Haemodynamic Status And Management Of Shock In Children With Severe Febrile Illness

Dr. Samuel Owuor Akech
KEMRI/Wellcome Trust Research Programme,
Kilifi
Kenya
&
Kellogg College
60-62 Banbury Road
Oxford
OX2 6PN

Supervisors

Prof. Kathryn Maitland

Imperial college, London & KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya

&

Dr Brian Angus

Nuffield Department of Clinical Medicine, University of Oxford

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ABSTRACT

Most in-hospital deaths secondary to infections in under-five deaths within sub-Saharan Africa (SSA) occur in the initial 24 hours of admission and shock has been identified as a major risk factor for the early deaths. However, controversies exist on the appropriate clinical diagnosis of shock, choice of ideal fluid for resuscitation (crystalloid or colloid), and safety of fluid resuscitation in severe malnutrition or severe malaria. This thesis investigates these aspects and also reviews the evidence base of current paediatric fluid resuscitation guidelines for children (aged >60 days and ≤12 years) with severe febrile illnesses.

Capillary refill time >2 seconds, weak pulse volume, or bradycardia, in the presence of abnormal temperature and severe disease are predictive of impaired perfusion (defined by lactic acidosis) and death. Tachycardia and temperature gradient are neither associated with increased risk of death nor predictive of hypoperfusion. Existing international definitions of shock have low sensitivities (FEAST=44%, WHO=2%, and ACCM=59%) and high specificities (FEAST=82%, WHO=100%, and ACCM=66%) for diagnosis of impaired perfusion. Clinical criteria derived (called derived shock) had a sensitivity of 30% and specificity of 93%.

Shock in children with severe febrile illnesses in Kilifi has a complex presentation but mainly presents with hyperdynamic circulation (high cardiac index) and vasodilatation. Cases with low cardiac index (myocardial dysfunction) are relatively rare but increase the risk of mortality when present.

Synthetic colloids (gelofusine, hydroxyethyl starch 130/0.4 (HES), and dextran 70) are safe for use in fluid resuscitation in children with severe malaria. However, HES is the most promising compared to other synthetic colloids concerns still remain about its renal safety. However, further evaluation of synthetic colloids for treatment of shock is not warranted due to the findings of FEAST trial.

A Pilot trial shows that bolus isotonic fluids are safe, have better efficacy, and produce faster resolution of shock compared to low-sodium solutions at volumes and rates recommended by WHO in children with severe malnutrition.

Evidence available from all ten the trials in children with sepsis show that fluid resuscitation using crystalloids and colloids result in similar survival. However, fluid bolus resuscitation results in increased mortality compared to no bolus (control) in children in SSA. This finding excludes children with gastroenteritis, trauma, burns, and malnutrition. Colloids are better than crystalloids for severe dengue shock but both have similar efficacy in moderate dengue shock.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Abbreviations

95% CI	95% confidence interval
ACCM	American College of Critical Care Medicine
ACCM/PALS	American College of Critical Care Medicine/Paediatric Advanced Life Support
ADP	Adenosine Diphosphate
ANOVA	Analysis of variance
aPC	Activated protein C
ATP	Adenosine triphosphate
ATPase	Adenosine triphosphatase
AUC	Area under curve
BCS	Blantyre Coma Score
BNP	β-type natriuretic peptide
BP	Blood pressure
CaO_2	Arterial oxygen content of blood
CI	Cardiac index
CK-MB	Creatinine Kinase-Muscle Brain
CO	Cardiac output
COP	Colloid osmotic pressure
CRT	Capillary refill time
CSA	Cross sectional area of valve
CTF	Clinical Trials Facility
CvO_2	Mixed venous blood oxygen content
CVP	Central venous pressure
dCRT	Delayed capillary refill time
DNA	Deoxyribonucleic acid
DO_2	Tissue oxygen delivery
DSS	Dengue Shock Syndrome
DVT	Deep Venous Thrombosis
ECMO	Extra-corporeal membrane oxygenation
EF	Ejection fraction
EPLS	European Paediatric Life Support
ETAT	Emergency Triage Assessment and Treatment
FEAST trial	Fluid Expansion As Supportive Therapy in critically ill African children
FIO_2	Fraction of inspired oxygen
FS	Fractional shortening
FT	Systolic flow time
GPI	Glycosylphosphatidylinositol
HAS	4.5% or 5% human albumin solution
Hb	Haemoglobin
HDU	High Dependency Unit
HES	Hydroxyethyl starch
HIV	Human Immunodeficiency Virus
HMGB1	High mobility group B1
HR	Heart rate
HSD/5D	Half-Strength Darrow's in 5% Dextrose
ICAM1	Inter-Cellular Adhesion Molecule 1
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IPSCC	International Paediatric Sepsis Consensus Conference
IQR	Inter-quartile range

ITT	Intention to treat analysis
IVC	Inferior vena cava
IVCCI	Inferior vena cava Collapsibility Index
JVP	Jugular Venous Pulse
KDH	Kilifi District Hospital
KHDSS	Kilifi Health and Demographic Surveillance System
KEMRI	Kenya Medical Research Institute
KEMRI-CMRC	KEMRI/Centre for Geographic Medicine Research-Coast
KWTP	KEMRI/Wellcome Trust Programme
LFTs	Liver function tests
LMPI	Left myocardial performance index
LPS	Lipopolysaccharide
LR	Likelihood ratio
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
LRS	Lactated Ringer's Solution
LVEDP	Left Ventricular End-Diastolic Pressure
LVEDV	Left Ventricular End-Diastolic Volume
LVES	Left Ventricular End-Systolic
LVSF	Left Ventricular shortening fraction
MAP	Mean Arterial Pressure
MHC	Major Histocompatibility Class II
MIF	Microphage Inhibitory Factor
MODs	Multi-organ (multiple organ) dysfunction syndrome
MSR	Macrophage scavenger receptor
MUAC	Mid-upper arm circumference
MV	Maximum value
nCRT	Normal capillary refill time
NO	Nitric oxide
NOD	Nucleotide-binding oligomerization domain
NPV	Negative Predictive Value
NS	Non-severe disease without clinical signs of impaired perfusion
NSIMP	Non-severe disease with clinical signs of impaired perfusion
OXTREC	Oxford Research Ethics Committee
$PaCO_2$	Arterial partial pressure of carbon dioxide in the blood
PAF	Platelet activating factor
PALS	Paediatric Advanced Life Support
PAMP	Pathogen Associated Molecular Pattern
PATD	Pulmonary artery catheter thermodilution
PCO_2	Partial pressure of CO_2 in blood
PE	Potential energy
pfEMP1	*Plasmodium falciparum* erythrocyte membrane protein 1
PICU	Paediatrics intensive care unit
PO_2	Partial pressure of oxygen in blood
PP	Per-protocol analysis
PPV	Positive Predictive Value
PVP	Polyvinylpyrrolidone
RCT	Randomised controlled trial
RL	Ringer's Lactate
ROC	Area under receiver operating characteristics curve

RVEDP	Right Ventricular End-Diastolic Pressure
RVEDV	Right Ventricular End-Diastolic Volume
S	Severe disease without clinical signs of impaired perfusion
SAE	Serious adverse events
SAFE trial	The Saline versus Albumin Fluid Evaluation) Study
SaO_2	Arterial oxygen saturation
SBP	Systolic blood pressure
SD	Standard deviation
SF	Shortening fraction
SIMP	Severe disease with clinical signs of impaired perfusion
SIRS	Systemic Inflammatory Response Syndrome
SMII	Smith-Madigan Inotropy Index
SSA	Sub-Saharan Africa
SSC	Surviving Sepsis Campaign
SV	Stroke Volume
SVI	Stroke Volume Index
SvO_2	Mixed venous oxygen saturation
SVR	Systemic Vascular Resistance
SVRI	Systemic Vascular Resistance Index
TCR	T-Cell Receptor
TD	Thermodilution
TLR	Toll-like receptor
TNF	Tumour-necrosis factor
UK	United Kingdom
USA	United States of America
USCOM	Ultrasonic Cardiac Output Monitor
VCAM1	Vascular cell adhesion molecule 1
VEDP	Ventricular End-Diastolic Pressure
VO_2	Tissue oxygen consumption
VTI	Velocity time integral
WHO	World Health Organization

CHAPTER 1 : SUMMARY

1.1. Summary

Approximately 40% of all under-five deaths worldwide occur in sub-Saharan Africa (SSA) and infection remains a major cause of those deaths[1]. Most of childhood deaths occur in the community, but for in- hospital deaths, about one-third occur within the first 24 hours of admission[2-4]. Children who die early in hospital often present with a typical range of complications that can be identified as emergency signs[2-4] that if identified, could trigger prompt life saving interventions. Prioritising emergency management of the sickest children, who present with signs of life threatening illness, is commonly known as triage. Over the last decade it has been increasingly recognised that triage and prompt treatment of these emergency signs may reduce in-hospital mortality[5 6]. Recognising good hospital care as an important component of efforts in reducing childhood mortality, which is in line with the fourth millennium development goal, the World Health Organization (WHO) has over the recent years produced a number of guidelines for care for children admitted hospitals within resource poor settings[7 8]. These include emergency triage assessment and treatment (ETAT) and management guidelines for common illnesses or syndromic presentations including malnutrition[9 10]. Similar to guidelines used in emergency settings worldwide, the ETAT guidelines recommend immediate treatment of life threatening conditions first before commencing specific treatment. This involves systematic assessment and treatment of problems with the airway (A), breathing (B), and circulation(C), in respective order (known as the 'ABC approach' to emergency care)[7 11 12]. One aspect of emergency care is the treatment of shock by rapid administration of isotonic fluid boluses to corrected disordered circulation.

The data on the frequency and definitions of shock and its management in African children are sparse. Most guidelines have not been informed by prospective evaluation or clinical trials. Whilst the ETAT approach is similar to international guidelines used in emergencies in well-resourced settings, the criteria to define shock in ETAT and its management are at variance with international guidelines. Firstly, the ETAT criteria for shock are more stringent, that is, they identify children at a much later phase of shock, when treatment is less likely to be successful. In ETAT/WHO guideline, shock is defined as cold hands with capillary refill longer than 3 seconds, plus weak and fast pulse (>160, >150 or >140 if aged ≤1year, 1 to ≤3years, or 3 to 6 years, respectively)[8]. Fluid resuscitation to treat shock is only recommended if child fulfils the WHO criteria[7 8]. The guideline was prospectively evaluated in Malawi and Brazil and found to identify very few children with very poor outcome[5 13]. However, the strict criteria result from legitimate concerns of the risk of fluid overload in children

without a fluid requirement and where, for those who may develop adverse complications of fluid resuscitation, access to intensive care facilities are generally rare. Therefore, a major focus for this PhD thesis is the examination of the clinical features compliant with international definition of paediatric shock to determine whether these define high risk groups that require fluid resuscitation.

There is currently little understanding of the haemodynamic status and cardiac function of children hospitalised with severe illness in sub-Saharan Africa. It is therefore unclear whether hypovolaemic and septic shock, which are common causes of death in children with severe infections in developed countries[14], underpin some of the high mortality observed amongst children admitted with severe infectious illnesses in SSA[1 15 16]. Studies in severe and complicated malaria suggest that hypovolaemic shock is the major risk factor for mortality and that fluid resuscitation, usual treatment for shock, leads to reduced mortality[17-21]. However, there is still considerable controversy about optimal fluid treatment, with differing views on the clinical criteria used to diagnose shock in the studies on severe malaria[22-24]. This has led to the relatively infrequent use of fluid resuscitation in emergency settings in SSA other than for severe dehydration due to gastroenteritis. More evidence needs to be generated, by physiological studies, to determine whether the usual clinical features used to diagnose children with all stages of shock are associated with central haemodynamic manifestations (myocardial function and measures of filling and output) determined by standardised methodology (echocardiography and ultrasonic cardiac output monitor (USCOM)). To date there have been few studies validating clinical signs used for bedside diagnosis of shock. A study evaluating these signs will be highly informative and lead to delineation useful data on the definitions of shock for clinicians working in low resource settings. The findings are likely to result in better understanding of fluid requirements and response to treatment of shock with the ultimate aim of a reduction of case fatality in children with shock.

With respect to the recommendations for volume and type of resuscitation fluids, WHO treatment guidelines for shock recommend different fluids and at different infusion rates depending on the underlying diagnosis rather than the integrated approach that is used in international guidelines. This is a marked departure from contemporary practice in acute paediatric care where resuscitation is usually based on preset resuscitation goals rather than underlying aetiological diagnosis. In severe malnutrition, which is common in SSA[25], slow infusion of low-sodium (hypotonic) solutions is recommended for treatment of shock[7-10]. This presents a major problem because more than one third of all children with severe infectious illness may also have underlying undernutrition[25]. The numbers are likely to increase due to the revised WHO definition for malnutrition which now include children with mid upper arm circumference (MUAC) below 11.5cm[26]. Frontline clinicians are

therefore often left with a dilemma as to which guideline, fluid, or infusion rate to use in treating shock. This thesis presents three trials in investigating the safety and efficacy of various fluids for treatment of shock in two special conditions common within SSA, malaria and malnutrition. In severe malaria, the safety and efficacy of various synthetic colloids is presented. In severe malnutrition an investigation of the safety and efficacy of isotonic fluids compared to WHO recommended low-sodium solutions is presented.

Other guidelines (non WHO) recommend solely the use of isotonic solutions (colloids or crystalloids) for fluid resuscitation in shock. But controversy still persists worldwide on whether isotonic colloids or isotonic crystalloids are superior for fluid resuscitation in children with infectious causes admitted with shock[27-33]. The most recent Cochrane meta-analysis concluded that colloids and crystalloids had similar survival benefit in heterogeneous group of patients[27]. However, the largest trial which influenced the findings of this meta-analysis also found that 0.9% (normal) saline (a crystalloid) resulted in better survival for adults with traumatic brain injury when compared to 4.5% human albumin solution (HAS) (a colloid)[34]; but in the sub-group with sepsis HAS appeared better than saline[35]. These adult findings can not be directly extrapolated to children but the practice in most paediatrics settings continues to be influenced by the adult findings[36]. In dengue shock syndrome (DSS) colloids result in better treatment compared to crystalloids in severe forms but the two are equally effective in the moderate form[37-40]. A number of clinical trials conducted in Kilifi in children with severe malaria and metabolic acidosis suggest that HAS may result in better reduction in mortality compared to NS[19-21]. Whether the survival benefits of HAS demonstrated in these Phase II trials could be achieved by using synthetic colloids (dextrans, starches, or gelatins) in unknown. HAS is more expensive than other colloids, not readily available in SSA, and the safety of other colloids has not been established in children within SSA. The aim was to provide data on safety and efficacy of the synthetic colloids for the treatment of shock. Finally, the thesis incorporates this knowledge with respect to the results of a large controlled multi-centre study examining three fluid management strategies normal saline, HAS and no bolus (control) (Fluid Expansion As Supportive Treatment trial; FEAST) which was adequately powered with mortality as the primary endpoint[41]

1.2. Scope of the thesis

This thesis will focus on two main themes; firstly, the investigation of the haemodynamic status and cardiac function of children admitted with severe illnesses in at Kilifi District Hospital, Kenya, a typical rural district hospital in sub-Saharan Africa. To achieve this, non-invasive haemodynamic monitoring has been included to supplement clinical diagnosis of shock. Secondly, clinical trials to

establish the safety and efficacy of volume expansion in two conditions where fluid resuscitation is controversial, severe malaria and severe malnutrition are presented. Two trials investigate the safety and efficacy of various colloids for resuscitation in children in shock with severe malaria and one trial investigates the safety of isotonic fluid resuscitation to treat shock in children with severe malnutrition. Finally, a systematic review and meta-analysis summarising the evidence behind the current fluid resuscitation guidelines is presented.

