A retrospective review of acute liver failure in children admitted at Red Cross War Memorial Children's Hospital

By

Rachel Mlotha Mitole (**MBBS**, FCPaed(SA), Cert Gastroenterology Paed SA)

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Supervisor: Dr Goddard EA (MBChB, MMed (Paed), PhD, Paediatric Gastroenterologist)

Co supervisor: Dr De Lacy RJ (MBChB, FcPaed(SA), Paediatric Gastroenterologist)

University of Cape Town

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DECLARATION

I, RACHEL MLOTHA MITOLE, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Signature: Signed by candidate

Date: 29 DECEMBER 2020

ABSTRACT

Acute liver failure (ALF) describes a clinical syndrome resulting from severe liver damage and extensive loss of functional parenchymal liver mass triggered by various factors. Early recognition and initiation of specific therapy may improve outcomes and reduce the need for liver transplantation, a treatment modality not universally available in resource constraint areas. There is paucity of data describing this syndrome in Sub-Saharan Africa in children.

Objective
This study aims to retrospectively review and determine the clinical presentation, aetiology, complications & outcome of ALF in children admitted at the Red Cross War Memorial Children's Hospital (RCWMCH).

Methods
All records of children from 0 to 13 years admitted at the RCWMCH over the period from January 2005 to December 2016 with ALF were retrospectively reviewed, after obtaining ethical approval. Patients with pre-existing evidence of chronic liver disease were excluded. Demographic variables as well as clinical presentation and investigations were captured, with determination of outcomes at 3 weeks and 6 weeks of diagnosis.

Results
Study included 24 children., 16 females (66.7%) and 8 males (33.3%). Median Age was 15 months, with interquartile range from 5 to 28 months.
Diarrhoea, jaundice, respiratory distress, hepatomegaly and encephalopathy were common clinical features.
Aetiology was infection in 37.5 % of cases (n=9, 2 of whom had autoimmune hepatitis comorbidity) and hepatitis A was most common infectious cause (n=4, 44%). Causes were indeterminate in 29.2%. Two patients had autoimmune hepatitis without co-morbidity; Reye syndrome 12.5% and 17% had miscellaneous causes. Transaminases were raised to thousands in viral causes of hepatitis, with a low C reactive protein. INR >4 and Total Bilirubin>210umol/L were associated with death outcome (p=0.04 and p=0.03 respectively.

Conclusion
Viral hepatitis A is the leading infective cause of acute liver failure in this study cohort and 29.2% of cases were indeterminable. INR >4 and Bilirubin > 210umol/l were predictors of poor outcome. Follow up study is recommended to better understand clinical spectrum and outcomes of children with acute liver failure in this low resource setting.

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Rachel Mlotha Mitole

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ABBREVIATIONS

AIH	Autoimmune Hepatitis
ALF	Acute liver failure
ALKMA	Anti-Liver-Kidney-Microsomal Antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASMA	Anti-Smooth-Muscle-Antibody
CLD	Chronic liver disease
CMV	Cytomegalovirus
Cr	Creatinine
CRP	C Reactive Protein
CT	Computerised Topography
DIC	Disseminated Intravascular Consumption
DILI	Drug Induced Liver Injury
EBV	Epstein-Barr Virus
FHF	Fulminant Hepatic Failure
GALD	Gestational Alloimmune liver disease
GGT	Gamma Glutamyl transferase
HAART	Highly Active Anti-Retroviral Therapy
HB	Haemoglobin
HBV	Hepatitis B
HHV 6	Human Herpes Virus 6
HIV	Human Immune Deficiency Virus
HLH	Haemophagocytic Lymphohistiocytosis
HPV	Human Papilloma Virus
HREC	Human Research Ethics Committee
HSV	Herpes Simplex virus
ICD	International Classification of Disease
IEM	Inborn errors of metabolism
INR	International Normalised Ratio
IQR	Interquartile Range
LDH	Lactate Dehydrogenase

LDL	Lower than Detectable Level
LT	Liver Transplant
MLD	Metabolic Liver Disease
MRCD	Mitochondrial Respiratory Chain Disorder
Na	Sodium
NAC	N- Acetyl Cysteine
NH4	Ammonia
OTC Def	Ornithine TransCarbamylase Deficiency
PALFSG	Paediatric Acute Liver Failure Study Group
PELD	Paediatric End Stage Liver Disease
PLT	Platelet
TB	Tuberculosis
TSB	Total Serum Bilirubin
UCT	University Of Cape Town
UK	United Kingdom
USA	United States of America
VL	Viral Load
WCC	White Cell Count

CHAPTER 1: INTRODUCTION

1.1 Context

Paediatric liver disease is a significant cause of morbidity and mortality worldwide. The natural history and outcomes have dramatically improved due to advances in diagnosis and management including the successful development of liver transplantation. (1,2)

In Sub-Saharan Africa, it has been demonstrated from the 2010 Global Burden of disease study that mortality due to liver disease has doubled between 1980 and 2010 including viral infections such as Hepatitis B which may cause acute liver failure (ALF) in children. (3) Most of this data was obtained through verbal autopsies hence the actual incidence and aetiology of paediatric ALF in Sub-Saharan is not well documented. At Red Cross War Memorial Children's Hospital (RCWMCH), ALF accounts for about 11.9% of paediatric liver transplants. (4) The Wits Donald Gordon Medical Centre (WDGMC), in Johannesburg, is the only other centre providing liver transplantation services in South Africa and they recently reported that 15% of liver transplants were due to ALF. (5) These are similar to the United States of America (USA) where studies in Paediatric Liver Transplantation database showed liver transplantation for ALF accounted for 12.9% of all the paediatric cases. In the USA, ALF is estimated to affect 2000 people per year (6), and 400 people per year in the United Kingdom (7).

Acute liver failure is a rare syndrome with rapid progression and potentially fatal clinical outcomes. It describes the loss of synthetic function of the liver as a consequence of acute hepatocellular necrosis with loss of functioning hepatic parenchymal mass. The liver is a special organ in that it is able to regenerate cell mass. Therefore, liver failure indicates significant necrosis with the resultant failure to carry out its normal functions. It may also be a result of progression of existing chronic liver disease in which case it is termed acute on chronic liver failure. (2, 8, 9, 10, 11). Various complications arise as a consequence of the insufficiency including coagulopathy, with or without encephalopathy and even death, in children without prior recognized chronic disease of the liver. (11)

The criteria used in literature to identify ALF for study entry includes:

a) hepatic based coagulopathy defined as a prothrombin time (PT) ≥15s or International Normalized Ratio (INR) ≥ 1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy OR a PT ≥20s or INR≥ 2.0 regardless of encephalopathy;

b) biochemical evidence of acute liver injury;

c) no known evidence of chronic liver disease. (12,13)

The severe hepatic necrosis may develop secondary to a trigger such as a microbial agent, toxin, immune-mediated attack or metabolic syndromes and the hepatic damage may be multifactorial

with co-morbid states, where more than one condition is identified. This may be grouped into infectious (where viral hepatitis refers to viral causes of hepatitis), drug induced, metabolic, ischaemic and immune dysregulation. (2, 14)

Aetiology

The aetiology of ALF varies according to age and differs from that in adults with metabolic liver disease being more common in young infants and Wilson's disease, viral and autoimmune hepatitis in older children (2, 15, 16, 17).

Aetiology also differs according to the development of the country as well as geographical location, susceptibility of the host and extent of injury (9,15,18,19), with hepatitis A being common in Asia and South America (20, 21, 22), and drug mediated injury is more common in Europe and North America (18, 17). In a Nigerian adult study looking at patterns of liver disease in a tertiary hospital, a significant proportion had ingestion of herbs and roots, and hepatitis B virus infection (23). There is paucity of data in Sub-Saharan Africa describing the pattern of paediatric ALF aetiology, risk factors and outcomes.

The Paediatric Acute liver failure Study Group (PALFSG) has conducted large multicentre trials in West Europe and North America, demonstrating metabolic disease more prevalent in younger children and drug toxicity in older children. Despite having studies as those performed in the Western countries that have analysed aetiology and derived prognostic indicators, there is still a significant percentage of children in whom aetiology is indeterminate (49%) and necessitates further investigation. The indeterminate group may have the worst prognosis after recovery (13). Narkewicz et al suggest the high number of indeterminate cases may be due to incomplete investigation (24). Other studies have suggested increasing the metabolic and genetic screening for younger children for detection of aetiologies due to metabolic disease. (25)

ALF should be recognised early and guidelines on its critical approach should be utilised to improve outcomes. The clinical course is determined by its aetiology and complications and hence specific therapy must be initiated early when the cause is identified, and early consideration for liver transplant where spontaneous recovery is highly unlikely. Survival outcomes may also vary according to the nature of the underlying disease. Children with mitochondrial liver disease have poorer outcomes than those with drug mediated liver injury. (10)

The following table highlights studies that have looked into describing the aetiological spectrum of ALF with limited data in Africa.

