Shah et al.(31) reported a relapsing hepatitis A infection, in about a quarter of their study cohorts, within 6 – 10 weeks and 3 – 12.8 weeks of initial presentation, respectively.

Seroprevalence of Hepatitis A virus:

Numerous studies, from areas with different endemicity levels, evaluated the prevalence of anti-hepatitis A virus antibodies(33,38–40,68).

It had been observed that there is a considerable difference in the seroprevalence of anti-hepatitis A antibodies among children of varying socioeconomic backgrounds with a lower prevalence reported among children from higher socioeconomic conditions(33,38–40,68).

In a community-based study conducted by Ikobah et al in rural areas in Southern Nigeria, 406 children aged 1 – 18 years were investigated for the presence of total anti-hepatitis A antibodies, the prevalence rate was found to be 55.2% and the median age for those with positive antibodies was 9 years. The prevalence was higher than that reported in a study carried out almost 20 years prior to this study in an urban hospital setting in South-west Nigeria(68).

The seroprevalence rate of anti-hepatitis A antibodies varied from 26- 85% in India(71). This was nearly comparable to the prevalence rates reported in Argentina, ranging from about 30% in the city of Buenos Aires to over 81% in the northern region of the country, with an overall seroprevalence of anti-hepatitis A antibodies of about 52%(34).

A small study, from Greece, including Roma children, a minority living under low socioeconomic conditions, aged 5 – 15 years found that the seroprevalence rate of anti-hepatitis A antibodies was 98.3%(39).

During 1988 – 1994, the National Health and Nutrition Examination Survey (NHANES) in the US estimated that prevalence rate of anti-HAV antibodies in adults aged ≥ 20 years was approximately 37.4% and the highest seroprevalence rates from US studies was noted to be among Mexican American and non-Hispanic blacks and the lowest reported rates were among non-Hispanic whites(37).

Improvement in sanitation and provision of safe drinking water have led to a dramatic decline of HAV prevalence in both developing and developed countries(34,37,40).

The introduction of targeted and universal hepatitis A vaccine into the immunisation programmes of many countries has also contributed significantly to the decrease of HAV infection in those communities(33,37,38,40,41,75).

Ciocci et al found that improved sanitation and the implementation of a 1-dose universal hepatitis A vaccination programme had significantly reduced the prevalence of hepatitis A infection and its dreadful complication acute liver failure. Not a single case of hepatitis A-related ALF was reported in the post-vaccination period (November 2006 – December 2008)(33).

The aforementioned measures have also resulted in a change in the epidemiology of hepatitis A infection and shifted the time of first exposure from early childhood to adolescence and adult age groups(39,40).

Implementation and impact of hepatitis A immunization programme:

Hepatitis A vaccine has been licensed for use in private market for over 2 decades, it was initially recommended for high-risk groups(33,37,40).

The Advisory Committee on Immunization Practices (ACIP) in the US recommended universal immunisation of children in areas in which the average annual incidence of hepatitis A disease is ≥ 20 cases per 100,000 population. This hepatitis A immunisation programme set a good example of the effectiveness of eliminating hepatitis A disease despite the disparities in disease incidence(37).

Since the introduction of a 2-dose universal Hepatitis A vaccination programme targeting children aged 18 and 24 months in Israel(38), many other countries subsequently implemented variable (1-dose vs 2-dose) hepatitis A vaccination programme(12,33,37,39–41,75).

Prior to the introduction of hepatitis A immunisation programme in Israel in 1999, Hepatitis A constituted > 95% of all acute viral hepatitis cases. The mean incidence of hepatitis A in Israel was 50.4 cases per 100,000 per year during the period from 1993 – 1998, that had strikingly declined to 2.2 -2.5 cases per 100,000 per year during 2002 – 2004, the highest incidence was

reported in the age group of 5 – 9 years. Notably, the greatest decline in disease rates was observed in the same age group. However, a remarkable decline was observed in all age groups(38).

Similarly, studies from countries that implemented the hepatitis A immunisation programme have shown a remarkable decline in the incidence, notification and hospitalisation rates of hepatitis A infection when comparing the results from pre- and post-vaccination era(12,33,37,39,40,75).

Thompson et al reported that the overall national notification rate had declined from 4.25 cases per 100,000 in 2000, before the introduction of hepatitis A vaccine in November 2005, to 0.97 cases per 100,000 in 2014(40).