1.3. Objectives

General objective

A description of haemodynamic status and management of shock in children with severe illness

Specific objectives

- To investigate the validity of various clinical signs and international criteria used in the diagnosis of shock.
- To describe the haemodynamic status and myocardial performance in children admitted with severe illness and/or impaired perfusion
- To investigate the safety of various colloids in the management of shock in severe malaria
- To determine the safety of fluid resuscitation using isotonic fluids in children with severe acute malnutrition with shock
- To review world literature, describe and evaluate the current evidence base for the management of shock in children

1.4. Organisation of the thesis

Chapter 2: An overview of origins of shock and historical evolution of treatment, pathogenesis of shock, critical review of existing clinical definitions of shock, and review of fluid management guidelines for shock.

Chapter 3: Study design and methods for the studies presented in the chapters 4-6.

Chapter 4: Reviews definitions of paediatric shock in severe illness. The first section of the chapter presents a retrospective analysis of data collected between years 2002 and 2003 to describe clinical features which predict elevated lactate and /or metabolic acidosis (elevated base deficit)- two common metabolic consequences of impaired perfusion (tissue hypoperfusion). The second part of the chapter uses data collected in the year 2004 as validation (test) set to test the performance of the clinical signs of shock derived from the first section-derivation/training set (2002 and 2003).

Chapter 5: A prospective study using two devices- echocardiography and USCOM, which describes haemodynamic status in children with severe illness. The relationship between various clinical features to haemodynamic measurements and myocardial performance is examined.

Chapter 6: Results of three studies on the fluid management of shock is presented. The initial two studies explore the safety of various colloids for the treatment of shock in children with severe malaria is presented. The first study compares the safety and efficacy of Gelofusine, a gelatin, to 4.5% human albumin saline (HAS) and the second study compares the safety of dextran (Dextran 70) and hydroxyethyl starch, HES 130/0.4. The third trial investigated the safety of isotonic fluid resuscitation to treat shock in children with severe malnutrition.

Chapter 7: A systematic review of the evidence for the current fluid management guidelines for shock in children including all evidence from paediatric clinical trials. The review will be restricted to children aged older than one month, with non-traumatic illness, and where shock is not secondary to severe dehydration (gastroenteritis).

Chapter 8: Discussion and synthesis of the results above are presented here.

1.5. Previous publications of sections of the thesis

The work in chapter 6 has been published as;

1. **Akech SO**, Karisa J, Nakamya P, Boga M, Maitland K: Phase II trial of isotonic fluid resuscitation in Kenyan children with severe malnutrition and hypovolaemia. *BMC pediatrics*, 10(1):71.

2. **Akech SO,** Jemutai J, Timbwa M, Kivaya E, Boga M, Fegan G, Maitland K: Phase II trial on the use of Dextran 70 or starch for supportive therapy in Kenyan children with severe malaria. *Crit Care Med 2010*.

3. **Akech S,** Gwer S, Idro R, et al. Volume Expansion with Albumin Compared to Gelofusine in Children with Severe Malaria: Results of a Controlled Trial. *PLoS Clin Trials* 2006;1(5):e21

Part of the work in chapter 7 has been published as;

4. **Akech S,** Ledermann H, Maitland K: Choice of fluids for resuscitation in children with severe infection and shock: systematic review. *Bmj*, 341:c4416

CHAPTER 2 : LITERATURE REVIEW

2.1. Origins of Shock and initial considerations for treatment

The term shock is derived from the French word 'choc' which means 'an encounter between to charging hostile forces'[42] and was first introduced in medical usage by Henri-Francois LeDran in 1740 and translated into English in 1743[42 43]. Initially the term was used to describe what was believed to be a neurological phenomenon following gunshot injuries that consisted of 'suspended laws of economy' (restlessness) and agitation, which left the victim 'stunned'. Until the early 19th century it was solely believed to result from gunshot injuries until the works of Gross and Chisolm during the American civil war (1861-1865) in which they reported that shock could result from a physiological response to any injury[44 45]. They described some of the signs of shock known today such as pallor, weak or absent pulse, confusion, prostration, anxiety, mental depression, coldness of the body, sweating, and incoherence of speech. These symptoms were however attributed to nervous depression and the recommended treatment was to stimulate a nervous reaction. Examples of the recommended nervous stimulants used included alcohol, ammonia, coffee, turpentine and ammonia carbonate. Both recommended wrapping the patient with blankets but Chisolm also recommended therapeutic bleeding (venotomy) if a patient had internal haemorrhage, a practice common at that time to treat shock and other ailments and which was promoted earlier by Galen[42].

Wider use of the word shock to describe a clinical syndrome was prompted by the publication of a critical review of the condition by Edwin Morris in 1868 entitled 'A Practical treatise on shock after surgical operations and injuries'[46]. Claude Bernard in 1865 demonstrated that autonomic nervous system was responsible for the maintenance of blood pressure and systemic perfusion[47]. He also produced the first accurate measurement of blood pressure measurement in the laboratory[42]. Due to Claude Bernard's findings, shock came to be understood as a 'nervous condition' in the late 19th century. This theory was underpinned by an assumption at the time that a 'strong emotion' together with physical commotion caused molecular changes in the brain[48]. A number of theories were proposed to explain the central nervous system connection. The first theory proposed that multiple afferent stimulations led to splanchnic dilatation and splanchnic pooling of blood resulting in fall in blood pressure. The afferent impulses were thought to cause a temporary vasoconstriction, followed by paralysis of vasoconstrictor centre and resulting in peripheral dilatation[49 50]. This theory is referred to as the 'vasoconstrictor theory'[42] and was proposed by a number of doctors of the time; Fischer in 1890 proposed that traumatic shock in frogs was due to vasomotor paralysis of the splanchnic nerves leading to accumulation of blood in the splanchnic circulation and anaemia in the

other parts of the body[48]. Groeningen around the same time proposed that all nerve centres suffered from exhaustion following over-stimulation while Mansell-Moullin in 1879 assumed that the nerve centre were inhibited rather than exhausted during shock. Second was the 'anoci-association' theory which was promoted by Dr George Crile and colleagues in 1899[51] who conducted experiments in dogs under ether anaesthesia. The dogs were subjected to strong irritations such as cutting, tearing, and extensive burning of the skin. Crile believed that low blood pressure resulted from excessive activity of visceral nervous system followed by exhaustion with resultant visceral vasodilatation and pooling of blood into the splanchnic vascular bed, portal vein, and other internal veins. Crile identified very low blood pressure as a characteristic sign of shock and also indicated that in shock, the low blood pressure could not be improved (increased) by any further stimulation. He noted that adrenalin or transfusions only temporarily raised the blood pressure and the blood pressure fell soon after because of nervous exhaustion. He identified low blood pressure as the sole cause of all symptoms of shock but insisted that it was caused by exhaustion of the vasomotor centre.

Thirdly, came the 'acapneic theory' introduced by Yandell Handerson around 1908[52] in which it was argued that reflexive hyperventilation, resulting in low carbon dioxide in blood (hypocarbia), created accumulation of blood in the splanchnic circulation. Handerson observed that animals which had bled heavily had abnormally low partial pressures of carbon-dioxide in their blood[52]. Treatments for shock that were recommended at the time were strychnine, ether, brandy, suprarenal extract (adrenalin), and ergot. By 1908, physiological saline was also being used with caution and measures such as raising foot of the bed were recommended[49].

William T. Porter in 1906 disagreed with the vascular exhaustion theory and asserted that vasomotor cells in shock were neither exhausted, depressed nor inhibited[53]. He observed the persistence of vasomotor reflexes at very low arterial pressures and expressed optimism that they would recover when blood pressure is raised to normal. During World War I, Porter instead proposed the theory of 'fat embolism' from which he believed that traumatic shock was a result[54]. His conclusion was influenced by observing shock in patients with long bone injuries in the war front. He later on injected various oils such as olive oil, cottonseed oil, and cod liver oil into jugular vein and the patients developed shock, strengthening his belief into the theory. During the same period, Cowell introduced the concept of 'wound shock' and proposed that the wound itself was the primary stimulus and liberated toxins which led to shock. This theory has been referred to as the 'toxic factor theory' of shock. He also divided shock into primary wound shock, within 15-20 minutes of injury, and secondary shock, due to toxaemia and continuing slight haemorrhage. This was advanced

thinking at the time since he had identified the difference between shock due to blood loss and later shock secondary septicaemia (secondary changes). Bayliss and Cannon argued against acapneic theory. Cannon measured the alkali reserve in the body and concluded that presence of a bicarbonate buffer system in the body could explain the hypocarbia and hyperventilation. He reverted to the Hippocratic term 'exemia' and believed that the state of shock was due to 'missing blood' as a result of pooling of blood within the body leading to reduced circulating volume, hence being the first to recognise reduction of circulating blood volume in distributive shock. Bayliss and Cannon believed shock was initiated by disturbance of nervous system leading to vasodilatation (nervous condition) and hypotension but secondary/sustained shock was as a result of increased permeability with loss of blood volume. They attributed the increased permeability to a toxic factor (toxic factor theory). Bayliss and Cannon experimented with a number of intravenous solutions to treat shock including blood transfusions, gelatins, and saline infusions but surprisingly concluded in 1923 that blanket wrapping was the best treatment for shock[55]. The concept of missing blood (exemia) and toxins would dominate research into shock pathophysiology for sometime after the World War I.

In 1927 Alfred Blalock reported that circulatory volume is reduced in all types of shock and reported that shock was a result of ''a decrease in the ratio of the blood volume in circulation to the capacity of the vascular tree"[42 56]. He also reported that this may be present even with normal arterial blood pressure, normal oxygen consumption, normal pulse rate, and normal temperature. He suggested that shock could not be produced by any event that does not cause a fall in cardiac output or oxygen content of mixed venous blood. Blalock pioneered the measurement of cardiac output using the Fick principle and his conclusions followed a series of experiments in dogs where he also measured blood gases, oxygen consumption, arterial and venous oxygen concentrations[42 56]. Blalock tried to change the name to 'acute circulatory failure' but this did not gain wide usage. He also classified shock into 'hematogenic' shock (hypovolaemia), neurogenic shock, vasogenic shock (anaphylactic and septic), and cardiogenic shock. The terms are still in used today and Blalock can be considered as the pioneer of the current understanding of shock.

2.2. Historical evolution of treatment of shock

The origin of intravenous fluid therapy use can be traced to the cholera epidemic in 1830[s] in England, before which emesis and blood letting were the normal treatments for shock secondary to cholera. It was believed that blood letting reduced venous congestion responsible for the thick-darkened blood seen in cholera and emesis was also used to remove 'poisons' that were believed to

be present[57]. Nitrous oxide and oxygen inhalations were also used to 'remedy the absence of arterialisation'[58]. Modern practice of intravenous therapy can be attributed to William Brooke O'Shaughnessy, a 22-year old medical graduate from Edinburgh University, who gave a graphic description of patient from Sunderland suffering from shock secondary to dehydration in cholera in December of 1831 and Thomas Latta who first administered intravenous saline infusion[59].

O'Shaughnessy observed "*a girl of slender make and juvenile height, but the face a superannuated hag. She uttered no moan, gave expression of no pain, but she languidly flung herself from side to side, and from supine to the prone position. The colour of her countenance was that of lead-a silver blue ghastly tint; her eyes were sunk deep into the sockets, as though they had been driven in an inch beyond their natural position; her mouth was squared; her features flattened; her eyelids black; her fingers shrunk, bent, and inky in their hue. All pulse was gone at the wrist, and a tenacious sweat moistened her bosom. In short, Sir, that face and form, I can never forget, were I to live beyond the period of man's natural age*"[60].

He immediately set out to conduct a series of experiments on blood from cholera patients and came up with a number of findings; "*The blood drawn in the worst cases of the cholera, is unchanged in its anatomical or globular structure; It has lost a large proportion of its water, 1000 parts of cholera serum having but the average of 860 parts of water; It has lost also a great proportion of its neutral saline ingredients; Of the free alkali contained in healthy serum, not a particle is present in some cholera cases, and barely a trace in others.*; Urea exists in the cases where suppression of urine has been a marked symptom; All the salts deficient in the blood, especially the carbonate of soda, are present in large quantities in the peculiar white dejected matters."*[61]. His experiments demonstrated severe dehydration, loss of sodium and depletion of bicarbonate rendering the blood severely acidotic.

O'Shaughnessy also gave the first description of impaired circulation in advanced cases of cholera when he wrote *"The all-but-unanimous evidence of those who have witnessed the disease in this its most appalling, though simplest shape, teaches us that universal stagnation of the venous system, and rapid cessation of the arterialisation of the blood, are the earliest, as well as the most characteristic of its effects. Hence the skin becomes blue-hence animal heat is no longer generated-hence the secretions are suspended; the arteries contain black blood, no carbonic acid is evolved from the lungs , and the returned air of expiration is as cold as when it enters these organs"*[57].

On the basis of above investigations he suggested intravenous replacement of water and salts (electrolytes) lost in the diarrhoea of cholera cases: *"It seems to me that if we could bring certain salts of highly oxygenated constitution fairly into contact with the black blood of cholera, we would certainly restore its arterial properties, and most probably terminate the bad symptoms of the case. It is however obvious, that in a disease so electric-like in its rapidity, and one moreover in which circulation is almost suspended…….I therefore conceive the idea of injecting into the veins such substances as an examination of the blood in cases of cholera would show to be most capable of restoring it to the arterial qualities*". From his experiments on a dog, he suggested that injection of nitrate of potash or chlorate of potash would be safe, especially in cases where the widely practiced venesection was impossible or when all known treatments failed. This novel approach remained untested owing to the reluctance by some physicians to adopt it. He also recommended the use of ivory or gold tubes, inserted into the external jugular vein and using warm distilled water.

Within less than two months after O'Shaughnessy recommendation, Thomas Latta, a physician working in Leith, Scotland, administered intravenous fluids to a number of cholera patients using O'Shaughnessy recommendations[62 63]. Latta used a solution containing "…*two to three drachms of muriate of soda and two scruples of subcarbonate soda in six pints of water..*"[58 64]. This was equivalent to 58 mEq/L of sodium, 49 mEq/litre of chloride and 9mEq/litre of bicarbonate. The solution was warmed and injected at temperature of 112°F (44°C)[65 66]. Latta later modified his solution to contain 134mEg/L of sodium, 118mmol/L of chloride, and 16mmol/L of bicarbonate[58]. Latta's patients had mixed outcomes and only about one-third survived. He recommended infusion of large amounts of the solution and repeating infusions. Despite the modest success seen with intravenous fluid resuscitation, the practice was not widely accepted by physicians of that time[67]. The reasons for poor success included restricting prescription to the terminal patients in extremis who died despite intervention and this led some clinicians at the time to believe that the treatment hastened death. Moreover, physicians failed to give repeat infusions hence patients relapsed into shock, the fluids used were often unsterile and the salts added were impure. Other problems included use of hypotonic solutions which caused haemolysis when given in large volumes, inadvertent air embolism due to cannulation, and the use of unsterile equipment for infusion[64 67-69]. Others therefore failed to realise the same success that was seen by Latta and this coupled with the death of Latta in 1833 and the end of cholera epidemic in England almost led to abandonment of intravenous fluid therapy. In 1834, John Mackintosh who had fully accepted intravenous therapy proposed by Latta noted that despite many excellent responses to saline injections, many patients relapsed into a state of collapse. He postulated that this problem could be reduced by making the

fluid to closely resemble blood serum as much as possible by adding egg albumin, hence making the first use of albumin (a colloid)[68].