Table 1. Summary of aetiological outcomes in previous studies of liver disease

	Site	Study period	Study size (Age)	Aetiological outcomes
1	Bangladesh (Asia) (15)	2011-2014	35 (0-18yrs)	Viral hepatitis 34% Wilson's disease 25%
2	Italy (26)	2004-2018	32-36 weeks (late pre-term)	Coxsackie B virus (40%) Echovirus 11 (10%)
2	Lithuania (27)	Jan 1996-Dec 2004	28 (>18yrs)	Acute viral hepatitis B 21% Drug induced hepatitis 21% Indeterminate 17.9%
3	Birmingham (UK) Queens Hosp (1)	1992-2008	1237 (8-78yrs)	Drug induced 90% Sero-negative hepatitis 15% Hepatitis B 2%
4	PALFG (USA, Canada, UK) (13)	1999-2004	348 (0-17.9yrs)	Indeterminate 49% Drug induced 14% Metabolic 10%
5	USA (28)	1998-2012	1887 (18-44yrs)	4 cases of EBV related ALF
6	UK (29)	1993-2012	78 (0-120days	Metabolic 36%, Hypoxic insults 17%, Herpes Simplex 2.7%
7	Spain (30)	2005-2010	92 (0-18yrs)	Drug induced 47%
8	India (31)	2011- 2014	30 (0-3yrs)	Metabolic 33% HLH 17% followed by Drug induced and hepatitis A
9	Birmingham Children's (25)	2009-2011	39 (0-2yrs)	Genetically proven mitochondrial liver disease 17%
10	Korea (9)	2010	110 (>18yrs)	Hepatitis B 37 % Herbal 19%,Hepatitis A 7% Indeterminate 10%
11	Nigeria (Africa) (23)	2005-2010	652 (28-64yrs)	Hepatitis B 49%, Herbal ingestion 45%, (7.9% medical admissions due to liver ds)
12	London, UK (20)	2001-2011	36 MLD of 127 (0-5yrs)	Galactosemia 47% MRCD 17% OTC DEF 11%

13	Turkey (32)	1994-2002	34 (0-18yrs)	Cryptogenic 44% Viral hepatitis 35% (hepatitis A n=9), Wilson's disease 12.5%

MLD: Metabolic liver disease, OTC DEF: Ornithine transcarbamylase deficiency, HLH Haemophagocytic lymphohistiocytosis, EBV: Epstein-Barr Virus, MRCD : Mitochondrial respiratory chain disorders

Infection

Viral infections due to hepatitis A and E, have been seen to be common in adult studies in countries with lower economic development with poor sanitation and overcrowding as they are spread by contaminated water and food. (4,10,33) Other viruses reported to cause ALF in children include hepatitis B, non-hepatitis viruses, herpes viruses including Herpes Simplex virus, Epstein-Barr virus, Coxsackie, Echovirus, and Parvovirus. (13,18, 26,28,34,35,36,37)

Herbal remedies

The question of whether the use of herbal remedies is significant in the local paediatric population would be interesting to look at. Traditional or herbal medication may cause metabolic derangement and risk factors for hepatotoxicity have previously been described which include younger age group, adolescent age group, abnormal renal function and concurrent use of other drugs. (38) A previous local retrospective study in South Africa, of the use of folk remedies, was conducted for patients with acute renal failure and of note was the reporting of higher mortality in patients with both acute renal and liver failure than those with renal failure alone. More widespread awareness of folk remedy use in African patients was recommended. (39)This study will note those patients with documented use of herbal medication as part of the review and determine whether folk remedy use contributes significantly to the presentation of ALF in the paediatric population presenting to RCWMCH. The high contribution of herbal ingestion towards liver disease in a Nigerian tertiary hospital has already been described (23).

Metabolic liver disease

Some studies have described ALF presenting in young children with the aim of identifying biochemical markers to metabolic liver disease by comparing those with metabolic liver disease (MLD) and non-metabolic liver disease (non-MLD). Factors that indicated MLD as a cause included young age, high bilirubin, synthetic dysfunction, hypoglycaemia, non-glucose reducing substances in urine and low survival with a native liver. (31) Metabolic diseases that may present

as ALF include galactosaemia, tyrosinaemia, mitochondrial liver disease in younger children, and Wilson's disease in older children. (10) There is lack of routine screening for inborn errors of metabolism in the developing setting. The identification of clinical or biochemical markers becomes significant for low resource settings where limited investigations may be done. For example, some literature has suggested that alkaline phosphatase to bilirubin ratios <2 differentiates Wilson's disease from other metabolic conditions causing ALF (40). A high index of suspicion for metabolic disease should accompany cases where family history of consanguinity, sibling deaths, recurrent miscarriages, recurrent diarrhoea, vomiting with failure to thrive and developmental delay is present. (41)

Drug induced liver injury

Drug induced hepatic necrosis has been commonly due to acetaminophen related toxicity. A study in Spain concluded that chronic acetaminophen poisoning is a potential risk factor for hepatotoxicity and ALF, and delays in seeking help are a contributory factor (30). In the developed world, drug induced liver disease is an important cause of ALF (1, 13, 27).

The anti-oxidant N-acetylcysteine (NAC) in the management of both acetaminophen and non-acetaminophen ALF is currently in use and has been reported by some studies to be safe and shown to reduce the length of hospital stay with higher recovery of native liver function without transplantation, as well as better survival after transplant. (40). The study did discuss management approaches for some of the patients.

This study will enhance knowledge in paediatric liver failure in an African setting, retrospectively highlighting the clinical presentation, aetiology and biochemical variables to identify predictors of outcome.

1.2 Ethical consideration

The study proposal was submitted to the University of Cape Town, Faculty of Health Science Human Research Ethics Committee (HREC REF NO: 561/2017), and approval was obtained

before commencement of data collection. Approval was also obtained from the Management team at Red Cross War Memorial Children's Hospital (RCWMCH) Research Committee. The Study being a retrospective study with no physical contact with patients implicated a minimal risk, and hence the obtaining of informed consent for the study was waivered. Upon retrieval of records, numbers were allocated to each enrolled client record to ensure anonymity. The data collection sheet was securely locked and password protected electronic data sets and laptop did not reveal personal identifiers. Information containing the allocation of study numbers to folders was separately kept to reinforce confidentiality and anonymity.

The benefit of dissemination of the findings would provoke improvements in the early recognition and aggressive management of patients with acute liver failure in the African setting, with or without transplant facilities.

1.3 Chosen journal for publication

The Journal chosen is a peer-reviewed local medical journal, the South African Medical Journal (SAMJ), which strongly attracts both a local and international audience, publishing on matters of interest to the global world at large, from local and international authors. This study, in addition to what the journal produces, would be contributing to the advancing medical knowledge arising from locally conducted research. This would be one of few published studies within Sub-Saharan Africa on paediatric acute liver failure.

The format applied is per the prescribed instructions for authors which have been highlighted in the appendix.

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CHAPTER 2: PUBLICATION-READY MANUSCRIPT

TITLE

PAEDIATRIC ACUTE LIVER FAILURE: A Retrospective Review From A South African Tertiary Centre

Authors: Rachel **Mlotha Mitole** (MBBS, FCPaed(SA))[1], Ronalda **De Lacy** (MBChB, FCPaed(SA))[1],

Elizabeth **Goddard** (MBCHB, MMed(Paed), PhD) [1,]

[1]Division of Paediatric Gastroenterology, Department of Paediatrics and Child Health , University of Cape Town and Red Cross War Memorial Children's Hospital.

Correspondence: Dr Rachel Mlotha Mitole

Division of Paediatric Gastroenterology, Red Cross War Memorial Children's Hospital, Klipfontein road, Rondebosch, Cape Town, 7700 [1]

Tel: +27837340777

Email: rechmitole@gmail.com

ABSTRACT

Acute liver failure (ALF) describes a clinical syndrome resulting from severe liver damage and extensive loss of functional parenchymal liver mass triggered by various factors. Early recognition and initiation of specific therapy may improve outcomes and reduce the need for liver transplantation, a treatment modality not universally available in resource constraint areas. There is paucity of data describing this syndrome in Sub-Saharan Africa in children.

Objective
This study aims to retrospectively review and determine the clinical presentation, aetiology, complications & outcome of ALF in children admitted at the Red Cross War Memorial Children's Hospital (RCWMCH).

Methods
All records of children from 0 to 13 years admitted at the RCWMCH over the period from January 2005 to December 2016 with ALF were retrospectively reviewed, after obtaining ethical approval. Patients with pre-existing evidence of chronic liver disease were excluded. Demographic variables as well as clinical presentation and investigations were captured, with determination of outcomes at 3 weeks and 6 weeks of diagnosis.

Results
Study included 24 children, 16 females (66.7%) and 8 males (33.3%). Median Age was 15 months, with interquartile range from 5 to 28 months.
Diarrhoea, jaundice, respiratory distress, hepatomegaly and encephalopathy were common clinical features.
Aetiology was infection in 37.5 % of cases (n=9, 2 of whom had autoimmune hepatitis comorbidity) and hepatitis A was most common infectious cause (n=4, 44%). Causes were indeterminate in 29.2%. Two patients had autoimmune hepatitis without co-morbidity; Reye syndrome 12.5% and 17% had miscellaneous causes. Transaminases were raised to thousands in viral causes of hepatitis, with a low C reactive protein. INR >4 and Total Bilirubin>210umol/L were associated with death outcome (p=0.04 and p=0.03 respectively.