Despite the large foodborne and waterborne outbreaks reported in many regions, the overall burden of hepatitis A infection remained low(37,40).

Hepatitis A vaccination programme not only reduced the disease burden and high economic cost of acute liver failure but also made additional liver transplants available for those with ALF from other aetiologies(33,75).

M. T. Valenzuela et al.(75) estimated the cost of vaccination programme (USD 5.4 – 6.4 millions) vs the disease cost (USD 9.2 – 9.4 millions), and reported that the mean duration of work loss was estimated be 28 days, based on review of Ministry of Health records, which was in line with reports from the US and Israel(37,38).

Hepatitis E virus:

In many Southeast Asian countries, Hepatitis E is now the most common cause of ALF(1,32).

Poddar U et al.(2) reported it to be the second most common viral aetiology of fulminant hepatic failure, and it is even more common than Hepatitis A as an underlying cause of acute viral hepatitis in some developed countries(1,32).

Although hepatitis E infection carries a low mortality. However, the outcome is worse in the elderly patients with established chronic liver disease and in pregnant women, transmission of hepatitis E from women with acute infection to their babies results in ALF in more than 50% of neonates(1). Infection with hepatitis E virus confers immunity for 8 -10 years and is lost thereafter, predisposing the individual to re-infection(32).

Hepatitis B virus:

Another vaccine-preventable disease, which accounts for almost 30% of ALF in some regions in Europe and is the leading cause in Asia, Sub-Saharan Africa and Amazon Basin(1).

Fewer than 4% of cases of acute hepatitis B infection develop ALF, but the mortality rate is higher than that due to hepatitis A and E infections(1).

In Taiwan, because of the hyperendemicity of the hepatitis B virus, it had been reported as the most common aetiological agent of ALF in children in the pre-vaccination era(34).

Other viruses:

Other uncommon but well-known viral causes of ALF include HSV 1 and 2, HHV 6, VZV, EBV, CMV and parvovirus B19(1,6,28).

Hosnut et al.(76) reported adenovirus infection as a potential cause of ALF in an 18-month-old boy who had been previously and whose work-up for all the other possible causes returned negative.

Cytomegalovirus was found to be the most common cause of viral hepatitis leading to ALF in Cuban infants(77).

A few reports from Brazil pointed out an unusual type of ALF affecting children and adolescents, known as Labrea fulminant hepatitis, and is related to hepatotropic (Hepatitis A-D) viruses, singly or in combination, and Yellow fever virus. It has a distinct histopathological pattern and it had been found in the Brazilian territory of the Amazon Basin as well as other South American and Central African countries(70,78).

Reported cases of rare causes of ALF in children:

Calve et al reported an 11-month old boy who presented with repeated episodes of ALF, he initially presented in ALF after having received paracetamol for 10 days, and although the dosages were therapeutic, his condition was still attributed to the chronic use of paracetamol and responded well to NAC and recovered, he subsequently had further episodes of ALF which warranted further work-up, including DNA analysis, which revealed mutations in the NBAS gene as the culprit of recurrent ALF in his case(79).

Kuloglu et al reported a yellow nail syndrome, in an 11-year old boy, as the cause of ALF, after all the other aetiologies have been ruled out, the child underwent a successful LRLT.

Surprisingly, the donor is the child's father who is also known with yellow nail syndrome(80).

Baranwal et al reported an apparently previously healthy 1.5-year old girl who developed ALF secondary to visceral leishmaniasis(81).

Whitney et al reported a 7-year old boy who was diagnosed with disseminated TB and developed ALF secondary to the first line ATT, he was then switched to a modified regimen for the treatment of disseminated, MDR-TB, including (which included) ethambutol, levofloxacin, amikacin, cyclosporine and linezolid, the child made a good recovery and survived without LT(82).

Turkova et al reported the first paediatric HIV case who developed ALF related to efavirenz-based HAART, who required a LT and showed a good response to raltegravir-based regimen post-LT(83).

Thakur et al reported a very rare case of a 6-year old child who developed ALF secondary to mixed falciparum and vivax malarial infections, the child eventually demised despite supportive and anti-malarial treatment(84).