During the next cholera pandemic of 1854, the use milk transfusion was practised mainly in North America. Milk transfusion was originally pioneered by James Bovell and Edwin Hodder of Toronto, Canada [65 70]Their rationale was based on an earlier notion that constitutive fatty acids and minute oily particles in milk were converted to white blood cells, which were also believed to be immature red blood cells. Transfusion of milk was therefore thought to be an ideal blood substitute. Cow, goat, and human milk were variously used until about 1884 when Bull reviewed all the previous 19 saline infusions and found the overall, saline was more beneficial compared to milk transfusion[70-72].

In a series of physiological experiments in frogs, Sydney Ringer discovered the effects of various electrolytes on the heart and involuntary muscles and concluded that precise proportions of calcium, potassium, sodium, and chloride salts are necessary for protoplasmic activity[73-75]. Interest in inorganic salts was provoked by observations in an experiment in which a laboratory assistant in Ringer's laboratory had used tap water instead of distilled water to make a saline solution for experiments on effects various blood constituents on contractility of frog's heart[73-78]. Ringer's observed that frog's heart bathed in tap water continued contracting but there were no contractions when he repeated the same experiment using saline made with distilled water. He proceeded to analyse the constituents of the tap water and concluded that inorganic salts present in the tap water were responsible for sustaining the heart's contractions. In 1876, he recommended a solution, now called Ringer's solution, containing 8 grams of sodium chloride, 0.3 grams of potassium chloride, and 0.33 grams of calcium chloride in 1 litre of distilled water[65 79].

In 1932, Alexis Hartmann recognised the need for alkali correction and maintaining electrolyte balance in children with acidosis and added sodium lactate to Ringer's solution and reduced chloride content, resulting in lactated Ringer's solution (LRS) or Hartmann's solution[80 81]. The solution contains 131 mEq of sodium, 5 mEq of potassium, 4 mEq of calcium, 29mEq of bicarbonate as lactate, and 111mEq of chloride in 1 litre of water[82]. A modification to the original Ringer's solution is the Darrow's solution (see Table below).

The use of normal (0.9%/physiologic/indifferent) saline (sodium ions=150-154mmol/L; chloride ions=150-154mmol/L) is attributed to *in vitro* experiments by Hartog Jakob Harmburger around 1900 who noted that mammalian cells, including humans, were isotonic with 0.9% sodium chloride solution as opposed to 0.6% solution that was isotonic in frogs[58 83]. The widespread use of 0.9%

saline has been attributed to its ease of preparation, low cost, and ease of mixing ingredients despite the high concentration of both sodium and chloride in the solution[58]. Table 2.1 shows properties of commonly used crystalloid solutions.

Table 2-1: Properties of commonly used crystalloids (electrolyte) solutions

Solution	Plasma	0.9% sodium chloride	Ringer's solution	Ringer's lactate/ Hartmann's solution	Darrow's solution	Plasmalyte B	Plasmalyte A
Osmolarity (mOsmol/L)	275-295	300	309	278		276	294
Plasma volume expansion (%)	-	20	20	20	20	20	
pH	7.35-7.45	5.0-5.5		6.5		5.5	
Na+ (mmol/L)	135-145	150-154	147	131	121	131	140
Cl– (mmol/L)	95-105	150-154	156	111	103	111	98
K+ (mmol/L)	3.5-5.3	-	4.0	5.0	35	5	5
Ca2+ (mmol/L)	2.2-2.6	-	2.2	2.0	-	1.8	
Glucose (mg/L)	2.8-6.1	-	-	-	-	-	
HCO3 – (mmol/L)	24-32	-	-	-	-	29	
Lactate (mmol/L)	<2.5	-	-	29	53	-	
Magnesium(mmol/L)	1.4-1.9	-	-	-	-	1.5	1.5
Acetate	-						27
Gluconate	-						23
Half life	-	20mins	20mins	20mins	20mins	20mins	20mins

References[84-89]

2.3. Origins of colloids

Once intravenous saline solutions were adopted for the treatment of haemorrhagic shock around the turn of the 20th century, it was noted that saline infusion only raised the blood pressure temporarily since the fluid was quickly lost from the intravascular space and the patients soon relapsed into shock [90-92]. In 1896, Starling described the importance of colloid osmotic pressure (COP) in maintaining fluid in the intravascular space[93]. A number of physicians reasoned based on Starling's findings that addition of a colloidal solution would prolong the intravascular half life of infused fluid and hence lead to more sustained increase in blood pressure/treatment of shock. Blood was considered the ideal solution but its use was considered dangerous and difficult to obtain at the time[90-92]. This led to the development and use of certain non-plasma colloid substitutes such as a gelatin (1915) and gum acacia (1916) [90-92 94]. Subsequently they fell out of use because gelatins had a high viscosity and gelled at low temperatures[95] , whilst gum acacia resulted in liver toxicity. The search for blood substitutes was mainly driven by a lot of cases of haemorrhagic shock in the casualties at the battle front in World War I.

The period between the end of World War I and 1930's saw the use of plasma transfusion and saline infusions but not much development of the other colloids[96]. A review during the early 1940s concluded that saline and glucose solutions were unsuitable because they were quickly lost from the intravascular space[97]. At the start of World War II when once again a lot of transfusions (and hence blood substitutes) were required, search for blood substitutes commenced again. Advancement in blood transfusion resulted in availability of large quantities plasma. Cournand[98] (1943) and Warren[99] (1944) separately used pooled human albumin solution (HAS) which had been separated from plasma using techniques earlier developed by Cohn to treat cases of shock[98-101]. In the same year, there was renewed interest in development and use of modified gelatins[95 102-104] and a new product, dextran, which was introduced in 1945[105]. Polyvinylpyrrolidone (PVP) (periston), an acetylene derivative, was also used by the German army during the same period but was found to be stored in the body[106].

2.4. Early crystalloid versus colloid controversy

Experiments performed by Moyer (1947)[107], Shires (1961)[108-110], and Moss (1969)[111 112] among others concluded that during haemorrhagic shock there was a greater reduction of interstitial fluid volume as compared to that of the intravascular volume and also proposed that interstitial fluid moved into the cells during shock[108 109 113 114]. Shires therefore recommended crystalloids as the ideal fluid for resuscitation because they would quickly expand the interstitial compartment since they freely move from the intravascular compartment. They also showed that infusion of large volume of crystalloids improved survival, and recommended volume replacement equal to 3 times (and a higher in sever shock, 8:1) the volume of blood loss[115]. The findings have however been disputed with many questioning the methods used for determining the extracellular volume[85]. Shires and colleagues used radioisotopes to measure various fluid compartments and red cell mass, and showed better survival in subjects who received balanced salt solution in addition to blood transfusion rather than blood transfusion alone [108]. They reported a shrinking of extracellular fluid compartment with the largest component being from the extravascular compartment in excess of that lost from the intravascular space. He attributed the losses to the 'third space' such as wound oedema and paralytic ileus. They reported that there was movement of this interstitial fluid into intracellular compartments resulting in oedema during experimental studies of haemorrhagic shock in dogs and man[108]. [108]Shires therefore advocated that restoration of extracellular fluid was more important for survival than that of intravascular fluid alone. This led to the later widespread practice of initial resuscitation with crystalloid infusion followed be colloids in cases non-responsive to crystalloids. Using different methodology, Shoemaker and Elwyn did not find decreased interstitial

fluid but instead demonstrated increased interstitial fluid in many critically ill post-operative and post-traumatic cases[116 117]. Since colloids increase plasma volume without expanding the interstitial volume and they have been proposed as the fluid of choice for resuscitation when there is need to increase circulating volume without increasing the interstitial volume. Massive infusions of crystalloids, about 5 times the volume of colloid, are required to increase plasma volume leading to increased risk of pulmonary oedema[113 118].

2.5. Modern colloids

The propensity of the synthetic colloids (gelatins and dextrans) to cause side effects , together with the high cost of human albumin solution, and colloid-crystalloid controversy motivated physicians to continue search for an ideal solution[119 120]. Hydroxyethyl starches (HES) were finally discovered in 1970s from amylopectin, a product of maize starch degradation[121]. Other colloids tried at various times but abandoned for various reasons, but mainly due to toxicity or long term storage in the reticulo-endothelial system, include: alginin, animal protein, casein, globin, glutamyl peptide, isinglass, methyl cellulose, pectin, and polyvinyl alcohol[122 123]. Table 2.2 shows properties of commonly available colloidal solutions.

Table 2-2: Properties of commonly used colloids

Solution	HAS	Dextrans		Gelatins		Starches			
	5% human albumin solution (HAS)	**40% dextran in normal saline**	**70% dextran in normal saline**	**4% Gelofusine**	**3.5% Haemacel**	**Pentastarch**	**Hetastarch**	**Tetrastarch (Voluven®)**	**Hextend®**
Osmolarity (mOsmol/L)	300	308	308		301	326	310	308	
Average molecular weight (D)	70000	40000	70000	30000	35000	260000	450000	130000	670000
Plasma volume expansion (ml/500ml infused)	500	500-1000	500-700	500	500	600-800	500-700		
Plasma volume expansion (%)	80	100	90	50	50	100	100	100	100
pH								4.0-5.5	
Na+ (mmol/L)	155	154	154	154	145	154	154	154	143
Cl– (mmol/L)	154	154	154	154	145	154	154	154	124
K+ (mmol/L)	4.0-6.0	-	-	4.7	5.1	-	-	-	3
Ca2+ (mmol/L)	-	-	-	5.85	6.25	-	-	-	2.5
Lactate	-	-	-	-	-	-	-	-	28
Magnesium	-	-	-	-	-	-	-	-	0.45
Glucose	-	-	-	-	-	-	-	-	5
Duration of plasma expansion	<24h	<6h	<24h	<4h		<12h	<36h	4-6h	
Half life	>24h		12h	3h	3h	2.5h	>24h	2h	

References [86 89 124 125]

2.6. Epidemiology of severe sepsis

Infection remains a major problem worldwide and accounts for ≈ 68% of the 8.8 million deaths in under-fives, the majority occurring in poor countries[126]. Many in-hospital deaths in African occur in children with proven bacterial infection. Berkley reported that 26% of all deaths in a rural hospital in Kenya were in children with community-acquired invasive bacterial disease[127]. The incidence of community acquired bacteraemia among hospital admission in Africa is 6-8%, which is much higher than developed countries[127-131]. *Escherichia coli*, groub B streptococcoci are common in children aged <60 days while *Streptococcus pneumoniae,* non-typhoidal salmonella species, *Haemophilus influenzae,* and *Escherichia coli* are the main pathogens in those older than 60 days. Malnutrition, which underlies 35% of all deaths in children aged <5 years[25], is a major risk factor for bacteraemia[127]. Human Immunodeficiency virus (HIV) infection, which has a higher prevalence in resource poor countries, also increases risk of bacteraemia[127]. Many children who die from malaria also have co-morbidities such as bacteraemia and malnutrition[132]. Infections in childhood have bimodal distribution, an initial peak in neonatal period and a second peak at about 2 years with both sexes equally affected.

In USA, of all paediatric deaths, 7% were in children with severe sepsis[133]. However, this reported estimate also included hospital-acquired infections and even in children undergoing cancer chemotherapy or organ transplant[133]. Understanding the burden of severe sepsis/septic shock has been hampered by lack of uniform definition and reliable single case definition. No studies currently report on the burden of severe sepsis in Africa but studies in the USA and UK both report that about 10% of all childhood deaths within hospitals are due to severe sepsis[130]. In USA, 751,000 cases of severe sepsis is reported annually[134]while in Europe, about 30% of all intensive care admissions have severe sepsis during their admission [135]Various rates have been reported in various parts of the world with, Slovakia reporting 8% and Brazil 17% of intensive care admissions having severe sepsis.

Mortality from severe sepsis, presenting as septic shock, has declined from 97% in the 1970s to about 10 % in 1999 in the USA and western Europe [133 136] . The success has mainly been and the success has been attributed to the use of effective antibiotics and early fluid resuscitation[14] but during the same period, access to intensive case (PICU) and other supporting treatments have also increased [137]. In developing countries, where infections is still the leading killer and invasive bacterial disease is a major risk factor for death, effective antibiotics are available as shown in a number of studies but the use of fluid resuscitation has not been widespread[127 128 132 138-140].

There is emerging evidence that circulatory shock may be more common than previously considered in children with infections admitted to hospitals in developing countries. Studies in Kilifi show that clinical evidence of hypovolaemic shock was the single most important risk factor for mortality in severe malaria[17 19-21 141] and severe malnutrition [4]. A study conducted in Ghana by Evans *et al* also showed that impaired consciousness and delayed capillary refill (a marker of shock) were the most important risk factor for death in severely ill children with malaria [138 142]. The majority of the in-hospital deaths in Africa occur soon after admission and there is some evidence that the fatal cases display signs of hypovolaemic shock[2 4 127].

2.7. Immunopathogenesis of severe sepsis

Infections have a complex pathophysiological presentation. Initial host immune response to different infecting pathogens may be different but there is convergence of subsequent immune response and activation of inflammatory mediators[143-146]. This results in a similar clinical picture, sepsis syndrome or systemic inflammatory response syndrome (SIRS), produced by different infecting pathogens. There is a common consensus that SIRS can result from a variety of infectious (bacterial, viral, fungal, parasitic, rickettsial, etc) and non-infectious causes[146-149]. Once established the clinical picture and progression is less distinct regardless of the initial insult although the tempo and outcome is more pathogen specific [150].

During infections, the innate immune system recognises certain patterns in the infecting organisms, called microorganism-associated molecular patterns or pathogen-associated molecular patterns (PAMPs)[146 149]. PAMPS are responsible for intracellular signalling that results in a cascade of host inflammatory response. Lipolysaccharide (LPS), also called endotoxin, is the main PAMP in gram negative bacteria and lipoteichoic acid is the equivalent in gram positive organism; however the exotoxins (superantigens) also play a greater role in gram positive infections. Other bacterial products recognised include peptidoglycans, other cell wall structures, such as flagellin and curli, and unmethylated CpG-motif-containing DNA, double stranded RNA, and carbohydrates (zymosan) [146 149]. Microbial PAMPs are commonly recognised by the Toll-like receptor (TLR) family of receptors located in dendritic cells, macrophages, endothelial cells, mast cells, B-lymphocytes, and adipocytes among other immune cell types. Recognition triggers a complex cytokine activation following a series of complex intracellular signalling. LPS is also sensed by intracellular receptors such as necleotide-binding oligomerization domain (NOD) and other cell surface molecules including macrophage scavenger receptor (MSR), CD11b/CD18, and ion channels which act through complex intracellular mechanisms resulting in release of cytokines. The superantigens of gram positive

bacteria cause T-cell activation and release of lymphokines through binding to major histocompatibility complex class II (MHC) and a limited population of T-cell receptor (TCR) Vβ domains[146]. Regardless of the mechanism of recognition, the final common outcome is the release of cytokines, which have own inflammatory actions, but also trigger release of lipid mediators, oxygen radicals, and cause endothelial and complement activation. PAMPS also directly activate the complement system and also induce factor expression on mononuclear and endothelial cells, the latter activating coagulation pathway.