Conclusion
Viral hepatitis A is the leading infective cause of acute liver failure in this study cohort and 29.2% of cases were indeterminable. INR >4 and Bilirubin > 210umol/l were predictors of poor outcome. Follow up study is recommended to better understand clinical spectrum and outcomes of children with acute liver failure in this low resource setting.

INTRODUCTION

Acute liver failure (ALF) indicates acute significant liver damage with the resultant failure to carry out its normal functions. It was first described in 1970 by Trey and Davidson as "a potentially irreversible condition, the consequence of severe liver injury with onset of encephalopathy within 8 weeks of appearance of first symptoms and in the absence of pre-existing liver disease" [1] . The Acute Liver Failure Study Group defines it as the outcome of a complex equation between hepatocyte death and regeneration [2,3]. Having said this, one should note the unique nature of the liver to regenerate cell mass and may function adequately with at least 20% of normal liver mass [4,5].

The processes leading to the hepatic damage are believed to be multifactorial and may be largely grouped into infectious, drug induced, metabolic, ischaemic and immune dysregulation [6,7]. It is equally important to investigate this underlying disease process for early specific therapy or prognostication, manage its complications and determine which candidates may benefit from liver transplant. Survival outcomes may vary according to the nature of the underlying disease [1]. Children with mitochondrial liver disease have poorer outcomes than those with drug mediated liver injury [8].

There is geographical influence in the causes of ALF with drug induced ALF being more common in the western population, and infectious aetiologies such as viral hepatitis in the developing countries [2,9,10,11,12,13,14,15].

Whilst there is large volume of literature describing this condition in the western setting, there is paucity of data on paediatric ALF in the Sub-Saharan region. Red Cross War Memorial Children's Hospital (RCWMCH) has a Paediatric Gastroenterology Division experienced in managing complex liver disease and liver transplant recipients in the Western Cape of South Africa [16].

The fundamental importance of describing and evaluating the pattern of this life threatening condition at RCWMCH, in addition to raising awareness about the occurrence of Paediatric ALF, is that it may also determine the aetiological spectrum, its complications and predictors of outcome in a developing country.

PATIENTS AND METHODS

All records of children from 0 to 13 years admitted over the period from January 2005 to December 2016 with ALF were retrospectively reviewed at the RCWMCH, which is the largest stand-alone paediatric hospital in South Africa. Ethical approval was obtained from the University of Cape Town, Faculty of Health Science Human Research Ethics Committee (HREC REF NO: 561/2017). The records were identified using the hospital ICD 10 code for acute liver failure: K72.9 [17], and were reviewed to ensure the inclusion criteria were met before data collection and entry commenced.

To identify study patients for inclusion, the following criteria were used:

a) hepatic based coagulopathy defined as a prothrombin time (PT) ≥15s or International Normalized Ratio (INR) ≥ 1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy OR a PT ≥20s or INR≥ 2.0 regardless of encephalopathy;

b) biochemical evidence of acute liver injury;

c) no known evidence of chronic liver disease

The study excluded patients with known chronic liver disease, and those with examination findings consistent with chronic liver disease; those not meeting the definition of ALF; and irretrievable records.

Database captured a detailed set of variables (Table 1) including demographic characteristics, symptoms and signs, investigation profile including laboratory results documented in the record charts, as well as the National Health Laboratory Service (NHLS), and short term outcomes defined as death or alive with native or transplanted liver, at 6 weeks. Participants were excluded from part of the analysis in case of certain unavailable data.

Demographic variables were summarised by descriptive statistics. Continuous data were presented as medians with interquartile ranges (IQR) between the 25^{th} and 75^{th} percentile, and this was determined by the distribution.

Categorical data such as the complications of acute liver failure for example, as nominal data, were presented as percentages

The data was dichotomised to analyse associations with outcome for the following variables: Age, sex, peak INR, peak Total bilirubin (TB) and White cell count (WCC), using cut offs previously reported to show differences in outcomes [6, 18, 19]. Fisher's exact test was used to calculate the associations between categorised variables with STATA version 14.2. P value less than 0.05 was considered to be statistically significant.

The Paediatric End-Stage Liver Disease (PELD) score was calculated for each patient at admission using the standard formula [20] that incorporates age, bilirubin, albumin, INR and presence of growth failure, using a cut off of -2 for weight for age Z score. PELD values were compared to the outcome to look for any association.

RESULTS

The K72.9 coding system availed 120 file numbers electronically, but after removal of duplicates. Medical records of 24 children were included in the study as shown in table 2. The majority (66.7 %) of patients were female. The median age was 15 months, (IQR of 5 - 28 months). Weight for Age Z scores were calculated to assess nutrition status using a cut off of -2 for the presence of moderate malnutrition, which was prevalent in 29.2% of children (n=7). Only 29.2% of patients (n=7) had a documented length, and of these, 2 were mildly stunted, both between 0, -1 height for age Z score. The incomplete length measurements limited evaluation for prevalence of stunting. Eleven children were HIV exposed (46%), and 3 of these children were HIV infected. One infant was diagnosed during admission and had not initiated anti-retroviral therapy. The other two were both on treatment. (Table 2). The prevalence of ALF in this cohort increased over the time period,

with 4 patients between 2005 and 2008, to 11 patients between 2013 and 2016 (Figure 1).The number of indeterminate cases also increased during the study period.

The demographic variables, clinical characteristics, laboratory results and outcomes have been summarised in Table 3 by aetiology. The causes of ALF, included viral and autoimmune hepatitis and indeterminate causes. Other causes were Gestational Alloimmune Liver Disease (GALD), malaria, congenital syphilis, anti-Tuberculous Drug induced liver injury, herbal intoxication, and Reye-like syndrome.

Two patients with viral hepatitis also had autoimmune hepatitis.

There was some variation in the clinical presentation across the aetiological groups. In viral hepatitis cases, the median age was 35 months but those with indeterminate causes and Reye syndrome were 15 months and 6 months respectively.

The most frequent symptoms reported at presentation were jaundice (11/24, 45.8%) and diarrhoea n=11 (45.8%). Vomiting was the second most frequent presentation (n=10/24, 41.67 % of cases).

Sixty percent of children with viral infections were jaundiced and 80 % had diarrhoea.

On examination, almost all children had an enlarged liver (n=23) except for one who had hepatitis A virus infection.

Splenomegaly was a rare finding, but present in the indeterminate category as well as children from the 'Other' group with GALD, congenital syphilis and herbal drug intoxication. None of the children with viral hepatitis had an enlarged palpable spleen. Respiratory distress with chest signs and hepatomegaly without jaundice were features in all children with Reye syndrome. The range of grade of encephalopathy was higher in viral hepatitis and Reye Syndrome. Just below a third of patients were febrile

Laboratory findings demonstrated the highest parameters in the viral infection category for aminotransferase enzyme levels (median alanine aminotransferase (ALT) of 2988 U/L) and peak TB (median value of 423umol/L). C Reactive Protein levels were within normal limits for the aetiologies except for mild elevation in the Reye and other group. Reye syndrome peak ammonia levels were significantly elevated with a median value of 651µmol/L. Complications were noted across all the aetiology groups and all patients were coagulopathic. Half of the patients had an INR greater than 4 (n=12), and 7 (58%) of these had bleeding complications. Gum bleeding was the commonest bleeding presentation (42%) in those who bled (Table 5). Only 4 of 12 patients with an INR below 4 bled. Hypoglycaemia occurred in 79.2 % of children (n=19), grade 3 or 4 encephalopathy in 66.7% of cases (n=16), and sepsis in 62.5% (suspected and culture proven cases) (Table 6). Factor 5 level was obtained in 18 (75 %) children. Thirteen children had a low level below 50 iu/dL, and of these, 46% presented with bleeding. As for ammonia levels, 94% of those with grade 3 to 4 encephalopathy had values above 140 µmol/L, more than four times the upper limit of normal (range 11-35 µmol/L). All children with a death outcome had ammonia levels above 140 µmol/L.

Outcomes were evaluated at 3 weeks and 6 weeks after admission to RCWMCH, grouped into alive with native liver and death with native liver. There were no transplanted cases. At 3 weeks and 6 weeks 79.2% (n=19) and 75% (n=18) respectively survived with native livers, giving a

mortality in this cohort of 20.8% at 3 weeks and 25 % at 6 weeks. Table 7 highlights the outcomes per variables and only two variables INR > 4 and TB >210umol/L showed p values of less than 0.05 for predicting outcome. In terms of survival with native liver by aetiology, the indeterminate group had the least survivors at 57%, followed by viral infection with 60% survival. All the children in the remaining groups survived. The indeterminate group had the highest PELD score, with a median value of 40.5.

The PELD scores varied from 9.3 to 57.5 with a median of 32.9. For those who were alive at 6 weeks, 10 of 18 (55%) had a PELD more than 30. And for those with poor outcomes 4 of 6 (67%) had PELD scores above 30 (p=0.876).