Cheung et al reported a premature baby, born at 31 weeks and 3 days, who presented at the age of 5 weeks with ALF. Thorough investigations for the causes of neonatal liver failure revealed an isolated cortisol insufficiency as the underlying cause, which had subsequently responded to oral hydrocortisone treatment with normalization of INR within 8 days of initiation of treatment(85).

Prognostic factors of outcome in children with ALF:

The early and rapid decline of hepatic functions in children with ALF has urged the need to develop sensitive prognostic indicators and predictors of outcome. The need is even more urgent in the developing world, where liver transplantation is either scarce or lacking in some settings, in order to guide the decision to either manage medically or refer early to a liver transplantation centre.

Compared with adult studies, few studies addressed the early indicators of prognosis in children with ALF and no standard prognostic criteria have been established.

Various clinical variables and biochemical parameters have been studied to evaluate its correlation with the outcome with or without liver transplantation.

Poddar et al, in a study of 67 children aged ≤ 12 years carried out in a tertiary hospital where LT is not available, found that younger age, higher grade of encephalopathy, higher serum bilirubin, prolonged PT and ascites with spontaneous bacterial peritonitis were good predictors of mortality. Serum bilirubin levels and grades of encephalopathy were significantly higher, serum albumin was remarkably lower, and PT was significantly prolonged in those who demised that in those who recovered. It was also observed that all 5 children who developed gastrointestinal bleeding (GIB) had died(86).

Similar results were reported by Ciocca et al when he found that higher grades of HE, higher levels of serum bilirubin and prolonged PT were significantly associated with death or need for liver transplantation(34).

Srivastava KL et al also found that serum bilirubin level, degree of come and GIB were independent predictors of mortality(87).

Psacharopoulos et al showed that prolonged PT, GIB, grade of encephalopathy and renal failure were related to poor outcome in children with ALF(88).

Lee et al found that prolonged time to onset of hepatic encephalopathy (HE) > 7 days, PT > 55 seconds and ALT ≤ 2384 IU/l were independent prognostic indicators for either death or need for LT. it was noted that children who had higher serum bilirubin levels, more prolonged PT, more delayed time interval between the onset of symptoms and the development of HE and lower ALT and on admission were more likely to die or require LT(25). compared to findings by Ciocca(34) et al and Kaur et al(26).

Lee et al suggested that etiology might be an important prognostic factor when he found that children with ALF from hepatitis A infection, autoimmune hepatitis and paracetamol overdose had a better survival, with supportive management, compared with those from other causes(25).

Srivastava et al, in a study looking at the predictors of outcome in children with acute viral hepatitis and coagulopathy, found that age < 3.5 years, serum bilirubin ≥ 17.6 mg/dl, PT > 40.5 seconds and clinical signs of cerebral oedema were independent risks of mortality, they also noted that mortality had increased with increased number of these risk factors and it was also found that children with AVH-associated ALF who developed hepatic encephalopathy with coagulopathy had poorer outcomes than those with coagulopathy alone(69).

Srivastava KL et al(87) and Kaur et al(26) found that hypoglycaemia (BG < 45mg/dl) is a good predictor of mortality, which highlights the fact that early recognition and timely management of this predictable but treatable complication can improve outcome.

Rajanayagam et al.(5) found that ALT < 4660 IU/l on admission, INR > 4, and peak serum bilirubin > 220 µmol/l to be independent predictors of poor outcome.

Bhaduri et al.(13) concluded that urgent LT should be considered when the INR reaches 4, especially in young children, after they had observed that the highest INR reached during the course of illness was the most sensitive predictor of outcome, with 86% of children with an INR ≥ 4 demising versus 27% (i.e 73% surviving) with an INR < 4, prognosis was worse in children aged < 2 years. Likewise, Bitar et al.(42) considered infants for LT when the INR was > 4.

Factor V concentration of < 25% of normal has been associated with either death or need for LT(11,28).

Poddar B et al, in a study undertaken in an ICU setting in which children comprised 40% of the study population, found that, in addition to the abovementioned clinical and laboratory variable, higher sequential organ failure assessment (SOFA) score (> 9.5) on admission was associated with higher mortality in ALF(89).

King's College Hospital criteria and Clichy criteria, the 2 most recognised criteria, have been used to predict the outcome in adult patients with ALF. However, trying to apply them to

predict outcome in children can be difficult as, for example, both criteria incorporate hepatic encephalopathy (HE) as a variable, which can be either absent, difficult to assess particularly in infants and younger children or progresses rapidly in some children with ALF(17,90).