Main pro-inflammatory cytokines are tumour necrosis factor alpha (TNF-ά) and interleukin-1 (IL-1). Both cytokines synergistically trigger a cascade of cytokine induced inflammatory response leading to production of other pro-inflammatory cytokines such as interferon gamma(IFN-γ), IL-6, IL-8, IL-12, IL-15, IL-18, macrophage inhibitory factor (MIF), high mobility group B1 (HMGB1). Anti-inflammatory mediators IL-10, TNF-ra, IL-1ra, IL-4, and IL-13 are also released. Lipid mediators released include arachidonic acid metabolites, bradykinin, histamine, platelet-activating factor (PAF), and prostaglandins, and oxygen free radicals include nitric oxide (NO), inducible-NO synthase (iNOS), superoxide and hydroxyl radicals [143 146 150 151]. Cytokine production and secondary release of mediators is perpetuated by fresh activation of cellular components (leucocytes, macrophages, and endothelial cells), by the cytokines and mediators. In severe sepsis the balance between pro-inflammatory mediators (TNF-ά, IL-1, and IL-8) and anti-inflammatory mediators (TNF-ra, IL-1ra, IL-4, IL-10, and IL-13) becomes dysregulated leading to uncontrolled inflammation. There is also imbalance in the coagulation pathway; normally there is a balance in the production of pro-coagulant factor (tissue factor expression, plasminogen-activating factor-1 (PAI-1)) and anti-coagulant factors (mainly activated protein C (aPC)) but the homeostasis is lost in severe sepsis.

The inflammatory cascade produced leads to impaired perfusion and multi-organ dysfunction syndrome (MODs) through a number of mechanisms. firstly, activation of endothelium, platelets and coagulation cascade result in pro-coagulant effect and capillary leak [150 152 153]. Secondly, the complex network of cytokines, mediators, and nitric oxide produced by activated endothelium produce vasodilatation resulting in peripheral blood pooling, reduced venous return to the heart, reduced stroke volume, and reduced cardiac output. Relative hypovolaemia due to circulatory maldistribution as a result of vasodilatation and peripheral blood pooling may result. Lastly, the inflammatory mediators and cytokines released produce a direct cytotoxic effect on the myocardium and may result in myocardial dysfunction[154-157]. However, impaired cellular respiration and cellular hypoxia may occur in sepsis even with adequate ventilation and perfusion. Mitochondrial dysfunction and damage as a consequence of cytokine release has been proposed as a possible

mechanism, resulting in anaerobic glycolysis and impaired oxidative phosphorylation[147 148 158]. Uncontrolled persistence of microcirculatory dysfunction and imbalance in favour of pro-inflammatory mediators leads to the development of severe sepsis and/or MODS.

Increasing literature supports the perspective that malaria pathogenesis proceeds like other infections. Like in bacterial infections the PAMPs triggers host immune recognition. Glycosylphosphatidylinositol (GPI) has been identified as the main malarial PAMP but others include haemozoin and isopentenyl pyrophosphate[149]. In addition to the PAMPs, *Plasmodium falciparum* infected red blood cells express members of erythrocyte membrane protein 1(pfEMP1) family of proteins on their surface. These bind to ICAM1, VCAM1, thrombospondin, chondroitin sulfate A, hyaluronic acid, and CD31 on endothelial cells. Following recognition of the PAMPs by a pattern recognition receptor, Toll-like receptor and/or T-cell receptor, the subsequent inflammatory response is indistinct in nature from that seen in other infections despite the presence of sequestration which is lacking in other infections.

2.8. Pathophysiology of shock

Global perfusion in shock

Shock, or circulatory failure, is defined as an acute state in which tissue perfusion is inadequate to maintain the supply of oxygen and nutrients necessary for normal cell function resulting in generalised cellular hypoxia, and accumulation of waste products of cellular metabolism[159-161]. Circulatory failure results in reduced oxygen delivery (DO_2) to the tissues. Reduced DO_2 is accompanied by decreased cellular partial pressure of oxygen (PO_2) - which can be measured using pulse oximeter. DO_2 is the amount of oxygen delivered to the tissues per minute and is dependent on cardiac output (CO) (amount of blood pumped by heart per minute) and arterial oxygen content of the blood (CaO_2). This relationship is summarised in the equation below;

- $DO_2 = CO \times CaO_2$; while,
- CaO_2=Haemoglobin oxygen carrying capacity (1.39ml of O_2/g Hb) × % Haemoglobin × % arterial oxygen saturation (SaO_2)
- Therefore, $CaO_2 = 1.39 \times Hb \times SaO_2$

Oxygen delivery (DO_2) can therefore be impaired by ischaemia secondary to reduced CO, anaemia (lower %Hb), or hypoxia (lower SaO_2). In physiological conditions of adequate oxygen and glucose supply to the tissues, each molecule of glucose is metabolised by oxidative phosphorylation in the mitochondria to produce of 38 ATP (adenosine triphosphate) molecules - a process requiring adequate oxygen delivery and uptake. The process of oxidative phosphorylation is called the Krebs

or citric acid cycle and uses pyruvic acid generated by glycolysis, which is the initial part of glucose metabolism that does not require oxygen. ATP is the cellular energy that is required for vital energy-dependent cellular processes such as the important sodium-potassium ATPase pump. The pump maintains homeostasis in the cells and a deficiency of ATP results in pump failure leading to intracellular accumulation of sodium, potassium efflux, calcium influx, cellular swelling and cell death. Decreased or lack of ATP is the final common pathway for cellular insult in all forms of shock. Widespread cell death leads to multi-organ dysfunction (MODs), hence the common consequences of end organ failure seen in patients with untreated shock.

However, there are mechanisms which protect, at least for some time, the development of MOD. During shock a critical PO_2 is reached when oxidative phosphorylation is limited by lack of tissue oxygen resulting in a switch of cellular metabolism from aerobic to anaerobic (anaerobic glycolysis). Anaerobic glycolysis, which uses the puruvate-lactate shunt pathway to metabolise glucose, is less efficient than oxidative phosphorylation at producing energy for cellular processes. Anaerobic glycolysis results in the production of only 4 ATPs for each glucose molecule (compared to 38 molecules produced by oxidative phosphorylation). Eventually if the DO_2 is not restored this results in impaired function of sodium-potassium ATPase pump and disturbed cellular homeostasis [159]. The switch to pyruvate-lactate shunt pathway leads to production of lactic and pyruvic acids (pyruvate). Pyruvate is not utilised by citric acid cycle but instead converted to lactate, a process that leads to inefficient generation of ATP[162]. Reduce DO_2 (tissue hypoxia) therefore leads to increased blood lactate/pyruvate ratio.

Accumulation of cellular and blood lactate, adenosine diphosphate (ADP) and hydrogen ion result in the development of systemic metabolic and lactic acidosis, where there is reduction in pH. Increased serum lactate is one of the earliest signs of cellular hypoxia[161 163-166]. There is also reduced removal and breakdown of the acids by the liver due to insufficient tissue oxygen delivery.

Regional perfusion in shock

Adequate tissue oxygenation depends on DO_2 that is enough to meet tissue demands. Oxygen demand however is different for various tissues and time of the day. Oxygen consumption/uptake (VO_2) is used as a proxy for oxygen tissue demand and is calculated by the following question;

- $VO_2 = DO_2 \times$ oxygen extraction ratio

During shock, where there is a fall in DO_2, VO_2 is maintained by compensatory increase in oxygen extraction ratio, which is the ratio of oxygen consumption to oxygen delivery (VO_2/DO_2). However if there is persistent fall in DO_2, a critical point is reached when increase in oxygen extraction ratio is

insufficient to maintain VO_2 (tissue demand). The critical point is usually higher for tissues with higher VO_2. Oxygen extraction ratio is increased by blood flow redistribution, through increased sympathetic adrenergic tone, from tissues with low extraction ratio (e.g. skin and gut) to those with high extraction ratio (e.g. brain and heart). Oxygen extraction ratio is also increased by capillary recruitment, which is responsible for peripheral vasodilatation. Kidney and brain possess a unique vasomotor autoregulation that enable them to maintain their circulation even in low flow states[159]. They also preferentially use lactate as a substrate for nephrons[167] and neurons.

Perfusion varies directly with perfusion pressure and inversely with resistance. For global (or whole body) blood flow perfusion pressure, determined by the difference between mean arterial pressure (MAP) and CVP divided resistance (represented by the systemic vascular resistance (SVR)). Whole body perfusion is dependent on CO and is represented by equation below;

- C0= (MAP-CVP)/SVR

Perfusion of specific organs (regional blood flow) depends on perfusion pressure for the specific organ and the vascular resistance for the specific organ/region. For example; renal blood flow = (mean renal arterial pressure-mean renal venous pressure)/renal vascular pressure.

Determinants of cardiac output in shock

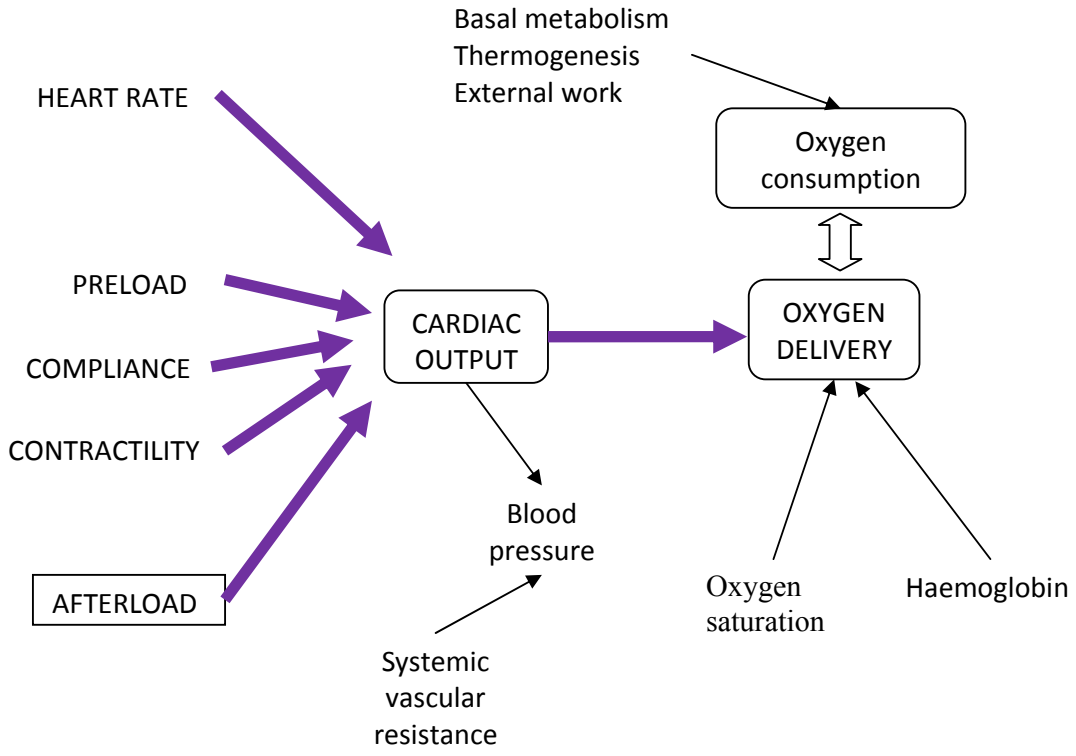
Cardiac output is determined by five difference variables; heart rate, preload (venous return), afterload, contractility, and compliance. The first four variables determine systolic function while compliance determines diastolic function. The variables are interdependent and apparent abnormality of a given variable may be secondary to an abnormality of another variable/s. During inadequate flow, compensatory tachycardia results to maintain cardiac out and this is the main compensatory mechanism to reduced flow in children. Heart rate is affected by conditions such as arrhythmias, extremes of temperature, and any condition that affects oxygen delivery[159]. Preload (venous return) is the ventricular end diastolic filling and is measured by methods such as CVP (right heart), pulmonary artery occlusion pressure (left heart), left and right ventricular end-diastolic volume (LVEDV/RVEDV), and corrected flow time. Inferior vena cava collapsibility index (IVCCI) has also been suggested as an echocardiography measurement of preload[168]. IVCCI measures the diameter and collapsibility index of the inferior van cava (IVC)[168]. Factors influencing preload include blood volume, venous capacitance, intrathoracic pressure, filling time, atrioventricular synchrony, diastolic function, pericardial restraint, atrioventricular valve competence, and pulmonary artery pressure[169]. Measurements of contractility include: end-systolic elastance, preload recruitable stroke work, cardiac function index (stroke volume divide by end-diastolic volume), shortening fraction (SF), ejection fraction (EF), and Doppler tissue imaging. SF=100 × (end-diastolic dimension-end-systolic

dimension) / (end-diastolic dimension) while EF=100 × (end-diastolic volume-end-systolic volume) / (end-diastolic volume)[159 169 170]. Contractility is affected by the following; myocardial oxygen supply, intracellular calcium ion concentration, acidosis, electrolyte imbalance, hypoglycaemia, catecholamines, sepsis, cardiomyopathy, or myocarditis. Afterload is the net force opposing left ventricular fibre shortening during ventricular ejection. It is affected by various factors including intrathoracic pressure, pericardial pressure, left ventricular end-systolic (LVES) intracavity pressure, LVES wall thickness and LVES dimension. Afterload is clinically measured using systemic vascular resistance (SVRI). Diastolic function is essential for maintaining adequate cardiac output and is measured by Doppler techniques such as myocardial performance index[171].

In addition to adequate CO, maintenance of adequate perfusion pressure (represented by mean blood pressure (mean BP)) and DO_2 is also affected by systemic vascular resistance (SVR); mean BP=CO × SVR. Oxygen delivery is also determined by other factors, non-dependent on CO, such as haemoglobin (haemoglobinopathies, anaemia, haemorrhage) and oxygen saturations (lung disease, carboxy/met-haemoglobin, and shunt). VO_2 is affected by basal metabolism (sedation, pain, anxiety, hormonal factors), needs for thermogenesis (shivering, fever, catecholamines), and external work (work of breathing, growth, trauma, catabolism, sepsis). These are summarised in figure 2.1.

During shock there is either relative or absolute reduction of intravascular volume and may be accompanied by reduced extravascular fluid volume (intracellular and /or interstitial). This leads to reduced venous return to the heart (preload), setting in motion compensatory mechanisms in an attempt to maintain cardiac output and tissue oxygen delivery as shown in the figure above. While adults may compensate by increasing contractility, children are unable to significantly increase contractility and mainly rely on increased heart rate when there is reduced preload.

Figure 2-1: Factors affecting tissue oxygen delivery and usage



2.9. Clinical progression and complications of shock

Clinically shock is progressive and evolves from early stages, which are reversible, to late irreversible stages unless promptly recognised and treated. For ease of understanding, shock is classified into three stages; early/compensated, decompensated/uncompensated, and refractory/irreversible stages[172]. These are defined as follows; compensated shock is the early stage when neurohormonal compensatory mechanisms are able to maintain blood pressure and tissue perfusion is preserved. Decompensated shock refers to the next stage when compensatory mechanisms have failed and specific therapeutic interventions are required but the patients may still respond to the interventions. The last stage is the refractory stage when shock has progressed to advanced degree of organ and tissue injury, is unresponsive to conventional therapy and death ensues.