DISCUSSION

This study retrospectively describes 24 African children admitted at the RCWMCH with ALF, reporting a 25% mortality. The patients studied are predominantly under 5 years of age, about a third of them (29.2%) being moderately underweight.

The number of children exposed to HIV at birth is high in this cohort at almost 50%. South Africa has one of the highest HIV infection rates in the world and that may explain the high prevalence of HIV exposure at birth in this cohort (n=11, 46%) [21]. These children varied in age from 7 days of age, to 23 months, except one who was 7years 10 months at enrolment. Aetiology of ALF in this group included anti-Tuberculous DILI, herbal intoxication and Reye syndrome. Cause was indeterminate in 6 (54.5 %) children and the remaining 2 children had hepatitis A infection. The patients with HIV infection are believed to have had comorbid conditions that increased their risk for hepatic dysfunction. Two had hepatitis A coinfection and the 3rd patient had an elevated CMV viral load (log value of 6) (Table 4). It is uncommon for HIV to cause severe hepatic dysfunction in isolation. Although it is well appreciated that HIV itself may cause direct damage to the liver, the risk for hepatic dysfunction is known to be increased when co-infected with hepatitis B and C, and this risk is further increased with non-nucleoside reverse transcriptase inhibitors (NNRTI), co-administered with Protease Inhibitors [22,23].

There was a general increase in the number of ALF cases over the years as seen in figure 1, and this may be due to improved case recognition and awareness, and may coincide with local certified paediatric hepatology training programs becoming officially available from 2008 [24].

The presentation of ALF may be nonspecific and share similar features with sepsis [25].

Common symptoms and signs in the study included diarrhoea, vomiting, jaundice, respiratory distress, hepatomegaly and encephalopathy, which may occur for any of the aetiologies (Table 3). ALF should be suspected in a child with any of the above features, plus evidence of

hepatocellular injury, with or without marked conjugated hyperbilirubinaemia and confirmed with an INR of 2 or with an INR of 1.5 in the presence of encephalopathy. Although encephalopathy may be difficult to assess in the paediatric population, especially infants, [26] this study cohort demonstrated a prevalence of 66.7% with grade 3 or 4 encephalopathy at admission, and of these, 63% were aged below 2 years (Table 3).

Children in ALF may present with bleeding as was seen in half of the patients. All patients had an elevated INR to meet the diagnostic criteria. A raised INR does not necessarily predict bleeding in ALF [27]. The test rather gives indication how well you are likely to clot. Table 5 illustrates that bleeding does not correlate with the level of INR.

Normally, with sufficient liver parenchymal reserve and function, the liver attains haemostasis through provision of haematologic procoagulants and anticoagulants. In the abnormal state of massive necrosis and loss of adequate parenchymal reserve for normal function, the balance may not be completely lost as the result would be of diminished production of both clotting and non-clotting factors. However, there is a possibility that the presentation may lean in one direction more than the other, to cause bleeding where dramatic loss of anticoagulants is prevailing, and thrombotic events where the opposite is true [2]. Although not demonstrated in this cohort, you may see a degree of Disseminated Intravascular Coagulation (DIC) - a phenomenon usually seen in septic children. This is because of the loss of hepatic synthetic function of pro- and anti-coagulatory factors and defective clearing capacity of toxins, inflammatory mediators and infections [28].

Besides the coagulopathy and bleeding, other common complications were, encephalopathy, hypoglycaemia and sepsis (Table 6). In some cases, ALF may complicate with bone marrow suppression, a phenomenon that has been described in literature [BM]. In this cohort, patients with new onset bicytopenia or pancytopenia were suspected to have bone marrow involvement. Bone marrow studies should be done to confirm suspicion or evaluate cause of bone marrow failure. This was not done routinely but one patient diagnosed with Parvovirus virus induced Haemophagocytic lymphohistiocytosis (HLH) did have bone marrow aspirates done. Children with ALF usually present with more than one complication which all need to be recognized and attended to promptly to improve outcomes [29]. The grade of encephalopathy and ammonia levels increase with worsening liver function and this explains the high ammonia levels in all patients who died [30].

It was anticipated to see the high transaminases with viral hepatitis, where alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are above 1 000 U/L, with jaundice and significant hyperbilirubinaemia above 3 times the Upper Limit of Normal (ULN). ALT and AST elevations indicate hepatocellular injury and typically rise above 5 times the ULN in acute liver injury resulting from viral hepatitis. The ALT and AST levels must be looked at considering the INR and total bilirubin (TB) trend to assess the progression of liver disease. A recovery trend is seen when the transaminases decline with improving INR and TB. However, in severe liver damage with deterioration, the ALT and AST also decline, but with worsening INR and TB levels [31,32, 33]. For the 8 children known with viral hepatitis, CRP value was available in 5 children, with median value of 6.4, excluding the patient with Malaria and EBV comorbidity

with a raised CRP of 50. In general, patients with viral hepatitis tend to have a low CRP and those with bacterial infections tend to have significantly higher CRPs [34].

There were 4 cases of autoimmune hepatitis (AIH), which showed variation in ALT values (971, 185, 1 689, 292 U/L). The latter two presented with hepatitis A and Human Herpes virus (HHV 6) comorbidity respectively, and these occurrences of HHV 6 and Hepatitis A in AIH have been described [35,36,37]. Case reports of ALF due to HHV 6 have been documented pre and post liver transplant. One case report of an 11 year old with ALF due to HHV 6, had typically raised transaminases above 1 000 U/L, and survived with a liver transplant. [38, 39].

All AIH patients met the definition of ALF and none had clinical stigmata of chronic liver disease such as ascites nor splenomegaly. Globulin fractions ranged from 34 to 50 umol/L and the autoantibodies detected included Anti-Smooth-Muscle-Antibody (ASMA) and Anti- Liver Kidney-Microsomal-Antibodies (ALKMA) in 50%. Three of the children had liver biopsies after the coagulation improved. There is need to suspect this treatable cause of ALF in patients with acute hepatitis, as management may be different, with the use of immunosuppressant therapy [40,41].

A 2 week old neonate diagnosed with Gestational Alloimmune Liver Disease (GALD) was jaundiced, had an enlarged liver with raised transaminases, coagulopathic, very high ferritin level 240 000 mg/L and a high transferrin saturation. She responded well to a dose of intravenous immunoglobulin, N- Acetylcysteine (NAC) infusion and high dose vitamin E, with normalization of ALT at 6 weeks. Early diagnosis and treatment of GALD removes the need for transplant which may not be an option in most resource constraint settings [42, 43].There is increasing use of NAC in non-acetaminophen ALF and recent literature shows its positive effect in reducing mortality and improving transplant free survival [44,45] .

The indeterminate ALF group accounted for 29.2% of this cohort and the median age was 15 months. The numbers of indeterminate cases in the literature have reduced over the years, 12-15% in the developed setting, owing to improved diagnostic ability, including genetic and mutation analysis for metabolic syndromes [8,46, 47, 48]. However, routine screening for inborn errors of metabolism and wide range of viral agents is lacking in the low resource countries, and might explain the increase of indeterminate cases over the years in this cohort, as in figure 1.

Emphasis must be placed on developing extensive age-appropriate approaches in managing children with ALF as younger infants may present in ALF due to inborn errors of metabolism (IEM). Treatable IEMs including galactosemia and tyrosinaemia, should be identifiedas well as other treatable metabolic conditions in older children such as Wilson's disease. Extensive work up should be done right from admission to screen for wide range of viral agents such as Hepatitis A, B, C E viruses, Herpes simplex virus, Coxsackie B virus, Echovirus, Epstein Barr virus, Parvovirus B19, Cytomegalovirus, HHV 7, HHV 6); immune dysregulation syndromes (GALD, AIH, HLH); as well as toxin screens to identify children with acetaminophen, salicylate and iron intoxication [9, 49, 50,51,52].

The pattern noted between age and aetiology in this cohort is that all those with hepatitis A infection were above 12 months of age (ranged from 17 to 94 months), as they receive maternal

immunoglobulins to protect from hepatitis A virus in the first year of life, and routine Hepatitis A vaccination after 1 year of age is not incorporated into the EPI schedule in most Sub-Saharan countries. The local practice is to administer later, giving the vaccine to contacts of children infected with hepatitis A [53,54,55,56]. The 17 month old was also HIV positive and may pose an immunosuppressive risk for hepatitis A virus causing ALF [57].

RCWMCH viral screens include Hepatitis A, B and C, CMV and HSV in all patients with ALF. Other infections noted in this cohort include congenital syphilis (n=1) and malaria (n=1). Both conditions have also been described previously to present with ALF [58,59,60].