Wilson's disease (WD) presenting with HE is nearly 100% fatal and the only treatment option is LT. But the decision to list a child with WD without hepatic encephalopathy, for liver transplantation, is very difficult. The Revised KCH Wilson's index, which incorporates bilirubin, INR, AST, white blood count and albumin at presentation, has been useful in identifying patients who have a high risk of mortality(17,28).

Is hypophosphatemia a predictor of outcome in patients with ALF?

Hypophosphatemia is a very common electrolyte abnormality in children with ALF, although it has been partly explained by the massive uptake of phosphate by the regenerating hepatocyte, However the precise mechanism by which hypophosphatemia develops is not clearly understood(91).

Since normal phosphorus level varies with age, hypophosphatemia is defined as serum phosphorus level that is at least 2 SD below the mean for the age of the child.

In a retrospective review of children with ALF, Quiros-Tejeira et al.(91) found that hypophosphatemia preceded the improvement in liver function in children who recovered either spontaneously or with LT. and that hypophosphatemia continued to improve until it normalised after the complete recovery of liver functions.

This observation suggested that hypophosphatemia might be a useful indicator of recovering liver synthetic functions in children with ALF and highlighted the significance of prompt and aggressive phosphate supplementation in patients with ALF(91).

Earlier studies had found that hypophosphatemia was specifically attributed to acetaminophen and amanita phalloides poisoning but more recent studies reported that serum phosphorus level is a potential predictor of outcome in adult patients with acetaminophen-induced and nonacetaminophen-induced ALF. Quiros-Tejeira findings were in line with the more recent studies as his review included children with ALF from various etiologies(91).

Ozturk et al found, in more than half of the 21 children who were retrospectively analysed, that serum phosphate was significantly lower in children who recovered spontaneously than in those who either died or required LT. they concluded(reported) that lower serum phosphate levels predicted a spontaneous recovery. By contrast, it was found that serum phosphate ≥ 2.9mg/dl and presence of hepatic encephalopathy were recognised (identified) as predictors of poor outcome(92).

On the other hand, normal or high phosphate levels can result from acute renal failure that commonly complicate ALF and results in impaired excretion of phosphate(91,93).

Clinical consequences of hypophosphatemia

Severe hypophosphatemia may cause derangement of leukocyte function, quantitative and qualitative platelet dysfunction, diminished oxygen transport and tissue hypoxia and generalised muscle weakness. These consequences can clearly worsen (aggravate) the complex clinical picture of ALF(91).

Liver transplantation:

In spite of the potential complications associated with liver transplantation and the adverse effects related to the lifelong immunosuppression, this surgical procedure remains the cornerstone in the management of ALF, it has changed the outcome of ALF.

However, depending on the aetiology, specific treatment options may be used.

Here are some historical facts regarding liver transplantation in children:

▪ The first successful living-related donor liver transplantation (LDLT) in a child was performed in Australia in 1989(27).

▪ From Jan 1989 to Dec 2005, 575 children received liver transplantation at King's College Hospital, 96 of the 575 were for metabolic liver diseases(94).

▪ There were 2 main regional paediatric liver units in the UK in the 1990s, Birmingham Children's hospital and King's College Hospital(43).

▪ The Hospital Nacionale de Pediatria Juan P. Garrahan in the city of Buenos Aires in Argentina has had a liver transplantation programme since November 1992(34) and nearly a year later, in September 1993, a whole-organ transplantation was performed(95).

▪ Paediatric liver transplantation programme in Chile was started in 1993 in Santiago(74). From January 1994 to March 2009, 52 children were transplanted for ALF(72).

▪ The Hospital de Clinical in Southern Brazil in the city of Porto Alegre, which serves a population of 1.5 million, has had a Paediatric LT programme since 1995(36).

▪ The Beatrix Children's hospital of the university medical centre Groningen is the only paediatric liver transplantation facility in the Netherlands(96).

▪ Hospital de Bicetre, the main Paediatric LT centre in France, initiated their Paediatric LT programme in March 1986(11).

▪ In the period between January 1988 and Jan 1998, the united network for organ sharing (UNOS) documented 84 Pediatric LT centres in the US, the UNOS recorded a total of 4679 pediatric OLT in the US from 1st of October 1987 to 31st of January 1997(62).