During compensatory stage, early and compensated shock, the homeostatic and physiological mechanisms counter progression of shock and the body is able to maintain tissue perfusion. This is achieved by the following mechanism; the excess hydrogen ions released form anaerobic tissue metabolism combine with bicarbonate ion, using the carbonic acid/bicarbonate buffer, to produce carbon dioxide and water. The medulla chemoreceptors are triggered by a rise in the partial

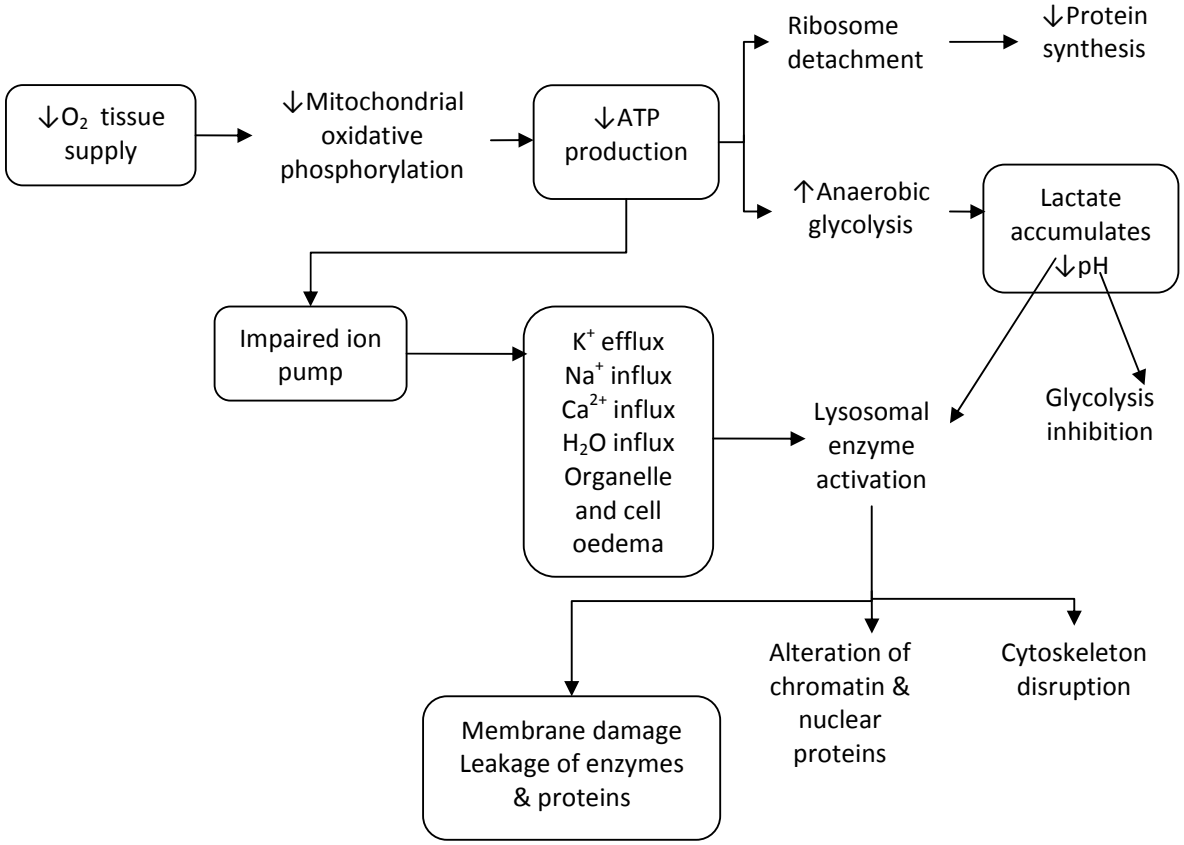
pressure of serum carbon dioxide leading to hyperventilation and hence removal of excess carbon dioxide and maintenance of pH. Aortic and carotid baroreceptors detect changes in circulating blood volume and stimulate compensatory mechanisms; adrenaline and noradrenaline are released, which cause vasoconstriction, and lead to an increase in blood pressure, heart rate (tachycardia), cardiac contractility. The catecholamine release also causes vasoconstriction to the skin, kidneys, gastrointestinal tract and diversion of blood supply to the key major organs responsible for sustaining life - the heart and the brain. Compensated shock is clinically manifested by: reduced urine output (oliguria), cold peripheries, core-toe temperature gradient, delayed capillary refill time, weak peripheral pulses, deep/acidotic (Kussmal) breathing, and increased gastric pH[173].

During decompensated stage, the compensatory mechanisms begin to fail if shock has not been corrected and inadequate perfusion begins. Due to cellular hypoxia, sodium-potassium pump fails and intracellular sodium increase while potassium escapes from the cells, leading to increased extracellular potassium concentration. Sodium entry into the cells is accompanied by water which leads to cellular and mitochondrial swelling. ATP production ceases due to the mitochondrial swelling causing rupture of lysosomal membranes, release of lytic enzymes (proteases, phospholipases, and ATPases), cell necrosis, disruption of cell membranes, cell death, and leakage of cellular enzymes and proteins[159]. Increased metabolic acidosis causes constriction of arteriolar and pre-capillary sphincters which leads to trapping of blood in the capillaries, increased hydrostatic pressure and histamine release (Figure 2.2). These mechanisms lead to leakage of fluid and proteins into the interstitial compartment, increased blood concentration and viscosity, obstruction of the microcirculation, and vital organ dysfunction if prolonged. Fluid leakage has been established in meningococcal sepsis[174] and dengue septic shock[175-177] but is yet to be definitively established in other severe infections. Decompensated shock is manifested clinically as hypotension due to impaired cardiac perfusion and impaired consciousness (irritability, lethargy, prostration, and coma) as result of reduced cerebral perfusion.

Untreated decompensated shock progresses to refractory/irreversible stage. At this stage, vital organs have failed, there is widespread cell death, multi-organ dysfunction syndrome (MODS) and

death usually follows in a few hours[160 173]. Figure 2.2 summarises the pathophysiology of shock.

Figure 2-2: Cellular pathophysiology of shock



2.10. Modern terminology in shock

Following infection the disease may involve from sepsis to its most severe manifestation, multi-organ dysfunction syndrome (MODS) or multi-organ failure. Definitions are as follows;

SIRS (systemic inflammatory response syndrome); abnormal temperature (<36.0^{o}C or >38.5^{o}C) or abnormal leucocyte count, plus either tachycardia/bradycardia or tachypnoea[178]. The heart and respiratory rates cut offs for definitions are age specific.

Sepsis; **SIRS** in the presence of suspected or proven infection caused by any pathogen or a clinical syndrome where infection is highly probable[178].

Septic shock ;Sepsis plus cardiovascular organ dysfunction[150 178]. Cardiovascular dysfunction is defined as the following despite administration of isotonic intravenous fluid bolus ≥40 ml/kg in 1

hour; hypotension or decrease in BP <5th percentile for age or systolic BP <2 SD below normal for age or need for vasoactive drug to maintain BP in normal range (dopamine >5µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) or any two of the following; unexplained metabolic acidosis (base deficit >5.0 mEq/L), increased arterial lactate >2 times upper limit of normal, oliguria (urine output <0.5 ml/kg/hr), prolonged capillary refill: <5 secs, or core to peripheral temperature gap >3°C).

Severe sepsis; Either septic shock or sepsis plus acute respiratory distress syndrome (PaO_2/FIO_2 ratio≤200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure), or two or more organ involvement (include respiratory, neurologic, haematologic, renal, or hepatic) if other systems are involved[178] as shown in Table 2.3. Once non-cardiovascular systems are involved, unless early and appropriately treated, the outcome is poor.

Table 2-3: Complications of shock

Cardiovascular system
Hypotension
Unexplained metabolic acidosis
Increased arterial lactate
Oliguria
Prolonged capillary refill
Core to peripheral temperature
Respiratory system
Abnormal PaO_2/FIO_2 in absence of cyanotic heart disease or pre-existing lung disease
Abnormal $PaCO_2$
Hypoxia
Need for non-elective invasive or non-invasive mechanical ventilation
Central nervous system
Impaired consciousness /altered mental status
Haematologic
Thrombocytopaenia
Abnormal International normalized ratio
Renal
Abnormal serum creatinine
Hepatic
Elevated total bilirubin
Elevated ALT

2.11. Classification of shock

Shock is traditionally classified depending on the cause; failure of the heart (pump) results in cardiogenic shock, reduction in blood volume causes hypovolaemic shock, abnormal vessel tone results in distributive shock, impaired oxygen carrying capacity causes dissociative shock, and obstruction of the vessels causes obstructive shock. These terms are still used currently however physiological studies suggest that rather than non-overlapping states, there are considerable components of many of these in patients with shock.

Cardiogenic shock may result from myocardial infarction or from heart failure from other causes. Hypovolaemic shock results when the circulating volume is reduced. Causes of such reduction include haemorrhage, gastrointestinal fluid loss due to vomiting or diarrhoea, and loss of fluid to the tissues or body cavities secondary to inflammation such as in trauma or infection. Others include fluid losses due to impaired surface barrier function such as in burns, increased urinary loss as a result of diabetes insipidus or hyperosmolar states such as diabetes mellitus, reduced fluid intake, and other metabolic or endocrine disorders.

There are two types of distributive shock[179]the low resistance, high cardiac output shock (also called 'warm shock') and the high resistance, low cardiac output shock (also called 'cold shock'). Warm shock is seen in the early stages of septic shock but later stages of septic shock also manifest with low cardiac output. Patients with warm shock have vasodilatation resulting in increased venous capacitance and peripheral pooling of blood. Low resistance distributive shock, but without increased cardiac output, may be seen following trans-section of the spinal cord. Untreated warm shock eventually progress to cold shock during which blood is pooled in the venous capacitance bed leading to reduced venous return and preload[180-183].Patients with warm shock have relative hypovolaemia due to increased venous capacitance. Obstructive shock is characterised by obstruction of mainstream blood flow as seen in pulmonary embolism, intra-cardiac ball-valve thrombus, and dissecting aortic aneurysm. Finally, shock may also occur as a result of insufficient oxygen carrying capacity of blood such as in anaemia and carbon monoxide poisoning and is called dissociative shock.

Sepsis causes shock by a complex mechanism that may result in hypovolaemia, myocardial impairment (cardiogenic shock), and distributive shock and if accompanied by anaemia – dissociative shock. Shock in this thesis will concentrate on the constellation of features and complications that complicate acute febrile illness leading to life threatening disease. This has elements of hypovolaemia, distributive shock, and myocardial impairment and where anaemia also complicates,

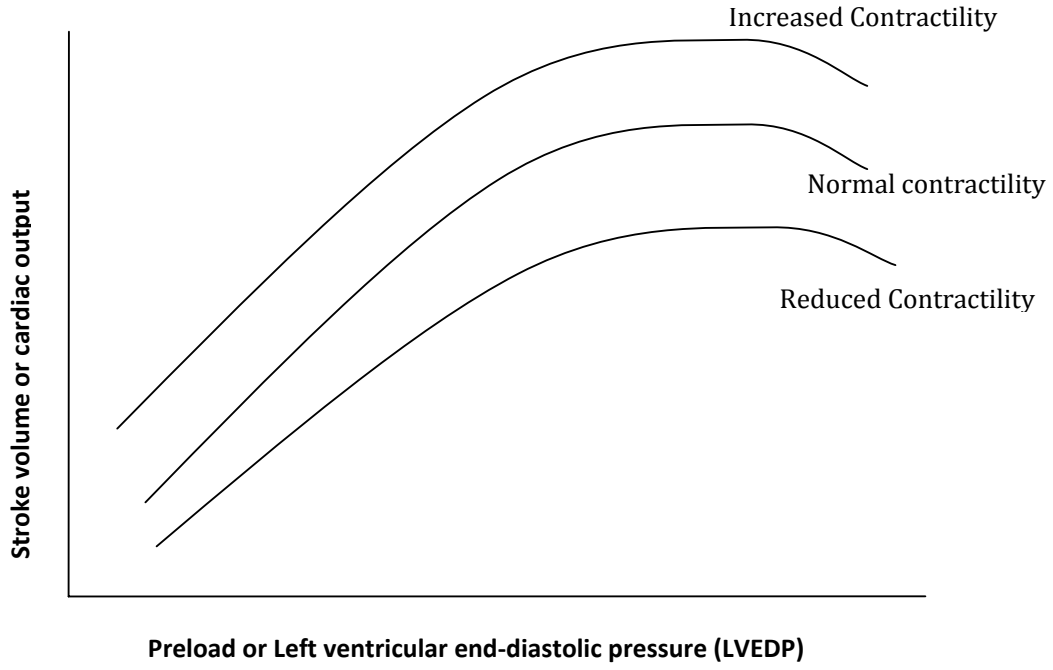
dissociative. The clinical manifestations and complications of sepsis too can arise from conditions or diseases other than bacterial disease. Therefore the use of the term shock or hypovolaemia shock and sepsis in this thesis recognises these a generic terms for children with severe febrile illness with the clinical manifestations of all degrees of circulatory failure (shock).

2.12. Principles of treatment of shock

Regardless of the cause of shock or therapy involved, the goal of treatment is restoration of cardiac output to ensure continued delivery of oxygen and substrates to the tissues and removal of metabolic wastes. Cardiac out is the product of stroke volume (SV), which is the amount of blood pumped by the heart with every beat, and heart rate. SV is determined by the preload, contractility, compliance, and afterload. Preload, also called the venous return, is the pre-systolic stretch of the ventricular fibres and is measured by ventricular end-diastolic pressure (VEDP). According to the Frank-Starling law of the heart (Figure 2.3), increase in preload (VEDP) results in a linear increase in tension generated by ventricular myocardial fibres, leading to increased SV and CO, until certain point reached beyond which further increased in preload results in no/decrease in SV and CO (Figure 2.3). In summary, when heart rate is constant, CO is directly related to preload until the ventricle is overfilled at which point the CO falls again. In the absence of tricuspid valve stenosis, right VEDP (RVEDP) is equal to the central venous pressure (CVP) or the right atrial pressure. Left VEDP (LVEDP) is determined by measuring the pulmonary artery wedge pressure in the absence of mitral valve disease.

Compliance is the change in ventricular volume for a given change in pressure. Ventricle with good compliance are able to increase stroke volume without with minimal change in (VEDP) but stiff ventricles experience significant increases in pressure even with minimal increase in preload. Contractility refers to the speed and force of ventricular contraction and is usually determined by measuring the left ventricular shortening fraction (LVSF). When contractility is good then the ventricular filling time is reduced and results in increased SV. Ejection fraction and peak ventricular pressure development also measure contractility. Afterload refers to the resistance or impedance to ventricular ejection and is dependent on the wall thickness, ventricular ejection pressure, and lumen radius. Afterload is inversely related to the stroke volume.

Figure 2-3: Frank-Starling Curve



2.13. Assessment of child with shock

Assessment of shock involves assessment of the various determinants of cardiac output, that is, preload, afterload, contractility, and compliance, both for diagnosis and for monitoring response to treatment. This is done clinically or by measuring various haemodynamic parameters or laboratory markers.

Various techniques are available for measuring cardiac output. Whilst thermodilution (TD) technique was once regarded as the gold standard measurement of cardiac output, it's usage has been hampered by the risk of infection during the procedure, invasiveness, thrombosis ,and haemorrhage [184 185] and is also restricted to sedated patients in intensive care. TD has largely been superseded by bedside Doppler ultrasound techniques (such as echocardiography), which directly calculate flow and volume [179 186-190]. The Doppler techniques have been validated in intensive care settings and found to have good correlation and agreement to pulmonary artery TD method [179 186-190].