For the confirmed metabolic cases, 3 were diagnosed with Reye syndrome. This is a non-inflammatory acute encephalopathy with fatty degeneration of the liver. It may not be as common owing to improved investigation and reduced use of aspirin containing medications in children. It may present with a viral illness in children who are genetically susceptible, upon exposure to aspirin or salicylate containing medication, in 80% of cases. The result is disruption of oxidative phosphorylation and fatty acid B oxidation due to mitochondrial dysfunction, resulting in a raised ammonia [61]. None of the 3 cases were jaundiced. One denied a history of ingesting aspirin containing meds, but clinical findings and investigations were in keeping with Reye syndrome, with urine salicylate levels of 3.3 (1.1-2.2 mmo/L) [62], an ammonia level 723 µmol/L and a Computerized Topography (CT) scan of the brain showing cerebral oedema and hypodense white matter, which has been described in Reye Syndrome. It should therefore be suspected even when history of ingestion of aspirin is denied. All 3 were encephalopathic, in respiratory distress with a big liver, hypoglycaemic and hyperammonemia (mean 605 µmol/L). All three had good outcomes, 2 of whom had normalization of ALT by 6 weeks. According to existing literature, 2/3 of those who survive recover fully [63,64].

All the children who died had a peak INR greater than 4, and as has been shown in other studies, this was statistically significant for predicting non-survival (p=0.037) [1,19, 65, 66, 67, 68].
Hyperbilirubinaemia, in patients with bilirubin levels above 210 µmol/l was associated with a poor outcome (p=0.041). Dhawan et al have reported bilirubin cut-off levels >235 µmol/l as a poor prognostic indicator, with additional risk factors of WCC >9 x 10 9/L, and age < 2 years in patients with Wilsons disease [67].

Other studies have reported a poorer outcome with higher grade of encephalopathy [69], but as seen in Table 7 statistical significance was not demonstrated in this cohort, likely due to the sample size.

The PELD score was developed to aid with prioritized listing of patients with chronic liver disease requiring transplant [70,71].
In this study cohort, 67% of non-survivors had a higher PELD score using a cut off of 30. There was no statistically significant correlation between PELD and outcome at 6 weeks (p=0.876). Few studies have been done to evaluate the accuracy of the PELD score for identifying children with poor prognosis in the ALF setting. In 2018, Perez et al reported high PELD scores at admission using a cut off of 27 to correlate with poor outcomes [72]. Sanchez et al also described

higher PELD scores at admission amongst non-survivors [73]. There may be a place for use of PELD in the acute setting but larger studies including more diverse populations may be required [19, 67, 74, 75]. There are other prognostic modelling scores such as the Kings College Hospital Criteria that are used in the ALF setting [19].
African data on ALF mortality is scarce. A study in Sudan reported an 84% mortality in an adult cohort [76]. Mortality rates were also significantly high in the Pre transplant era in the western world (72% in London, UK) [77], with increasing survival in the post-Transplant era. Though transplantation has increased survival, it is encouraging to note the increasing survival with native livers to 73.4 % in the USA from 2008 to 2012 [78].

In this study, 6 of 24 patients died, representing a six week mortality of 25% and none of the patients in the study underwent a liver transplant, hence 75% survived with their native liver.

The declining mortality over the years is attributed to improved awareness, diagnostic and management approaches, with early recognition and referral to liver transplant or intensive care units for emergency orthotopic and living donor related liver transplant, which were first accepted as a treatment modality for ALF in the 1980's [19, 79, 80]. The management principles may be applied in the developing setting where transplant is not an option, to improve outcomes for aetiologies where spontaneous recovery is possible. Spearman et al previously reported acute liver failure accounting for about 11% (10/84) of cases of all transplants performed from 1987 to 2006 at RCWMCH [15], and the Wits Donald Gordon Medical Centre in Johannesburg recently reported doing 15% of liver transplants for ALF [81] . Worldwide, ALF accounts for 10-15 % of all liver transplants [19].

LIMITING FACTORS

This was a retrospective review of medical records of a rare clinical syndrome with a small sample size, limited further with missing records or data. There may have been reduced neonatal cases as they may not have been referred from the available specialized neonatal centres and referring facilities may not always refer fulminant hepatic failure cases with poor prognostic indicators and poor socioeconomic factors working against their favour for transplant. Misdiagnosis of ALF as sepsis for example may contribute to reduced record for review.

CONCLUSION

Although ALF is rare, it does occur in the Sub-Saharan setting. Hepatitis A is the common infectious cause of ALF. Viral causes of hepatitis may be suspected in coagulopathic and/or encephalopathic, jaundiced children with a big liver, transaminases above 1 000 U/L regardless of CRP. Therefore, an INR should be done in all patients with acute hepatitis. This study showed encouraging findings for a developing setting, encouraging early recognition of ALF and

thorough investigation. Aggressive supportive measures and therapy should be instituted and cases referred to centres where critical care and monitoring may be provided with transplant services where applicable. Further studies are required to reduce the indeterminate cases, considering routine screening for a wide range of viral agents including hepatitis E virus, as well as genetic and molecular studies for metabolic disease. The outcomes of these would further inform and advise on strategies for improving and strengthening public health measures to reduce the incidence of infectious cases and drug induced liver injury, reducing the number of cases of acute liver failure. Peak INR above 4 and peak bilirubin levels above 210 µmol/L were shown to predict a poorer outcome. Further collaborative research on ALF within the African paediatric setting is required to understand this clinical syndrome better and develop local evidence based protocols.

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TABLES AND FIGURES

Table 1. Variable definition for data collection

Demographic characteristics: Date of birth, age at presentation, gender, ethnicity, geographic location
History: referral facility if referred, any treatment prior to RCWMCH, family history of consanguinity, early infant deaths or miscarriages

Clinical Symptoms: jaundice, anorexia, abdominal pain, malaise, fatigue, vomiting, diarrhoea, abdominal distension, bleeding, irritability, disturbed level of consciousness , duration of symptoms

Examination findings: Weight, height, pallor, jaundice, clubbing, hepatomegaly, splenomegaly, ascites. These will be drawn from the clinical examination done on initial presentation.

Investigation profile:
Liver Function Tests: Total and direct bilirubin, total protein and albumin, alanine transferase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP), γglutaryl transferase(GGT), International normalised ratio(INR), Prothrombin time(PT), fibrinogen, Lactose dehydrogenase (LDH)
Renal function tests: Sodium, Potassium, Urea, Creatinine

Infectious screen
Full blood count
Urine dipstix, urine microscpy and culture
Blood Culture
For Hepatitis A, B, C viruses, cytomegalovirus, herpes simplex virus, Epstein Barr virus, Human Immunodeficiency Virus (HIV), Syphillis serology, Coxsackie, Parvovirus

Autoimmune screening and inflammatory markers
C Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR)
Serum immunoglobulin (IgG).
Autoantibody (Anti nuclear antigen, anti-Smooth Muscle and anti-Liver kidney Microsomal)

Metabolic screening
Ammonia
Glucose
Lactate
Urine for reducing substances with thin layer chromatography if positive, Galactose 1 phospate uridyl transferase activity (GALT).
Urine and serum organic acids
Urinary copper and serum caeruloplasmin
α1 antitrypsin
serum ferritin
Other investigations done will be noted
Liver biopsy
Genetic screening
Radiological imaging

Treatment information.

All therapy given, including pre-referral treatment to RCWMCH, and their duration will be recorded. Clinical course and response to management will be recorded and gauged from the results of serial liver enzymes (ALT and AST), bilirubin and coagulation profile, as well as the clinical symptoms.

Short term outcomes on Day 21 of hospital admission and 6 weeks

Death with native liver
Alive with native liver

Table 2. Inclusion and exclusion of patients

120 file names identified
using K72.9 ICD 10
List truncated with removal
of duplicate names

Final list of 90 patients
Death files irretrievable,
destroyed folders and boxed folders

53 folder records retrieved
25 not meeting criteria

28 meeting criteria
Clinical notes missing

24 patient records reviewed for study

Table 3. Cumulative demographic, clinical features, laboratory and outcome data by aetiology

	Viral hepatitis N=5	**Viral hepatitis+ Autoimmune hepatitis N=2**	**Autoimmune hepatitis N=2**	**Indeterminate N=7**	**Reye Syndrome N=3**	**Other N=5**

Age (median months)	35	32.5	15	15	6.5	5
Sex (%)	80	50	100	42.9	100	60
Jaundice (%)	60	100	50	71.4	-	60
Diarrhoea (%)	80	50	100	42.9	33.3	20
Vomiting (%)	60	50	50	28.6	66.7	20
Fever (%)	20	50	0	28.6	66	20
Respiratory distress (%)	20	-	50	42.9	100	40
Hepatomegaly (%)	80	100	100	100	100	100
Splenomegaly (%)	-	-	-	28.6	-	60
Bleeding (%)	60	50	50	71.4	33.3	20
Hepatic Encephalopathy (%) Grade 3/4	100	50	50	71.4	100	20
Hypoglycaemia (%)	60	-	50	85.7	100	80
ALT (median u/L)	2988	1330	238.2	1946	985	752
AST (median u/L)	3849	1635	268.5	2510	868	4742
Peak TB (median umol/L)	423	315.5	155.5	404	28	72
Peak INR (median)	4.4	4.3	3.2	7.98	2.3	6.2
Peak NH4 (median u/L)	315	182	147	164	651	134
CRP (median mg/l)	6.4	8.3	-	4.6	14	20.6

Survival with native liver (%)	60	100	100	57	100	100
PELD (median)	28.6	34.7	26.9	450	12.8	36.9