▪ In Japan, 6097 LDLT were performed between November 1989 – December 2010, of these, 2224 were children aged < 18 years (the largest LDLT cohort in the world), biliary atresia was

the leading indication for LDLT (n=1471) followed by metabolic disorders (n=194) and ALF from various aetiologies (n=190)(97).

▪Paediatric cadaveric and living-related donor LT were started, at the department of Paediatric surgery at Ege university in Turkey, in March 1997 and October 1999, respectively(47).

▪ As of 2007, Paediatric liver transplantation at Schneider Children's Medical center in Israel was initiated in 1996, and since then, 72 LT had been performed, including 19 living related(27).

▪ ALF accounted for 8% of LT indications in Europe during 1988-2009, and according to reports from the European Liver Transplant Registry (ELTR), there were 87,963 LT performed in 79,063 patients in 23 European countries over 43 years (according to a study published in 2003)(98).

▪ The Queensland Liver Transplant Service (QLTS) at Royal Children's Hospital in Brisbane, established in 1985, was one of the 3 paediatric liver transplant centres in Australia that accepted ALF patients from as far as New Zealand, South Pacific and Asia(90).

The only 2 centres that presently offer liver transplantation to the entire paediatric community in SA are Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town and Wits Donald Gordon Medical Centre (WDGMC) in Johannesburg and they are the only 2 well-established paediatric liver transplant units in Sub-saharan Africa(99,100).

In 1984, a 2-year old girl, Simone Georgiades, was the first SA child to receive a liver transplant, she initially had a hepaticoenterostomy for biliary obstruction secondary to obliterative sclerosing cholangitis. Simone subsequently developed end-stage liver disease and was transferred to Cambridge where she had a successful liver transplant(101).

In December 1987, the first paediatric LT performed at RCWMCH was for end-stage liver disease due to alpha-1 antitrypsin deficiency, the paediatric liver transplantation programme was then suspended until November 1991(102).

The WDGMC paediatric liver transplantation programme (PLTP) was initiated in the November 2005 and it was initially established in the private sector which was subsequently expanded into the provincial sector after receiving government approval(99). Since its inception in November 2005 the PLTP at WDGMC had run up against many challenges, most importantly the lack of funding from the National Health authorities, lack of adequately trained personnel, shortage of organs, problems with regular provision of essential medications and lack of a reliable laboratory service(99,101,103).

The lack of resources has resulted in slowing the progression of the programme during 2010 and 2011. However, many of the challenges were subsequently overcome and the programme was revived and expanded shortly thereafter, and its outcome is comparable with some of the world-class PLT centres(100).

During the period between November 2012 and June 2014, eight children with ALF requiring LT were referred to WDGMC. However, only 3 were successfully transplanted for Wilson's disease, hepatitis A infection and Hepatitis B infection while the remainder died awaiting LT(100).

Methods

Patients in this case series were retrospectively identified by searching the database of the Paediatric Gastroenterology Service medical records and the electronic laboratory service at Tygerberg hospital. Between January 2009 and December 2013, 19 patients less than 13 years old, with acute liver failure, were included in the study and their medical records were reviewed.

Acute liver failure was defined according to the PALF study group definition, which is:

1. Having no pre-existing liver disease. 2. Biochemical evidence of acute liver injury e.g raised plasma bilirubin and raised liver enzymes. 3. Coagulopathy defined as prothrombin time (PT) ≥ 15 seconds or International normalized ratio (INR) ≥1.5 not corrected by Vitamin K, in the presence of clinical hepatic encephalopathy, or PT ≥20 seconds or INR ≥2 regardless of the presence or absence of clinical encephalopathy.

The following variables were recorded: demographic information, aetiology and outcome.

Baseline investigative work-up included liver enzymes, coagulation profile, urea and electrolytes, sepsis screen, blood glucose and hepatotropic viruses.

Further investigations, including investigations for inherited metabolic diseases, were performed depending on the clinical presentation of each patient.

All patients were managed according to a standard treatment protocol for management of ALF in children. Hypoglycemia was being monitored and treated, fresh frozen plasma and platelets were given when clinically indicated, antibiotics were prescribed for suspected and proven sepsis and were tailored according to the culture results and depending on their clinical condition, mechanical ventilation was instituted to patients who needed it.