Transthoracic echocardiography is non-invasive and has the extra advantage of providing extra information on the structural abnormalities, myocardial function, and contractility. It measures the state of left ventricular function by measuring CO, SV, shortening fraction (SF), ejection fraction (EF),

and left ventricular myocardial performance index (LMPI). LMPI is calculated from aortic and mitral Doppler echocardiography recordings using the formula; LMPI=[isovolumic contraction time + isovolumic relaxation time]/ejection time[191]. It also enables measurement of preload/venous return by measuring the diameter and collapsibility index of the inferior van cava (IVC), IVC collapsibility index (IVCCI)[168]. Children with shock have reduced calibre of the IVC and increased IVCCI[192]. IVCCI may in future replace the need for central venous pressure monitoring. However, the main disadvantage of echocardiography is that it requires more training and experience for good measurements.

The other Doppler ultrasound device used in non-invasive haemodynamic monitoring is the ultrasonic cardiac output monitor, USCOM (USCOM Pty. Ltd., Sydney, NSW, Australia). USCOM measures blood flow through pulmonary (transducer placed in left parasternal position) and aortic (transducer in the suprasternal position) valves. USCOM uses continuous-wave Doppler ultrasound and a 2.2-3.3 MHz transducer is place on the suprasternal notch to measure flow through aortic valve and 3rd to 4th left intercostal space parasternally to measure pulmonary valve flow. Each flow represents the velocity time integral (VTI) (calculated from peak flow), defined as the distance travelled by a column of blood for each stroke. Stroke volume =VTI × CSA (cross sectional area of valve) and the device multiplies stroke volume by heart rate to give cardiac output. The devise uses sex and height based algorithm to determine the CSA and CO. The systemic vascular resistance (SVR), which represents afterload, is calculated by the device using the formula; SVR= [(MAP-CVP)/CO] × 80[179 159 193]. When central venous pressure (CVP) measurement is available the device assumes CVP is equal to zero. These measures are automatically calculated after entering the patient's height and weight. The patient's SVR and SVRI are also calculated after the systolic and diastolic blood pressures are entered. USCOM also measures the contractility of the heart as inotropy, which is calculated from the Smith-Madigan formula automatically by the device.

- Total inotropy = PE + KE (= blood pressure + blood flow)
- Inotropy (Watts) = (BPm x SV x 10^{-3})/ (7.5 x FT) + (D x SV x 10^{-6} x Vm^2)/(2 x FT) This is the Smith-Madigan formula
- Smith-Madigan inotropy index (SMII)=Inotropy/body surface area (Watts/m^2=W/m^2)

Where, BPm= (MAP-CVP) in mmHg; SV=stroke volume; D=density of blood (1.055kg/m^3); Vm=mean velocity; FT=systolic flow time.

Studies in cohorts of intensive care patients have demonstrated that CO, CI, and SVI obtained using USCOM have good correlation to thermodilution technique and there is good reproducibility [179 186-190 194 195]. USCOM® measurements are also easy to learn and each measurement lasts only 30 seconds[179] and can be easily used outside intensive care. There are doubts about the need and accuracy of CO measurement in paediatrics for diagnosis of shock, but it is agreed that sequential measurement of CO is important to assess response to treatment[185].Need for CVP value limits the interpretation of the SVR/I and inotropy index values when the default value of zero is used in their calculation.

2.14. Biochemical markers of shock

Mixed venous oxygen saturation

A common proxy measure used in intensive care to measure CO is the mixed venous oxygen saturation (SvO_2). SvO_2 is used to assess the relationship between whole body oxygen consumption/uptake/demand (VO_2) and delivery (DO_2) by using the Fick principle;

- $VO_2 = CO \times (CaO_2 - CvO_2)$; where CvO_2=mixed venous blood oxygen content

Because CaO_2 and CvO_2 are proportional to SaO_2 and SvO_2, respectively, the equation above can be written as;

- $VO_2 = CO \times (SaO_2 - SvO_2) \times Hb \times 1.39$
- And $SvO_2 = SaO_2 - VO_2/(CO \times Hb \times 1.39)$

Therefore SvO_2 is decreased by hypoxaemia, increased tissue oxygen consumption, reduced cardiac output, and anaemia. Cardiac output has to increase proportionately whenever there is a fall in CaO_2 (secondary to anaemia or hypoxia), therefore SvO_2 represents adequacy of the cardiac output response to a fall in CaO_2. Measurement of S_VO_2 is invasive and is unsuitable for use in emergency settings in low resource settings. Its utility has been greatest within intensive cares settings where it is used for monitoring response to treatment. It has been evaluated by Rivers et al for goal directed therapy which was found to result in better survival [196].

Serum lactate

Serum lactate is widely used as an indicator of septic shock[137 178 197 198]. While there is universal appreciation of prognostic value of lactic acidosis[198-201], its aetiology is complex and two main mechanisms described; type A lactic acidosis where lactate accumulation is secondary tissue hypoxia and body generates ATP without oxygen, and type B lactic acidosis[202 203], which encompasses all other conditions of elevated lactate where the primary problem is unrelated to tissue oxygen debt[204]. Causes of type A lactic acidosis include circulatory shock (poor oxygen delivery), severe

anaemia (low oxygen carrying capacity) and pulmonary problem (low PO_2). Causes of type B lactic acidosis are thought to include increased epinephrine production in injury or sepsis which via β_2-adrenoceptor stimulation (including iatrogenic) causing increased sodium-potassium ATPase (ATP dependent) pump activity in skeletal musculature[202]. Glycogenolysis and glycolysis are increased in order to support increased ATP production resulting in increased production of pyruvate and lactate once mitochondrial oxidative capacity is overwhelmed. Other causes of type B lactic acidosis include cytokine-induced mitochondrial dysfunction, reduced lactate clearance, pyruvate dehydrogenase dysfunction, and protein degradation (with production of amino acids which are converted to pyruvate then to lactate). Some authors, using experimental studies involving localised inhibition of sodium-potassium pump[205], have proposed that type B acidosis is the predominant mechanism responsible for elevated lactate levels which would imply that the use of this parameter as a marker of impaired perfusion (shock) is inappropriate[206].

However studies aimed at reduction of lactate levels while being successful in clearing lactate, have not been successful in reducing mortality in sepsis and septic shock[207]. The 'lactate shuttle' theory has been used as one explanation for these of unexpected results. In the theory, hyperlactataemia is explained as an adaptive process where lactate is oxidised to produce energy in tissues where oxygen is available or for neoglucogenesis (in Cori cycle) while preserving glucose in oxygen-deficient tissues[162 202]. Proponents for predominance of type A lactic acidosis highlight that reduction in lactate level following treatment to improve tissue perfusion result in reduced mortality. Studies have also shown that persistence of lactic acidosis even after treatment for shock is associated with increased morbidity and mortality[198 199 208 209]. Two major critical care groups, the Surviving Sepsis Campaign[137] and the International Paediatric Sepsis Consensus Conference[178] both use elevated lactate and increased base deficit as part of their criteria for definition of septic shock.

Base deficit

Base excess, referred to as base deficit if negative, is the amount of base (in mmol) that would be required to restore 1 litre of blood to normal pH (assuming normal CO_2) at 37°C. In metabolic acidosis there is base deficit, the ratio of bicarbonate: PCO_2 falls leading to a fall in pH and bicarbonate. Compensatory hyperventilation results in reduction in PCO_2 and normalisation of pH. Acidosis in most critically ill children, regardless of the underlying causative disease, is most frequently associated with impaired perfusion, and is generally, treated by volume expansion, optimisation of tissue and organ perfusion and the provision of adequate glucose to reduce metabolic production of organic acids[210]. However the complex aetiology of lactic acidosis and the

presence of unmeasured ions (organic acids rather than lactate, phosphate and albumin) in metabolic acidosis make the interpretation of base deficit difficult[211-214].

Markers of cardiac injury

Cardiomyocytes are prone to damage during shock because they have a high concentration of mitochondria (which is a high energy consumer) and when damaged, troponins and creatinine kinase muscle-brain (CK-MB) are released[154 215]. B-type natriuretic peptide (BNP) and inactive pro-BNP are peptides released from the ventricles in response to ventricular volume expansion and pressure overload suggesting myocardial dysfunction[216]. Severity of ventricular dysfunction correlates with BNP levels and is regarded as a sensitive measure of left ventricular function[217].

Marker of renal hypoperfusion

Reduced renal blood flow in shock may result in reduced urine output, reduced creatinine clearance, increased levels of serum creatinine, increased urinary concentration with increased urine osmolality, and elevated serum urea[159 160 218]. Because these measures of urinary function may be normal in early stages of shock, they may not be suitable for diagnosis of shock as the early stages would be missed and they are affected by pre-existing renal disease. Normal creatinine levels are also dependent on muscle bulk and age of the patient. Urea is product of protein breakdown that is synthesised in the liver through the urea cycle. Urea may also be elevated due to high protein intake, gastrointestinal tract bleeding, conditions with increased catabolism such as trauma, post-surgery, acute myocardial infarction, or corticosteroids. To overcome the shortcomings in the use of creatinine and urea, urea to creatinine ratio has been used[219]. Urea to creatinine ratio is useful for determination of whether elevation of urea is due to pre-renal causes (such as shock, dehydration, congestive cardiac failure) or intrinsic causes (acute or chronic renal disease)[219]. Pre-renal causes of elevated urea result in elevated urea: creatinine ratio (> 0.1 mmol/µmol or >20:1 mg/dL /mmol/L). Despite the stated shortcomings, these renal function tests can be used to monitor response to treatment.

2.15. Clinical diagnosis of shock

Clinical signs of early or compensated shock are subtle and can be easily missed when clinicians rely solely upon clinical signs[160 218]. The overt form of shock, hypotension (decompensated shock), is a late pre-terminal event. There is no single gold standard clinical definition of shock and various criteria, each comprising a number of clinical signs, are currently used. Table 2.4 summarises various definitions of shock currently in clinical use.

Table 2-4: Various clinical definitions of shock

Shock criterion	Definition of shock
FEAST inclusion criteria[41]	History of fever or temperature ≥37.5C or <36.0C Plus Impaired consciousness (prostration or coma) and/or respiratory distress (deep breathing or increased work of breathing) Plus ≥1 of: CRT >2s; lower limb temperature gradient; weak pulse; HR >180 (<12 months), >160 (12 months-5 years), >140 (>5 years)
American Academy of Critical Care Medicine (ACCM) shock criteria[220]	Hypothermia or hyperthermia Plus Clinical signs of inadequate tissue perfusion including any of the following: decreased or altered mental status; CRT >2 secs, diminished pulses, mottled cool extremities (cold shock); flash capillary refill, bounding peripheral pulses, wide pulse pressure (warm shock); urine output <1ml/kg/hr. Hypotension not necessary for clinical diagnosis of septic shock, but its presence in a child with clinical suspicion of infection is confirmatory
Pediatric Advanced Life Support (PALS) shock criteria [11]	Typical signs of compensated shock include: tachycardia; cool and pale distal extremities; CRT >2 seconds despite warm ambient temperature; weak peripheral pulses compared with central pulses; normal systolic blood pressure Decompensated shock characterised by signs & symptoms consistent with inadequate delivery of oxygen to tissues (pallor, peripheral cyanosis, tachypnoea, mottling of skin, decreased urine output, metabolic acidosis, depressed mental status); also weak or absent peripheral pulses, weak central pulses, hypotension (systolic BP <70mmHg 1-12 months; <70mmHg + (2 x age in years) 1-10yrs; <90mmHg ≥10 years)
Surviving Sepsis Campaign[137]	Systemic inflammatory response syndrome (SIRS): Core temperature >38.5C or <36C plus ≥1 of: tachycardia: HR >180 (1mth-1yr); HR >140 (2-5 yrs); HR >130 (6-12 yrs); tachypnoea: RR >34 (1mth-1yr); RR >22 (2-5yrs); RR >18 (6-12 yrs) Plus: Cardiovascular dysfunction: Despite ≥40ml/kg isotonic fluid bolus in 1 hour, either: Hypotension: Systolic BP <75mmHg (1mth-1 yr), <94mmHg (2-5yrs), <105mmHg (6-12 yrs) or ≥2 of: Arterial lactate >2 times upper limit of normal; urine output <0.5ml/kg/hr; CRT >5 secs; core-peripheral temp gap >3°C
European Paediatric Life Support Course (2006)[12]	Compensated circulatory failure: although the blood pressure is normal, poor skin perfusion (CRT >2 secs, mottled, cool peripheries, peripheral cyanosis), weak peripheral pulse, tachycardia: HR >180 (3mths-2 yrs); >140 (2-10yrs); >100 (>10yrs), tachypnoea (RR >40 <1yr; >34 (1-2yrs); >30 (2-5yrs); >24 (5-12 yrs) and oliguria are observed Decompensated circulatory failure: hypotension (SBP <70mmHg (1-12 months); <70 + (2 x age in yrs) mmHg (1-10yrs); <90mmHg (>10 yrs); decreased mental status
WHO/ETAT[7 8]	The presence of cold hands or feet with both capillary refill time >3 seconds and weak and fast pulse.
International Paediatric Sepsis Consensus Conference (IPSCC) definition of shock[178]	Sepsis (SIRS plus proven or suspected bacterial infection) plus cardiovascular dysfunction defined as : Despite ≥40ml/kg isotonic fluid bolus in 1 hour, either: Hypotension: Systolic BP <75mmHg (1mth-1 yr), <94mmHg (2-5yrs), <105mmHg (6-12 yrs) or ≥2 of: Arterial lactate >2 times upper limit of normal; urine output <0.5ml/kg/hr; CRT >5 secs; core-peripheral temp gap >3°C

The WHO definition is stringent and only identifies children in advanced stages of shock. The guideline was prospectively evaluated in Malawi and Brazil and found to identify very few children with very poor outcome[5 13].The ACCM and PALS definitions for shock are less stringent as compared

to the WHO definition but have some risks[136]. Using the two definitions, children with meningitis or any other cause of reduced consciousness would receive fluid even if they do not have any other feature of impaired circulation. Previous studies have shown that when WHO criteria is made less stringent by adopting capillary refill > 2 seconds as indicative of shock then a larger number of children at risk of early fatality can be identified at hospital admission[4].

These definitions have been developed through consensus and no definitive prospective studies have been conducted to evaluate the criteria. Clinical signs used by these criteria also have low specificity and high sensitivity and may result in inappropriate diagnosis and treatment of shock. Capillary refill time may dependent on patient's age, choice of limbs (may be lower in lower as compared to upper limbs), limb position in relation to the heart (should be above the heart to avoid venous refill), room lighting and ambient temperature[169 221-223]. There may also be inter-observer variability, especially for borderline values, and there has been poor relationship cardiac output measurement. Skin temperature gradient (cold hands and/or feet) is also affected by the ambient temperature[224] , may fail to identify early stages in sepsis when there vasodilatation and hyperdynamic circulation (so called warm shock). Pamba *et al* reported that capillary refill time was only useful as a prognostic sign for mortality when other features of severe disease severity were preesent[225].