ALT Alanine aminotransferase **AST** Aspartate aminotransferase **TB** Total bilirubin **INR** International Normalised ratio **PELD** Paediatric End Stage liver disease **NH4.** Ammonia**;**
OTHER: Malaria (1), Congenital syphilis (1), Gestational alloimmune liver disease (1), Anti-Tuberculosis drug induced liver injury (1), Herbal ingestion (1)

Table 4. HIV infected children profile

	Age at Admission	Sex	HAART Regimen	HAART duration At admission	CD4 Viral load	Growth Failure?	Clinical Presentation	Outcome
1.	5 months	F	Lamivudine Kaletra Abacavir	15 days	CD4 Abs 104, 3.92%	Yes	Irritable, Bilateral Creps, hepatomegaly	Alive

							Splenomegaly	Unknown ALF cause. ? DILI + high CMV VL
2.	17months	F	Nil: newly diagnosed	-	-	No	Cough, crepitations Right, encephalopathic, hepatomegaly splenomegaly	Death Hepatitis A
3.	94 months	F	Stavudine Efavirenz Lamivudine	6 months	CD4 ABS700 VL: LDL	No	Fever, jaundice, poor perfusion, crepitations, palatal petechiae	Alive Hepatitis A

·**HAART** Highly Active Anti-Retroviral Therapy, **VL** Viral load, **LDL** Lower than detectable level, **ABS** Absolute value, DILI Drug Induced liver injury, **CMV** Cytomegalovirus

Table 5. Summary of Bleeding Presentation (N=12)

Presentation Of Bleed	Number Of Patients N (%)	Description Of Case, INR Values (Number of patients)
GI Bleed	5(41.6)	Coffee ground aspirates, INR<4, (2) Coffee ground aspirates and epistaxis, INR>4, (1) Coffee ground aspirates and melena stools, INR>4,(1) Rectal bleed, pulmonary haemorrhage and ecchymosis, INR<4 (1)
Gum bleed	4(33.3)	Gum bleeding alone, INR>4 (3), , INR<4 (1)
Petechia	2(16.7)	Palatal petechiae, INR>4 (1) Sublingual petechiae, bleeding at puncture sites INR>4, (1)
Bleed from ear canal	1(8.3)	Ear canal bleed alone, INR <4 (1)

Table 6. Complications

Complication	Prevalence of Complications %

Coagulopathy (n=24)	100
Hypoglycaemia (n=19)	79.2
Hepatic Encephalopathy (n=16)	66.7
Sepsis (n=15)	62.5
Cerebral Oedema (n=12)	50
Bleeding (n=12)	50
Bone Marrow Suppression (n=9)	37.5
Circulatory collapse (n=5)	20.8
Death (n=6)	25
Kidney Injury (n=3)	12.5
Multiorgan failure (n=3)	12.5

Table 7. Comparing Variables Vs Outcome at 3 weeks

Variable	Alive	Death	P Value

Age	< 1 Year >1 Year	9 10	0 5	0.118
Sex	Female Male	14 5	2 3	0.297
G3/4 Encephalopathy	<1 Year >1 Year	4 7	0 5	0.245
Peak Total Bilirubin	<210 >210	11 8	0 5	0.041
Peak INR	<4 >4	12 7	0 5	0.037
WCC At Admission	<9 >9	4 15	1 4	1
PELD Score VS 6 week outcome	1 (<19) 2 (19-24) 3 (25-40) 4 (>40)	6 1 6 5	1 0 2 3	0.876

INR International Normalised Ratio**, WCC** White Cell Count**, PELD** Paediatric End-Stage Liver Disease

Figure. 1 Prevalence of Acute of failure over time.

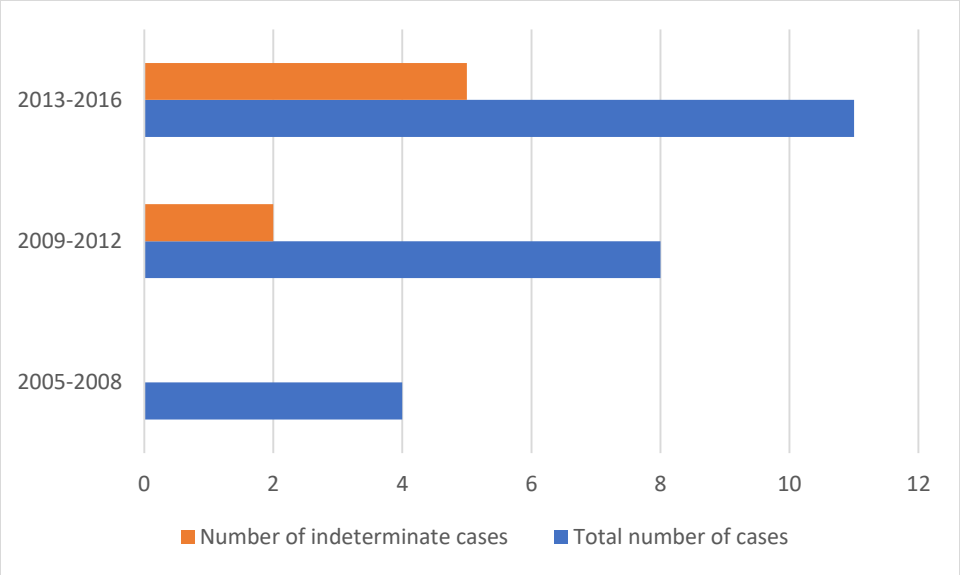
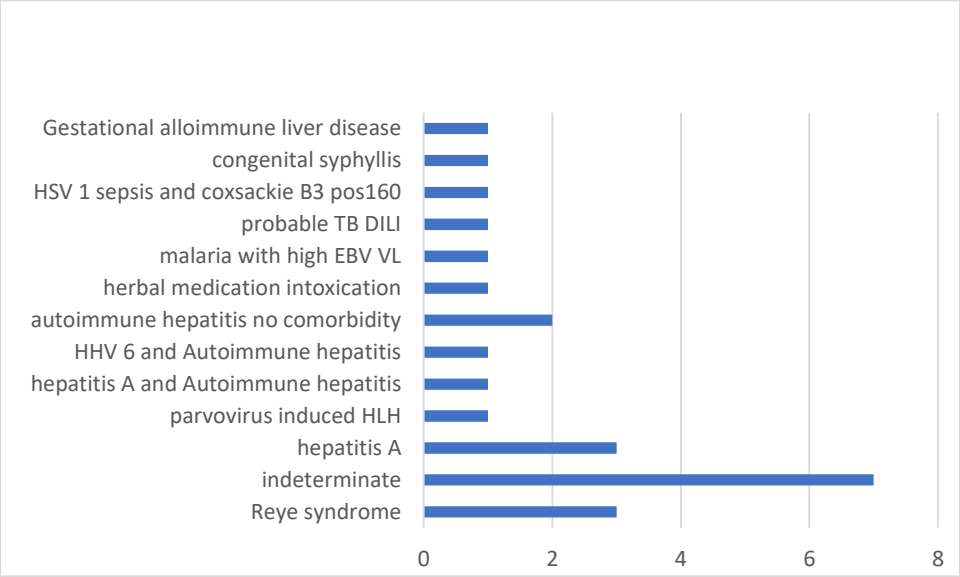


Figure 2. Aetiology of Acute liver failure



APPENDICES

1. DATA COLLECTION SHEET

Data Collection Sheet

CASE ID: ……

Date of admission: (dd/mm/yyyy) _____/ _____/ _____

1. Date of birth: (dd/mm/yyyy) _____/ _____/ _____

2. Age: _____ Years/ Months/ Days .

3. Sex: Male / Female

4. Place of residence: City: _____ Province: _____

5. Does patient live in an institutional setting? YES/NO

If YES, Name of facility: _____

Type of facility: Nursing home/long-term care facility Residential program/treatment facility

6. Family history

Consanguinity/ recurrent or early infant deaths/ miscarriages/ siblings with acute liver failure in infancy

Other …… ……

SYMPTOMS

Date of illness onset: _____/ _____/ _____ (dd/mm/yyyy)

Duration of symptom (days)				
1. Fever	YES	NO	U	…….
2. Jaundice	YES	NO	U	…….
3. Anorexia	YES	NO	U	…….
4. Abdominal pain	YES	NO	U	……...
5. Vomiting	YES	NO	U	……
6. Diarrhoea	YES	NO	U	……
7. Abdominal distension	YES	NO	U	……
8. Altered sleep	YES	NO	U	……
9. Irritability	YES	NO	U	……
10. Reduced level of consciousness	YES	NO	U	…….
11. Seizures	YES	NO	U	……
12. Fatigue	YES	NO	U	……
13. Bleeding	YES	NO	U	……
14. Cough	YES	NO	U	……

15. Shortness of breath/ breathing difficulty YES NO U ……..

16. Joint pain/swelling YES NO U ……..

17. Other symptoms:

……

……

PHYSICAL SIGNS

Weight:…… kg

Height:…… cm

EWFH:……z score BMI:…… z score

EHFA……. z score

Fever	YES	NO
Respiratory distress requiring support with Oxygen?	YES	NO
Jaundice	YES	NO
Clubbing	YES	NO
Pallor	YES	NO
Hepatomegaly	YES	NO