None of our patients received liver transplantation as we unfortunately lack this service in our hospital, although some patients were considered for transfer to a nearby centre where they could have received it.

Based on the final outcome, patients were classified in to 2 groups as either survivors or non-survivors.

Statistical analysis:

Data was captured on a data collection sheet and entered into a Microsoft Excel® spreadsheet.

Patient confidentiality was ensured by using a numbering system as described in Ethical Considerations (please refer to the attached protocol).

Standard descriptive and inferential statistical techniques were used. Continuous variables are reported as medians and interquartile values in parenthesis or means with standard deviations in parenthesis where appropriate.

Medians were compared with the Wilcoxan Rank Sum test and categorical data with the Chi-square test. Statistica®version 13 (Dell Software) was used for the analysis. A p value of less than 0,05 was considered statistically significant.

Results:

There were 19 children (12 boys), aged 5 weeks to 6 years with a median age of 18 months and an interquartile range (IQR) of 36 (7,43) months, with ALF that could be traced during the 5-year study period.

Age distribution:

There were 6 (31.6 %) children aged ≥ 1 month - ≤ 1 year, 12 (63 %) children aged ≥ 1 year - ≤ 5 years and only 1 child aged 6 years old.

Underlying aetiologies of ALF are summarized in Table 1.

Infective causes: there were 13 children with an infectious cause of ALF. Ten were hepatitis A IgM positive. Herpes simplex virus type 1 (HSV-1) infection was diagnosed in an 18-month old child, CMV hepatitis was the cause of ALF in 1 RVD positive child, 1 child had a Human Herpesvirus 6 (HHV-6) infection.

Drugs and toxins:

Two patients had INH-related ALF and one child presented with ALF secondary to ingestion of unknown substance.

Indeterminate causes: the diagnosis could not be identified in 2 (10.5%) patients.

Metabolic causes:

A 5-month old child, with no history of parental consanguinity, presented with ALF after a history of herbal ingestion, however, his postmortem findings were in keeping with a metabolic disorder. The family history was also highly suggestive of an inherited metabolic disorder: 3 previous early infantile deaths in whom there was no specific disorder was identified. Unfortunately, the child demised so early before a complete metabolic work-up could be carried out.

Outcome:

The overall mortality was 52.6% (10 of 19 died) and the survival rate was 47.4%.

Mortality was higher among children with ALF associated with acute viral hepatitis, 60% (6 of 10) of children with hepatitis A demised. Children with HSV-1, HHV-6 and CMV infections also died. Children with INH-related ALF and those with indeterminate causes recovered spontaneously.

Overall, hepatitis A-related ALF constituted the highest morbidity and mortality.

All hepatitis A patients who survived were males, and the 2 INH-related ALF who survived were males also and, in their case, the INH was discontinued at the appearance of first signs of liver disease.

Table 1: Demographics, aetiology and outcome of children with ALF

Patient	Age	Gender	Aetiology	Outcome
1	4 yr	M	Hepatitis A	Died
2	2yr 7m	F	Hepatitis A	Died
3	3 yr 11m	M	DILI (INH)	Recovered
4	5 wks	M	Indeterminate	Recovered
5	1yr 6m	F	HSV-1	Died
6	3.5m	F	HHV-6	Died
7	1 yr	M	DILI (unknown toxin	Recovered
8	7 m	M	Hepatitis A	Recovered
9	2yr 4m	M	Hepatitis A	Died
10	2 yr 9m	F	Indeterminate	Recovered
11	2 yr 5m	M	DILI (INH)	Recovered
12	1yr 6m	M	Hepatitis A	Died
13	5.5m	M	Toxin /?metabolic	Died
14	5m	M	CMV	Died
15	3yr 7m	F	Hepatitis A	Died
16	1yr 5m	F	Hepatitis A	Recovered
17	1yr 5m	F	Hepatitis A	Died
18	6 yr	M	Hepatitis A	Recovered
19	3 yr 7m	M	Hepatitis A	Recovered

Prognostic factors:

There was no noticeable difference in liver enzymes levels between infectious and non-infectious aetiologies.

All patients (except one) who had demised had an INR > 4. An INR > 4 has been found to accurately predict death or need for LT(13). In fact, our patients with INR > 4 would have been considered for LT according to the criteria of NHS UK Blood and Transplant(42).