2.16. Factors influencing choice of resuscitation fluid

The ideal resuscitation fluid should achieve rapid and sustained restoration of intravascular volume, with minimal adverse effects and result in survival benefits since it is given as a life-saving treatment. The physiological principal of fluid to restore circulating volume is dependent on Starling forces operating at the vascular endothelium. According to Starling, fluid exchange is dependent on hydrostatic pressure, the colloid osmotic pressure (COP) (negligible in the interstitium), and capillary permeability, represented by Staverman reflection coefficient (explained below). There is normally a net loss of fluid into the interstitium which flows into the lymphatic system. The semipermeable capillary endothelial membrane is freely permeable to water and small ions such as sodium, potassium, chloride, and urea among others but is relatively impermeable to large molecules such as plasma proteins (albumin, globulins). Fluid movement across the capillary wall is dependent on forces described by Starling[93] and summarised in the Starling equation[226 227]:

$$Q = LS[(P_c - P_{is}) - \sigma(\pi_c - \pi_{is})]$$

Where;

Q=rate of transvascular fluid exchange

L=endothelial hydraulic conductivity

S=endothelial surface area

P=hydrostatic pressure

π =osmotic pressure

c=capillary

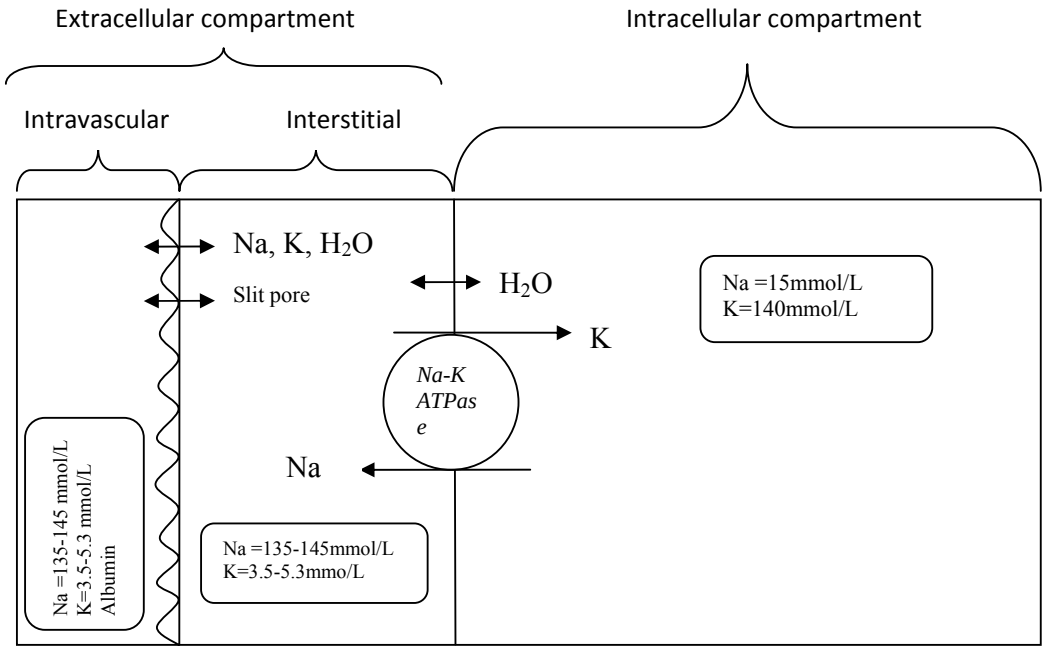
is =interstitium

σ=Staverman reflection coefficient, has values between 0 and 1, reflects the degree to which capillary membrane prevents free transfer of colloid molecules. Zero (0) corresponds to free passage and 1 corresponds to total impermeability.

According to Vant Hoff COP is proportional to the molar concentration of the colloid, however, the normal plasma COP is usually greater than would be expected from calculation as a result of Gibbs-Donnan equilibrium phenomenon, excluded volume effect, and chloride binding by albumin[226-228]. Due to the Gibbs-Donnan phenomenon, the freely permeable ions are also not uniformly distributed across the capillary membrane leading to an increase in COP, which is responsible for preventing the escape of water and small ions from the intravascular space. Water freely permeates into the intracellular compartment but the small ions do not because of existence of sodium-potassium energy-dependent pump, which actively pumps out sodium ions into the extracellular space exchange for potassium ions the two respective major extracellular and intracellular cations-see Figure 2.4.

Resuscitation fluid should also ideally have ion composition similar to that of plasma[88] (Osmolarity (275-195 mOsmol/L); pH(7.35-7.45); Na^+ (135-145mmol/L); Cl^- (95-105 mmol/L); K^+ (3.5-5.3 mmol/L); $Ca2^+$ (2.2-2.6 mmol/L); Glucose (3.5-5.5 mg/L); $HCO3^-$ (24-32mmol/L); and Na:Cl ratio(1.28-1.45:1). Colloids increase COP while crystalloids do not.

Figure 2-4: Body fluid compartments and electrolyte distribution



2.17. Colloids

Colloid solutions comprise of homogenous large non-crystalline molecules, which are ultra-microscopic, suspended in crystalloid solutions. The colloids in these solutions increase the COP and like plasma proteins do not freely permeate the capillary membrane. COP is further increased by excluded volume effect and chloride binding but not through the Gibbs-Donnan phenomenon because they are electroneutral; and more of the ions are also retained intravascularly due to these forces. Colloid infusions result in large increases in circulating/intravascular volume with the resultant volume increase dependent on the molecular size of the infused colloid. Colloids are largely retained in the intravascular space. Therefore, theoretically, colloids should the preferred fluid for treatment of shock when rapid and sustained expansion of intravascular volume is a priority to prevent impaired perfusion, organ failure and death.

Colloids can be classified as naturally occurring, which are derived from plasma (HAS, plasma protein fraction, fresh frozen plasma, and immunoglobulin solutions) or semisynthetic (gelatins, dextrans, and hydroxyethyl starches (HES))[86]. They can also be classified based on distribution molecular sizes into monodisperse solutions, with molecules of uniform size and polydisperse solutions, with molecules having a wide distribution of molecular sizes. The osmotic effect, hence volume expansion effect, and duration of effect of colloids depend on the molecular sizes and surface charge

of the particles[124 227 228]. Lower molecular weight colloids exert a larger initial osmotic effect leading to rapid expansion of circulating volume but they are rapidly cleared from the circulation therefore their effect is not sustained. On the contrary larger molecular weight colloids exert smaller osmotic pressure but they have a longer sustained effect on volume expansion. However, in conditions were there is endothelial injury with capillary leak, it is feared that infusion of colloid would result in colloid leakage into the interstitium where it would continue to exert oncotic pressure and result in drawing of additional water into the interstitium and leading to extracellular oedema. Conditions where increased capillary leak has been suspected include meningococcal sepsis[174 229 230], dengue shock syndrome (DSS)[177 231], acute respiratory distress syndrome, anaphylaxis, aspiration pneumonia, bacterial or viral pneumonia, burns, cardiopulmonary bypass, disseminated intravascular coagulation, drug overdose (salicylates, cocaine, opioids), inhalation injury, head injury, massive blood transfusion, near drowning, pancreatitis, sepsis, thromboembolism, trauma, and venom exposures among others. Use in conditions with capillary leak is thought to pose risks but increased risk of death has only been shown in meta-analyses in children with burns and heard injury[27]. However, this assumption is not supported in meningococcal sepsis and DSS, two conditions where capillary leakage is dominant pathogenesis mechanism. Definitive trials have shown that colloids are superior to crystalloids for treatment of shock in severe dengue shock (DSS)[38-40]. Shock in DSS evolves over 2-3 days[231] and mortality is low in DSS therefore mortality has not been used in these trials. Observational studies from the group at St. Mary's, London, UK have also reported superiority of 4.5% HAS over crystalloids for treatment of shock in meningococcal sepsis[229 230 232 233]. Absence of randomisation in the meningococcal studies however makes interpretation of the findings difficult.

Ideal colloids are considered those with the following features; free of antigenic or allergic properties, lead to sustained intravascular osmotic pressure, poses no infectious risk, does not require cross-matching, has a long shelf-life, has simple storage requirement and can withstand wide range of temperatures, and inexpensive[124 226 227]. Unfortunately none of the colloids presently in use possess all these characteristics. Table 2.2 summarises properties of commonly used colloids.

2.17.1. Human albumin solution (HAS)

It is a natural monodisperse colloid prepared from pooled human plasma with a molecular weight of 69000 Daltons and has a net charge of -17 at a pH of 7.4. It is viral and particulate free and undergoes heat and cold fractionation during preparation[234]. Storage is recommended at room temperature not exceeding 30°C. The volume expansion effect of HAS depends on initial oncotic pressure, vascular permeability and adequacy of volume resuscitation[124 226 227 235 236]. Five percent or

4.5% HAS expands plasma volume equivalent to the volume infused and is the form used for intravascular volume expansion. Twenty percent or 25% HAS, also called 'salt poor' or 'albumin-rich', is used in the treatment of hypoalbuminaemia in presence of salt and water overload. These concentrations achieve volume expansion of 3-5 times the volume infused[227].

In addition to its colloid osmotic pressure albumin is reported to have other unique propertied not present in other colloids including; particular neuroprotective effect, direct effects on the vascular endothelium through binding to the endothelial glycocalyx, and maintenance of normal permeability of microvessel walls [237 238]. Albumin also acts as a carrier of various metabolites, scavenger of free radicals that are required for lipid peroxidation, binds and inactivates toxic products produced during disease states, binds and transports many drugs, lipids and lipid soluble materials such as fatty acids, hormones, enzymes, dyes, and trace metals. Albumin also has anticoagulant properties through its inhibitory effect on pathologic platelet aggregation and is also reported to have some activity in preserving microvascular integrity hence potential role in reducing oedema formation[235]. Albumin also exerts direct effects on vascular endothelium, by binding to the endothelial glycocalyx to maintain normal permeability [239] and influences erythrocyte aggregation by increasing low-shear viscosity and decreasing erythrocyte sedimentation under no-flow conditions [237 238]. Side effects of HAS include adverse reactions such as seen in transfusion reactions (fever, chills, urticaria, vasodilatation), hypocalcaemia due to calcium binding which may result in myocardial depression, reduced glomerular filtration rate consequent to increased oncotic pressure leading to reduced excretion of sodium and water, and rare cases of aluminium toxicity[124]. The manufacturers reduce the risk of prion disease by use of plasma from populations in which prion disease has not been reported as a public health problem[234].

These non-colloid properties of albumin may be of particular importance in the pathophysiology of cerebral malaria, where adherence of parasitised red blood cells to the endothelium, and aggregation of red cells due to the phenomenon of rosetting, may be influenced by the highly negative charge of the albumin molecule[213 235 240]. Relevant to the possible neuroprotective effects of albumin in cerebral malaria, is the growing literature on the use of human albumin solution as a neuroprotective therapy in patients with stroke[241-243]. This includes extensive pre-clinical testing and clinical trials showing that high grade protection is offered by albumin, which is thought to act via multiple mechanisms including the amelioration of brain swelling [241 244] and the improvement of blood flow to critically perfused brain regions [245].

2.17.2. Dextrans

These glucose polymers of 200000 glucose units derived from the action of bacteria, *Leuconostic mesenteroides*, on sucrose. They are polydisperse and there are two preparations based on weighted molecular weight; 6% dextran 70, average molecular weight 70000 Daltons, and 10% dextran 40 with an average molecular weight of 40000 Daltons. Both are in solution of 0.9% saline and can be stored at 15-30°C[124]. About 65% of dextran 40 and 40% of dextran 70 have molecular weights <55000 Daltons, the renal threshold, and are consequently eliminated rapidly through the kidneys. The remaining large molecules are removed by enzymatic degradation by the endogenous enzyme, dextranase. Their volume expansion effect of dextran 40 is 1-2 times the amount infused, half life is 3 hours and 60% is removed within 6 hours. Dextran 70 is lost lest rapidly from the circulation and only 35% has been cleared from the circulation at 12 hours[124 227 228 236 246].

Dextran molecules weighing >60000 Daltons aggregate red blood cells *in vitro* and reduce viscosity while those weighing less disaggregates them. Dextrans, especially dextran 40, coat the endothelium and cellular elements reducing their interactions (e.g. erythrocyte and platelet sludging, leukocyte adherence), and prevent thromboembolism and are used therefore used to prevent deep venous thrombosis[124 227 228].

The main side effects of dextrans include dilution of clotting factors, reduced fibrin clot formation, reduced factor VIII/von Willebrand factor complex, and allergic reactions[124 227 228]. Allergic reactions can be either anaphylactoid or 'true allergic' reaction; anaphylactoid are normally secondary to high molecular weight with multiple branching while 'true allergic' reactions occur as a consequence of preformed antibodies and can be prevented by pre-treatment with monovalent hapten which binds the antibodies.

2.17.3. Gelatins

Gelatins are polydisperse, derived from bovine collagen and there are 3 modifications; cross-linked gelatins (e.g. Gelafundiol), urea-linked gelatins (e.g. Haemaccel 3.5%), and succinylated gelatins (e.g. Gelofusine 4%)[124]. They have low molecular weight, Haemaccel 35000 and Gelofusine 30000; therefore have short intravascular half life, approximately 2-4 hours, with rapid initial but non-sustained expansion of circulating volume after which the gelatin is lost by glomerular filtration. Volume effect last for about 3 hours but detectable gelatin is present up to one week and it has no dosage limitations[124 227 228 246]. Urea-linked gelatin (Haemaccel) has higher potassium and calcium levels therefore can cause clotting if infused with blood. Gelatins are reported to cause

haemodilution and have a high incidence of allergic reactions. Infection with prion disease has not been demonstrated[236].

2.17.4. Hydroxyethyl starches (HES)

These are polydisperse solutions of ethoxylated amylopectin derived from maize, potato, or sorghum starch that are prepared from partial hydrolysis of insoluble amylopectin followed by substitution of hydroxyethyl groups at C_2, C_3 and C_6 positions of the glucose molecules[124 227 228 246]. Higher degrees of substitution increase intravascular persistence (range from 0.4 to 0.7). Pharmacokinetic profile is also determined by hydroxyethylation (addition of alcohol groups) which prevent enzymatic degradation and therefore half-lives of different products also depend on the number of alcohol moieties. Like other colloids, the molecular weight is also an important determinant of colloidal effect and pharmacokinetics. HES solutions can be stored at temperatures up to 40°C and have long shelf lives. Molecules with molecular weights <50000 Daltons are rapidly removed by renal excretion while larger molecules are hydrolysed by amylase before eventual excretion by the kidneys. HES molecules with a high degree of substitution and high C2/C6 ratio undergo minimal hydrolysis and are removed by the reticuloendothelial system. A small proportion of administered HES is transiently stored in the tissues and removed in the urine after redistribution. Breakdown of larger molecular weight molecules into smaller molecular weight compounds also increase the osmotic effect because of the increased number of circulating molecules. Molar substitution ratio also increases slightly compared to that of the infused solution following hydrolysis because highly substituted molecules resist hydrolysis. HES solutions can be classified according to the following characteristics: concentration (high and low); initial molecular weight (high-450-480kDa, medium-130-200kDa, and low 40-70kDa); degree of substitution (high-0.6-0.7 and low 0.4-0.5); and C2/C6 ratio (high->8 and low -<8)[247]. High molecular weight HES have prolonged circulation and accumulate in the body following repeated administration and therefore have dosage limitations. HES solutions also have side effects such as impaired coagulation through increased prothrombin time, increased partial thromboplastin time, increased bleeding time, decreased factor VIII:C and VIII:Ag, unstable thrombus formation due to accelerated conversion of fibrin to fibrinogen, reduced factor VIII activity, and altered platelet adhesiveness. The adverse effects on coagulation plus other such as impaired renal function and pruritis are more common with high molecular weight starches however all HES solutions may impair coagulation by haemodilution[236]. A recent trial in adults (VISEP trial)[248] comparing a medium molecular-weight starch (HES 200/0.5), 10% pentastarch, to modified Ringer's lactate in adults with sepsis, reported an earlier normalization of central venous pressure/oxygen concentration in the HES group. However, the HES group a higher

number of dose-related episodes of renal failure (doubling of creatinine levels), requirement for renal replacement therapy, and poorer survival over a 90-day follow-up duration. A meta-analysis also concluded that HES starches in larger doses result in increased incidence of acute renal failure and late death[249].