If Yes: consistency: Soft Firm Hard Nodular

cm from costal margin ……

Splenomegaly	YES	NO
Ascites	YES	NO
Encephalopathic	YES	NO

IF Yes Grade of encephalopathy: ……

Grade 0: No abnormalities detected

Grade 1: short attention, mood changes, anxiety, irritability, abnormal sleep patterns

Grade 2: forgetful, behaviour changes, slurred speech, difficulty doing mental calculations,lethargy

Grade 3: confusion, responds to stimuli, somnolence

Grade 4: Coma

Central hypotonia YES NO

Other physical signs:

……

……

……

INVESTIGATION AND RESULTS SHEET

Date time	@ admission	@21 days	@ 6 weeks
Lactate			
WCC			

Neut			
Lymph			
Mono			
Hb			
MCV			
DATE	@admission	@21 days	@6weeks
RDW			
PLT			
CRP/PCT	/	/	/
ESR			
Na			
K			
CL			
U			
Ca			
Mg			
PO4			
TSB			
CB			
T protein			
Albumin			
ALT			
AST			
ALP			
GGT			
LDH			
INR			
PTT P/C	/	/	/
Fibrinogen			
Ammonia			

Factor v

Parameter	Highest level during admission	Date
Bilirubin		
INR		
Grade of encephalopathy		
NH3		

Further investigations

Diagnosis	**Test**	**Date**	**Result**
Urinary Tract infection	Urine dipsix, MCS		

Syphillis	RPR/TPHA		
Hepatitis A	Hepatitis A IgM		
Hepatitis B	HepBsAg, eAg, Core ab Igm		
Hepatitis C	Hepatitis C Ab		
HIV	ELISA/PCR		
CMV	CMV VL		
	CMV Urine Culture		
DIAGNOSIS	**TEST**	**DATE**	**RESULT**
EBV	EBV VL		
Other viruses	Herpes Simplex Igm		
	Herpes PCR		
	Varicella Zoster Igm		
	Coxsackie Ab		
	Parvovirus B19 PCR		
Toxoplasmosis	Toxo IgM		
Cystic Fibrosis	Sweat test		
Galactosemia	Urine reducing sub/TLC		
	GAL-1-PUT enzyme activity		
α1 antitrypsin	Serum α1 antitrypsin		
Inborn errors of met	Blood gas Ph/pO2/pCo2/HCO3/Base Def		
	Glucose		
	Urine organic acids		
	Urine and serum amino Acid		
Neonatal haemochr-omatosis	Ferritin, Transferrin sat		
Wilson's disease	Serum copper		
	Serum Caeruloplasmin		
	24 hr urinary copper		
Autoimmune hepatitis	Protein electrophoresis		
	ANA, ssDNA, ALKM, ASMA		
IMAGING	Ultrasound (presence of hepatomegaly, abnormal liver echotexture, splenomegaly, ascites) MRI/CT SCAN Abdomen		
Histology	Liver biopsy		
Other			

TREATMENT GIVEN

Pre-referral treatment

At onset of illness, medication given at home? YES NO NOT KNOWN

Paracetamol/ Herbal medication/ Other medication. Give detail of duration and drug dosing if known……
……
……

Patient referred? YES NO NOT KNOWN

IF YES, complete table.

NAME OF FACILITY	
LEVEL OF CARE FACILITY	
DATE VISITED FACILITY	
IV FLUIDS Y/N	
NAC Y/N	
ANTIBIOTICS Y/N	
VITAMIN K Y/N	
OTHER	

<u>During admission at RCWMCH</u>

<u>COMPLICATIONS IDENTIFIED</u>

Hypoglycaemia YES NO
Coagulopathy YES NO
Bleeding YES NO
Circulatory collapse /shock YES NO
Kidney injury YES NO
Hepatic encephalopathy YES NO
Cerebral oedema YES NO
Given mannitol? YES NO
Sepsis YES NO
Organism isolated on Culture? YES NO ,
IF YES TICK SOURCE : BLOOD URINE CSF
IF YES STATE ORGANISM :
……
Multiorgan failure YES NO
Bone marrow suppression YES NO
Liver transplant? YES NO
IF YES DATE OF TRANSPLANT: ……..
Other Complications and therapy administered:
…….
……
……
……
……

<u>Patient summary</u>

Time from onset of illness to diagnosis of acute liver failure:
…….
Time from onset of jaundice to encephalopathy
…….

At diagnosis:	At 21 days	At 6weeks
INR ……	……..	……..
ALT……	……	……..
AST……	…….	……
ALP……	…….	……..
GGT……	……	…….
LDH……	……	……..
TP……	……	…….
ALB……	……	…….
TB……..	……	……
CB…….	……	…….
Grade of encephalopathy	0 I II III IV	0 I II III IV

6 WEEKS REVIEW

AETIOLOGY OF LIVER FAILURE ESTABLISHED? YES NO

STATE CAUSE IF KNOWN……..

OUTCOMES:	21 days	6 weeks
Alive with native liver , normalisation of LFT	…….	…….
Alive with native liver, abnormal LFT	…….	……..
Alive with transplanted organ	…….	……..
Death with native liver	….....	……..
Death with transplanted organ	…….	……..
Normal development (yes/no)	……..	…….

2. Supplemental Digital Content

2.1 TIME FROM ONSET OF JAUNDICE TO ENCEPHALOPATHY

		N (%)
JAUNDICE	**NO**	**8(33)**
	YES	**16(67)**
	</= 1 DAY	**9(38)**
	2-7 DAYS	**3(13)**
	>7 DAYS	**4(17)**

The majority of children admitted with jaundice were also encephalopathic at admission or developed encephalopathy within 24 hours of jaundice being noted.

2.2 SUMMARY OF DEMOGRAPHIC AND BIOCHEMICAL VARIABLES FOR 24 PATIENTS WITH ACUTE LIVER FAILURE

VARIABLE	VALUE
AGE (MONTHS) MEDIAN	15 IQR 5-18
SEX (F) N (%)	16 (66.7)
WEIGHT (KG) MEAN	10.5 SD - 0.5
WCC X10 9/L MEDIAN (RANGE)	19.4 (4.6-62.6)
HB g/dL MEDIAN(RANGE)	10.1 (6.3-14.7)
PLT X10 9/L MEDIAN (RANGE)	239 (41-576)
CRP mg/L MEDIAN (RANGE)	10.2(3-206)
ALT U/L MEDIAN (RANGE)	1257.5 (518-1959)

AST U/L MEDIAN (RANGE)	2414)(706-4201)
TB umol/L MEDIAN (RANGE)	261 (37-425)
ALBUMEN g/L MEDIAN (RANGE)	29 (21-34)
ALP U/L MEDIAN (RANGE)	408(269-576)
GGT U/L MEDIAN (RANGE)	90(58-143)
LDH MEDIAN (RANGE)	1261 (678-2615)
PEAK INR /S MEDIAN (RANGE)	3.49 (–2.26-5.2)
PEAK NH4 umol/L MEDIAN (RANGE)	156.5 (76-165)
FACTOR 5 iu/dL MEDIAN (RANGE)	42 (32-58)
NA mmol/L MEDIAN (RANGE)	135 (131 - 138)
CR umol/L MEDIAN (RANGE)	) 34 (16-47
UREA mmol/L MEDIAN (RANGE)	3.3(1,2-4.1)
LACTATE mmol/L MEDIAN (RANGE)	5.8 (4.2-9.6)
HIV POSITIVE N (%)	3 (13.6)

WCC White `cell count, HB Haemoglobin, PLT Platelets, CRP C Reactive Protein, TSB Total Serum Bilirubin, ALT Alanine Transferase, AST Aspartate transferase, ALP Alkaline Phosphatase, GGT Gamma Glutamyl Transferase, LDH Lactate Dehydrogenase , INR International Normalised Ratio, NH4 Ammonia, Na Sodium, Cr Creatinine, HIV Human Immunodeficiency Virus

Figure 3. Grade of encephalopathy by age

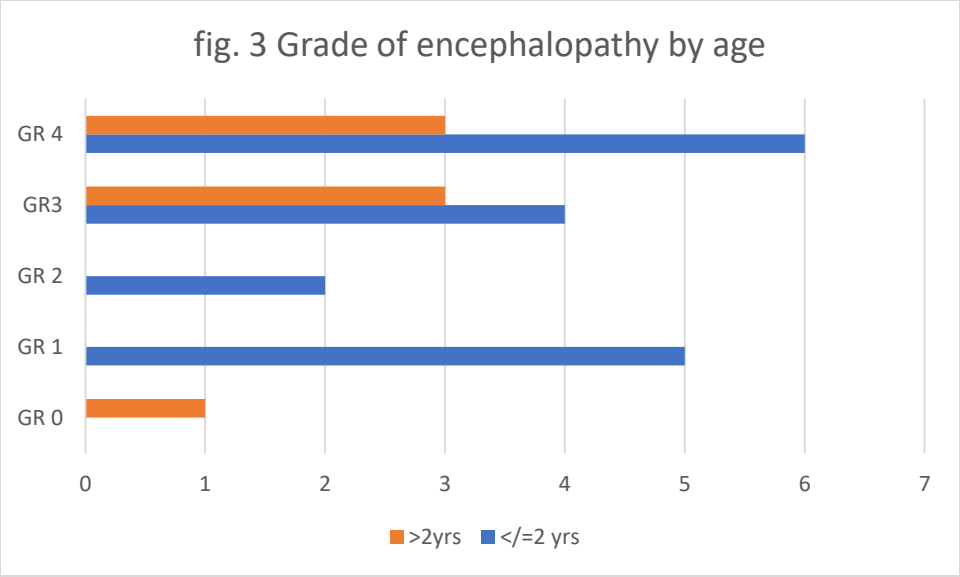


fig. 3 Grade of encephalopathy by age
GR 4
GR3
GR 2
GR 1
GR 0
0
1
2
3
4
5
6
7
>2yrs
</=2 yrs