The mean, median and interquartile range of the INR were calculated using the maximum INR reported, for all the patients, throughout the duration of illness.

The mean, median and IQR, for the total number of study patients, were 6.85, 6.56 and 6.06 respectively. Those who recovered had a mean of 4.37, a median of 3.9 and an IQR of 2.02, whereas those who demised had a mean of 9.09, a median of 10 and an IQR of 1. This was statistically significant (p= 0.0001).

Table 2 shows the mean, the median, the IQR and the standard deviation of the INR for the total number of patients, survivors and non-survivors.

Table 2.

	INR (n = 19)	INR (survivors)	INR (non-survivors)
Mean	6.85	4.37	9.09
Median	6.56	3.9	10
Interquartile range (IQR)	6.06	2.02	1
Standard Deviation (SD)	3.1010	2.348	1.621

Four of the 6 hepatitis A patients who had died were less than 3.5 years and their PT levels were > 40.5. All the other three patients who also had viral causes of ALF, namely HSV-1, CMV and HHV-6, were found to be below the age of 3.5 years and their PT levels were > 40.5.

Factor V levels (median = 37%, IQR = 109) were measured in 11 patients (5 survivors and 6 non-survivors) of the 19 patients. Only two of them had factor V levels (8%, 15%) less than 25%, and they both demised. Survivors had a median of factor V levels of 39 and an IQR of 114 vs a median of 35.5 and an IQR of 30 for non-survivors. And there was no significant statistical difference between survivors and non-survivors (p = 0.3483).

Hepatic encephalopathy grading and charts of blood glucose were missing from the notes of many patients as they were being reported on separate charts (Blood glucose readings are recorded in the nursing chart).

Phosphorus levels have not been shown to be of any prognostic value in our study.

Discussion:

Acute liver failure is a rapidly progressive and potentially fatal medical condition. It is defined by a combination of clinical signs and biochemical findings in a patient without a pre-existing liver disease.

The Pediatric Acute Liver Failure Study Group (PALFSG), which was formed in 1999, defined ALF in children as 1. Having no pre-existing liver disease 2. Biochemical evidence of acute hepatic injury e.g raised plasma bilirubin and liver enzymes 3. Coagulopathy defined as prothrombin time (PT) $\geq$ 15 seconds or International normalised ration (INR) $\geq$ 1.5 not corrected by vitamin K, in the presence of hepatic encephalopathy (HE), or PT $\geq$ 20 seconds or INR $\geq$ 2 regardless of the presence or absence of HE.

Our study results demonstrated that acute viral hepatitis is the most common cause of ALF in children, which are comparable with results from the developing countries. Of the viral aetiologies, hepatitis A was the most predominant and carried the highest morbidity and mortality.

Although it is well-documented that Hepatitis A infection is prevalent among people living under low socioeconomic circumstances with poor sanitation and no access to safe drinking water(1,12,32,33,38,40,68,104), neither the seroprevalence of hepatitis A is known in our setting nor is Hepatitis A vaccine included in our EPI.

Many countries have implemented the hepatitis A vaccine in their national immunisation programme and this measure, together with improvement in sanitation and provision of safe drinking water, have proven to be effective in reducing the incidence of hepatitis A infection and its complications.

Despite the high burden of paediatric TB disease in the country(56,105), only 3 patients who developed INH-related ALF were found in the medical records during the study period and the 3 survived. Two of the three patients were followed up and it had taken the liver enzymes 2 months to normalise in one patient while it had taken the other one 6 months to return to normal levels.

Two patients had only INH-related ALF and the third patient was on IPT which was stopped a few days after he was diagnosed with Hepatitis A infection.

Fourteen of the 19 patients tested negative for HIV, 2 were HIV positive, and the HIV status for 3 patients was not recorded in their medical records (not known). One of the 2 patients aged 5 months, who was HIV positive, developed CMV-induced ALF and demised, and the other HIV positive patient, aged 17 months, who developed ALF as a result of hepatitis A infection, had not even been on antiretrovirals, had surprisingly recovered.

No patients with paracetamol toxicity were found in our study.

The 2 patients in whom the diagnosis was deemed indeterminate had recovered before the workup was completed, thorough investigations could have revealed an aetiology.