3. APPROVALS

3.1 HREC APPROVAL

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

25 August 2017

HREC REF: 561/2017

Dr Liz Goddard
Paediatrics
Room 2.19, 2nd floor
ICH Building
Red Cross War Memorial Children's Hospital

Dear Dr Goddard

PROJECT TITLE: A RETROSPECTIVE REVIEW OF ACUTE LIVER FAILURE IN CHILDREN AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL (MPHIL CANDIDATE - DR R MLOTHA-MITOLE)

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee dated 17 August 2017.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 August 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Rachel Mlotha-Mitole will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

4. INSTRUCTIONS TO AUTHORS: SOUTH AFRICAM MEDICAL JOURNAL

4.1 SOUTH AFRICAN MEDICAL JOURNAL

Author Guidelines
The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.
To submit a manuscript, please proceed to the *SAMJ* Editorial Manager website:
www.editorialmanager.com/samj
To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.
Please take the time to familiarize yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ policies
Types of articles considered by the SAMJ
Article Processing Charges
Authorship
Conflict of interest
Research ethics committee approval
Clinical trials
Protection of patient's rights to privacy
Copyright notice
Privacy statement
Ethnic classification
CPD

Manuscript preparation
Preparing an article for anonymous review
General article format/layout
Preparation notes by article type
Illustrations
Tables
References

From submission to acceptance
Submission and peer-review
Production process
Changing contact details or authorship

Publication
Online versus print
Errata and retractions
Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

Research
Reviews
Clinical trials
Editorials
In Practice (Previously Forum incl. Case Reports)
Correspondence
Obituaries
Book reviews
Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

Guest editorial
Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journa*l are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R5 250 (ex vat) for each research article published. The charge applies only to **Research** articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publication fee is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received. Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.
Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript. If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:
whether individual DE identified participant data will be shared;
what data in particular will be shared; whether additional, related documents will be available;
When the data will become available and for how long; by what access criteria data will be shared.
Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials
Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrolment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Patient Consent

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ.*

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative Commons Attribution - Non-commercial Works License. Authors are required to complete and sign an Author Agreement form that outlines Author and Publisher rights and terms of publication. The **Author Agreement form** should be uploaded along with other submissions files and any submission will be considered incomplete without it.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication. The *SAMJ* does not hold itself responsible for statements made by the authors.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please

also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions. Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.

Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.

Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

Manuscripts must be written in UK English.

The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).

Please make your article concise, even if it is below the word limit.

Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).

Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.

Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:
- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.
**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.
- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:
Human Gene Mapping Workshop (HGMW): genetic notations and symbols
HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research
Editorials
CME
In Practice and Case reports
Reviews
Clinical trials
Correspondence
Obituaries
Book reviews
Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

This should be 250-400 words, with the following recommended headings:

Background: why the study is being done and how it relates to other published work.
Objectives: what the study intends to find out
Methods: must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
Results: first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
Conclusion: must be supported by the data, include recommendations for further study/actions.
Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
Do not include any references in the abstracts.
Here is an example of a good abstract.
Main article
All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.
The following are additional heading or section options that may appear within these:
Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results
Start with description of the population and sample. Include key characteristics of comparison groups.
Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
Do not replicate data in tables and in text.
If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.
Discussion
Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:
Statement of principal findings
Strengths and weaknesses of the study
Contribution to the body of knowledge

Strengths and weaknesses in relation to other studies
The meaning of the study – e.g. what this study means to clinicians and policymakers
Unanswered questions and recommendations for future research
Conclusions
This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words
These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.
Please make clear the type of evidence that supports each key statement, e.g.:
expert opinion
personal clinical experience
observational studies
trials
systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.
From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.
In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)21 789 2331).

Review process
The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials
Guideline word limit: 1 000 words
Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles
Guideline word limit: 2 000 - 3 000 words

Each article requires an abstract of ±200 words.
The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details
Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words) and a few words about your current fields of interest.

In Practice
Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.
In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

Case report
Clinical practice
Clinical alert
Issues in medicine
Issues in public health
Healthcare delivery
Consensus/Position statement
Medicine and the environment
Medicine and the law
Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:
Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
Short abstract: does not need to be structured, but should capture the essential features of the article
Introduction: the reason for the article and the issue being addressed
Recent research, discussion, local policy around the issue – include your own research where appropriate
All statements should be referenced and, if opinion only, this should be stated
Discussion: how this article adds to the discussion around a particular topic
If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.
Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports
The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a

completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.
Please use the following format for case reports:
Title of case: do not include the words 'a case report' in the title
Summary/abstract: up to 150 words summarising the case presentation and outcome
Background: why is this case important and why did you write it up?
Case presentation: presenting features, medical, social, family history as appropriate
Case management: should be according to best practice, and if not, please explain why
Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
Differential diagnosis, if relevant
Treatment, if relevant
Outcome and follow-up
Discussion – a VERY BRIEF review of similar published cases
Teaching points: 3 - 5 bullet points
References: as per the *SAMJ* house style
Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials
Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles
Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)
Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership
May include only one illustration or table
Must include a correspondence address.

Book reviews
Guideline word limit: 400 words
Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries
Guideline word limit: 400 words
Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines
Guidelines should always be discussed with the Editor prior to submission
Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.
All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.
All guidelines should be structured according to Agree II.
Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.
All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.
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Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
Chapter/section in a book: Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
Legal references

- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.
In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)
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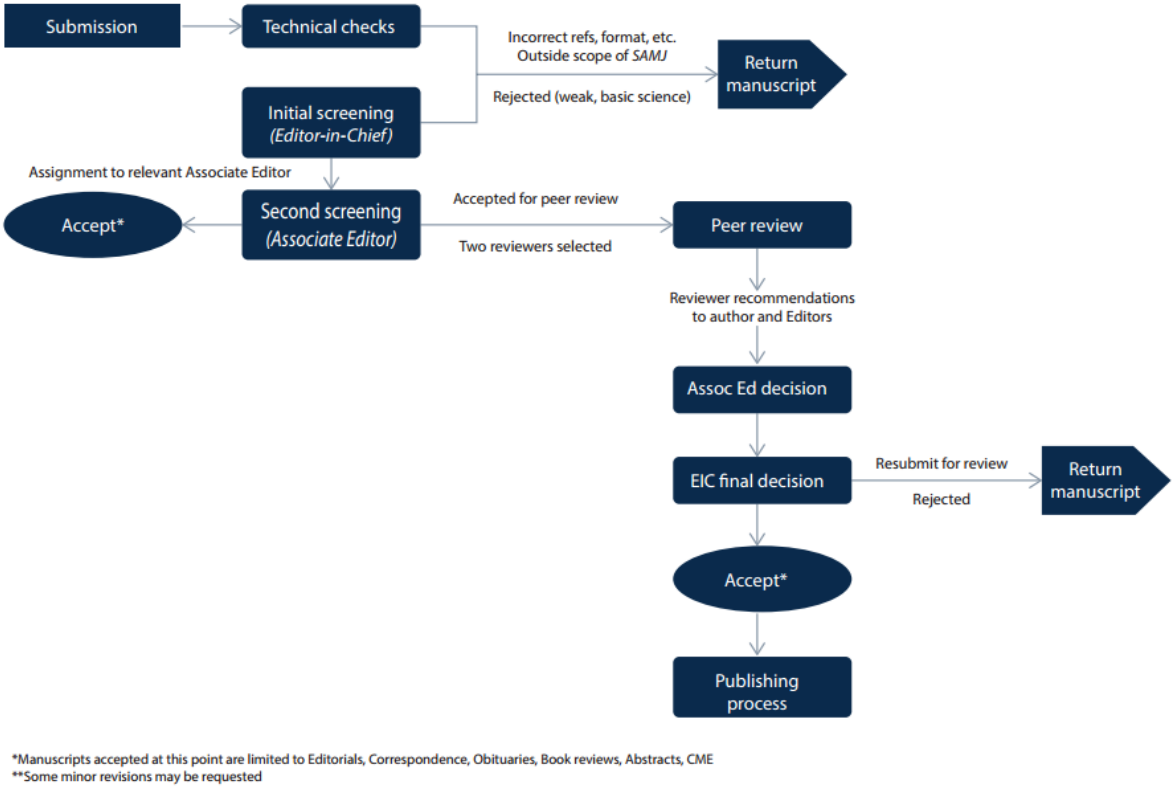

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