No confirmed case of metabolic disorder was reported in any of our patients despite the thorough metabolic investigation that had been carried out whenever it was thought indicated, and this could be partly due to the small number of patients enrolled in the study or could be attributed to the fact that there were no neonatal data found in our GI service database or it could also be due to the absence of history of consanguinity in our study.

The only one patient who was suspected to have an underlying inborn error of metabolism was a 5 and a half-month old infant who presented in liver failure after being given some herbal medication by a traditional healer, the infant had a strong positive family history of unexplained early infantile death of 3 siblings and the post-mortem findings (neurodegenerative changes) were consistent with inherited metabolic disorder but no definitive diagnosis could be made, and it was not clear whether the herbal medication caused severe liver injury and ALF or it triggered a state of metabolic decompensation in an infant with suspected underlying inherited metabolic disorder who had been otherwise previously well.

Prognosis:

Of the proposed predictive markers for either death or the need for liver transplantation, the predictors of outcome in children with acute viral hepatitis in children that were suggested by Srivastava et al(69) were the most applicable to our setting.

All patients who demised, except one, were under the age of 3 years, comparable to the PALFSG, which showed an increased risk of death/LT among < 3-year-old versus ≥ 3-year-old groups(4).

We found that the widely used King's College Criteria(3,17,34,89) not to be applicable to our patients as, for instance, the HE grade, which is difficult to assess but yet an important criterion, had unfortunately not been documented in the notes of most of our patients and what is considered unfavourable causes (DILI, indeterminate) according to those criteria had been shown to be favourable in our patients.

Neither liver enzymes levels nor factor V levels were not found to be good predictors of mortality or need for LT, and this could be because of the small number of our study population.

Weaknesses and limitations:

The study sample is relatively small, and it was conducted in a single paediatric GI unit in the Western Cape province, and although our unit lacks LT service and we had the option of transferring our potential LT candidates to a nearby facility where LT could be performed, but the scarcity of liver donors remains one of the enormous challenges.

The data were collected retrospectively which means that there had been some missing and incomplete data.

Our neonates with suspected or proven ALF are admitted to the neonatal wards and although they would be discussed with the GI team, but they would not be transferred physically to the GI ward which means that they would not be registered with the GI unit and hence impossible to trace from the GI database.

Hepatic encephalopathy grading score forms were not filled out for most of the patients which meant losing valuable information and precluded the possibility of contrasting signs of cerebral oedema with other studies as an invaluable predictor of mortality.

Strengths:

To the best of our knowledge this is the first recently published study that has shed some light on the outcome of ALF in children in Africa.

Recommendations:

Although a small number of patients were enrolled and it was carried out in a single centre, which does not represent the outcome of the other GI units in the RSA, but we hope that our findings will lay the foundations for larger, multicentre and prospective studies to better evaluate the outcome of ALF in children nationwide.

There is an urgent need for implementation of hepatitis A vaccine in the EPI in the RSA, as its cost-effectiveness has been proven by many studies from developed and developing countries.

Other measures that would, together with introduction of hepatitis A vaccine, temper the incidence of hepatitis A infection is the improvement of sanitation and provision of safe drinking water and the overall improvement of socioeconomic conditions.

Besides the need for a multicentre and prospective studies, our study points up the need for the establishment of more well-structured paediatric liver transplantation centres and the encouragement of organ donation. Argentina and Chile have set a successful example of an efficient LT programme for developing countries, provided that local limitations are taken into account(72,95).

Neonates with ALF who are being managed in the neonatal units in our hospital need to be registered with the GI service in order for their records to be easily traced for future studies.

Time to referral, and its effect on the outcome, needs to be determined.

Conclusion:

Some aetiologies of the ALF in children can be prevented and others can be ameliorated via prompt evaluation and timely interventions.

Hepatitis A infection, although preventable, is the most common cause of ALF failure in children. Measuring the risk of infection and its dreadful complications and the cost and complications of LT and lifelong immunosuppressants against the cost and benefits of 2 shots of hepatitis A vaccine favours the introduction of hepatitis A vaccine in the EPI in South Africa.

The unprecedented major drought in the Western Cape province will take its toll on the health system in the province.

Larger, prospective and multicentre studies are needed to better evaluate the aetiology and outcome of ALF in children in South Africa.

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