2.18. Crystalloids

Crystalloid (saline) solutions contain inorganic ions dissolved in water. Crystalloids expand extracellular space and are distributed between the intravascular and extracellular compartments in the putative ratio of 1:4 and 3-4 times the volume lost is usually required to replace intravascular losses. Crystalloid infusion result in reduction of plasma oncotic pressure, acid-base disturbances, and excessive volumes required for adequate resuscitation may result in adverse effects such as oedema formation[250]. Crystalloid solutions for volume resuscitation can be broadly classified into 0.9% saline and balanced salt solutions.

2.18.1. Normal saline

The name normal saline, used to refer to 0.9% saline solution, is erroneous because its sodium and chloride concentrations are much higher than that of plasma[58]. Infusion of 0.9% saline has been shown to cause metabolic acidosis due to hyperchloraemia although clinical significance for this form of acidosis is not yet fully established[89]. However, excessive administration of chloride have been shown to result in decreased survival in animals, abdominal discomfort, impaired cerebral function, and delayed renal clearance of fluid loads[89 251]. Chloride regulates resistance within the renal vessels and hyperchloraemia results in dose-dependent constriction of renal vessels and reduction of glomerular filtration rate[88 252]. Administration of 0.9% saline is also reported to result in decreased water clearance and greater fluid retention as compared to Ringer's Lactate[89]. Excess administration of chloride may also impair coagulation. Theoretical arguments have been advanced that 0.9% saline should be safer than Ringer's lactate in patients with renal dysfunction and hyperkalaemia but this in not supported by any studies. Conversely a study in patients undergoing renal transplantation showed less hyperkalaemia and less development of metabolic acidosis in patients receiving Ringer's lactate compared to those receiving 0.9% saline[253]. The higher incidence of hyperkalaemia seen in 0.9% saline recipients has been thought to be a consequence of the hyperchloraemic metabolic acidosis which results leading to extracellular migration of potassium from the cells. Studies however also report less need for correction of metabolic acidosis using bicarbonate, less dilutional coagulopathy, and requirement smaller volumes when using Ringer's lactate compared to 0.9% saline[254 255].

2.18.2. Balanced salt solutions

These solutions have been prepared to have to have electrolyte concentrations similar to that of plasma and are therefore thought to be more physiological than 0.9% saline. A number of these solutions have osmolality slightly below plasma level are thought to present increased risk of causing cerebral oedema in critically ill patients with impaired blood-brain-barrier[250]. Lactate added to Ringer's lactate and Hartmann's solution is metabolised by both gluconeogenesis (70%) and oxidation (30%) and bicarbonate is produced in both processes over a duration of 1-2 hours[256]. Both processes consume H^+ resulting in an excess of bicarbonate and slow-steady alkalinising of plasma. Rapid metabolism of lactate may however cause metabolic alkalosis and gluconeogenesis may impair glucose control in patients with diabetes. Other solutions have used acetate or gluconate instead of lactate to avoid above theoretical concerns. Acetate is metabolised by peripheral tissues, metabolism requires less oxygen, does not solely rely on liver for breakdown however it is also metabolised and this may result in metabolic alkalosis. Plasmalyte A is currently the most ideal crystalloid but it has not gained widespread usage. There are concerns about hypercoagulation and increased risk of thrombosis with use of Ringer's Lacate[257]. Table 2.1 summarises properties of commonly used colloids.

2.19. Fluid refractory shock

Fluid refractory shock is defined as shock persisting after administration ≥60ml/kg of fluid over a period of 15 minutes. Children with fluid refractory shock receive inotropes; for cold shock, dopamine is given centrally and if resistant (referred to as fluid refractory, dopamine resistant shock) then central epinephrine is recommended but for warm shock, central norepinephrine is recommended[137 220]. If there is no response to catecholamines (catecholamine resistant shock), hydrocortisone infusion is recommended if there is risk of absolute adrenal insufficiency. It is recommended that further management should be goal directed to achieve normal mean arterial pressure, CVP, haemoglobin >10g/dL, and SvO_2 >70% but the intervention required is dependent on the type on shock. Reduction of the afterload in cases of shock with low cardiac index (CI), normal BP (blood pressure), and high resistance (cold shock normal BP) is advised using vasodilators in addition to volume loading. Nitrovasodilators (nitroprusside or nitroglycerin) are first line, and milrinone or inamrinone are used in cases of persistent low cardiac output or nitrovasodilator toxicity[137]. Levosimendan and enoximone may be used in recalcitrant low CO syndrome. Shock with low CI, low BP, and low resistance (cold shock with low BP) should be treated with epinephrine infusion in addition to volume loading[181]. Further norepinephrine, followed by dobutamine, milrinone, enoximone, or levosimendan is recommended if there is no improvement. Shock with

high CI low vascular resistance (warm shock with low BP) should be treated with norepinephrine, followed by vasopressors (vasopression, terlipression, or angiotension) if still hypotensive, and then epinephrine if the patient still has low SvO_2. A recent systematic review in a heterogeneous group of patients reported that norepinephrine was better than dobutamine as first-line vasopressors[258]. Evidence for the fluid volumes are only based on two retrospective case-control studies[259 260]. Subgroup analysis of a muti-centre study supported the use of steroids only in with adrenal insufficiency but not in the whole population[261].

Children with septic shock not responding to above interventions, referred to as 'persistent catecholamine resistant shock', should have further management (fluids, inotropes, vasopressors, and hormonal therapies) based on achieving present treatment goals and CI 3.3L/min/m^2-6.0 L/min/m^2[2220]. Children not responding to all above measures are referred to as having 'refractory shock' and extra-corporeal membrane oxygenation (ECMO) is recommended as a consideration by two groups[137 220]. Evidence for the use of ECMO for refractory shock is either inconsistent or only from well done observational studies (level of 2C)[137 220] therefore its use is still controversial.

2.20. Other treatment options

Early effective broad-spectrum antibiotic and elimination of source of infection when present are essential for the management of shock. A recent meta-analysis has found no evidence of benefit but increased risk of bleeding in children with sepsis/shock treated with recombinant activated protein C (drotrecogin alpha, APC) to prevent coagulopathy[262]. Glycaemic control has been advocated but a recent study in adults and a meta-analysis showed that tight glucose control resulted in increased risk of death[248 263]. Other treatments with varying levels of evidence include intravenous immunoglobulins, deep venous thrombosis (DVT) prophylaxis, stress ulcer prophylaxis, and renal replacement therapy for anuria/severe oliguria and fluid overload[137]. These therapies have not shown consistent benefit and routine use is not recommended[137].

2.21. Therapeutic studies of treatment

Prospective randomised trials comparing colloids to crystalloids for fluid resuscitation were done from the mid-1970s with the primary endpoint being mainly pulmonary dysfunction[28 264]. The trials were small in size, comprised heterogeneous population of patients, and had inconsistent findings. The controversy on the use of crystalloids versus colloids therefore persisted. Most recent Cochrane meta-analysis concluded that there is no difference in mortality between the groups of children resuscitated using either fluid[27 32]. However the main study that influenced the findings of this meta-analysis also reported a non-significant reduction in mortality among adults with sepsis resuscitated

using HAS compared to saline. It is also unclear whether the findings in adults can be extrapolated to children due to their different physiological and pathological response to illness. Successive meta-analyses have, however, consistently found that crystalloids are preferable to colloids in burns, trauma, surgery, traumatic head injury and in gastroenteritis[29-31 34 264-267].

2.22. Current paediatric fluid resuscitation guidelines

The ACCM, SCC, IPSCC, PALS and other widely used paediatric critical care guidelines recommend infusion of 60ml/kg or more of isotonic saline or colloid within the first 15 minutes[11 136 137 220]. Fluids are given until perfusion improves or unless crepitations or hepatomegaly develops in aliquots of 20ml/kg unless there are signs of fluid overload (i.e., the development of increased work of breathing, rales, gallop rhythm, or hepatomegaly)[220]. If there is no improvement after 15 minutes the child then patient is managed as a case of refractory shock. Up to 200ml/kg of fluid may be given over one hour. Same guidelines are also taught in paediatric life support (PALS) courses[268].

The World Health Organization (WHO) guidelines that are widely used in resource poor countries recommend 20ml/kg of Ringer's lactate or normal saline (maximum 60ml/kg) to be infused as rapidly as possible in children without severe malnutrition having shock secondary to dehydration (diarrhoea)[7 8]. For well nourished children with shock but no dehydration, a maximum of 40ml/kg of either fluid is recommended followed by 20ml/kg of blood infused over 30 minutes if no improvement is seen. If there is no improvement in either case after the full protocol, then WHO recommends that further management should be guided by the disease-specific guidelines. The WHO guideline proposes slowing of pulse rate and improvement of capillary refill time as signs of improvement but it is unclear on the duration of each bolus. In children with severe malaria, WHO guidelines propose intravenous infusion of 20ml/kg of normal saline or isotonic glucose-electrolyte solution over 30 minutes in children with respiratory distress and haemoglobin ≥5g/dL (suspected to have hypovolaemia)[8 269 270] but a cautious blood transfusion for those with haemoglobin<5g/dL with respiratory distress. However caution is recommended during fluid infusion and WHO guidelines recommend frequent monitoring of jugular venous pulse (JVP), skin turgor, peripheral perfusion, venous filling, urine output and CVP (target is 0-5cm of water) where facilities can allow. The WHO guidelines for management of shock in children with severe malnutrition propose 15ml/kg infused over 1 hour of either Ringer's lactate with 5% dextrose, half-normal saline with 5% dextrose, half-Strength Darrow's solution with 5% dextrose (HSD/5D), or Ringer's lactate (RL), respectively in order of preference and according to availability[9 10]. A second infusion of 15ml/kg of fluid over 1 hour is to be given if there is clinical improvement and no deterioration (breathing increases by 5

breaths/minute or pulse by 15 beats/minute). If there is no clinical improvement then the child receives 10ml/kg of fresh whole blood over 3 hours and packed cells if in cardiac failure. The child otherwise receives maintenance fluid at 4ml/kg/hour while waiting for blood transfusion

2.23. Evidence base for paediatric current fluid resuscitation guidelines

All the above fluid management guidelines were arrived at by either consensus or expert opinion. The 2008 Surviving Sepsis Campaign Guidelines, which were informed by a modified Delphi process, graded the existing paediatric recommendations (by American College of Critical Care Medicine-ACCM[220]) for fluid resuscitation as 2C[137]. This indicates a weak recommendation based on low quality of evidence, largely from observational studies and expert opinion[137]. The bases of these are largely from the following studies: Carcillo *et al* in 1991[259] reported a retrospective study of 34 patients with septic shock who presented the emergency department of a hospital over a period of 6 years who received 3 different fluid resuscitation strategies. All children in the study were on PICU with pulmonary wedge catheters and were on vasopressors and/or inotrope. Of these children, 14 received <≤20ml/kg, 11 received 20-40ml/kg, and 9 received >40ml/kg of crystalloid (Ringer's lactate or normal saline) or colloid preparations (5% albumin, packed red cells, fresh frozen plasma, or cryoprecipitate). The volumes were given within the first hour. Endpoints reported included hypovolaemia at 6 hours after presentation to emergency department, cardiogenic and non-cardiogenic pulmonary oedema in 24 hours following treatment, and survival to hospital discharge. Overall mortality was 16/34 (47%); 8/14(57%), 7/11 (63%), and 1/9(11%) in those who received ≤20, 20-40, and >40ml/kg respectively. The study further reported that mean volumes received within first 1 hour was higher in survivors compared to non-survivors (42±28ml versus 23±18ml, respectively) but they received similar volumes at 6 hours (97±49ml versus 94±37ml, respectively). The former finding was highlighted as evidence for benefit of early aggressive fluid resuscitation. They concluded that fluid infusion of ≥40ml/kg of fluid within the first hour of shock presentation was associated with better survival due the better survival in those who received higher volumes rapidly. Lack of randomisation and post-hoc nature of the analysis in this study should be noted when interpreting the study results Using a similar retrospective cohort study design (review of hospital records), the same group reported in 2003 a 9-fold increase in survival when this practice was implemented in 91 children over a period of 9 years[260]. The study enrolled children with septic shock who presented to local community hospitals in Pittsburgh and required transport to the tertiary care centre. Endpoints included reversal of shock (normalisation of systolic blood pressure and capillary refill time), adherence to ACCM-PALS guidelines, and hospital mortality. Shock was reversed in 26% of participants by the time of arrival at hospital and in these subjects, odds of

survival increased >9-fold (9.49[1.07-83.89]). They also reported >2-fold increase in risk of death for each additional hour of persisting shock. There was increased use of inotropes and vasopressors but less fluid volumes in fatal cases compared to survivors. Overall 29% (26/91) died but mortality was significantly lower when there was adherence to ACCM-PALS resuscitation guidelines compared to non-adherence (8% versus 38%, respectively). The reported findings are however based on retrospective chart review therefore prone to multiple biases. Lack of randomisation introduced a lot of potential confounders and the differences seen cannot be solely attributed to fluid therapy.

Surviving Sepsis Campaign fluid resuscitation guidelines also relied on results of three other trial which were all done in children with dengue septic shock[37 38 40]. The three studies were conducted by the same research group in Vietnam and applied similar study methodology across in all the trials. One further trial was conducted in The Philippines' comparing hydroxyethyl starch (6% Haes-Steril®) to Ringer's lactate in 27 patients[271]. The four trials consistently show that colloids infusion result in better resolution of severe shock compared to crystalloids. In moderate shock, crystalloids have similar results to colloids [272]. The four trials in dengue enrolled 690 children and 5 deaths were reported. Since mortality in dengue is very low and mortality was not a stated endpoint, no conclusions can be drawn about the survival benefit between colloids and crystalloids.

Rivers et al[196] in 2001 reported better survival in randomised study of 263 children who had early goal-directed therapy, to achieve certain pre-determined targets. The group with better survival received more fluid, more transfusions, and more inotropic supports compared to non-survivors. Better survival was therefore the result of multiple interventions aimed at early haemodynamic optimisation.

In adults with shock, initial Cochrane meta-analyses concluded that colloids, especially human albumin solution (HAS), resulted in increased mortality[29 31 265]. However a meta-analysis that incorporated the finding of SAFE trial, which enrolled 7000 adults in intensive case in Australia and New Zealand, found that administration of HAS and 0.9% saline resulted in similar survival[30]. The conclusion of the meta-analysis is therefore largely influenced by the results of the SAFE study. Successive meta-analyses have however consistently found that crystalloids are preferable to colloids in burns, trauma, surgery, traumatic head injury and in gastroenteritis[29-31 34 265-267]. The SAFE study also reported a non significant trend towards improved survival in the sub-group of patients with sepsis treated with HAS. The SAFE study randomised to fluid intervention arms and there was no control arm (no bolus) arm therefore comparison with control cannot be made.

WHO/ETAT recommendations for volumes, fluids and regimens for treatment of shock are therefore based on imperfect studies except for dengue shock. Other international guidelines have similar weaknesses to the WHO/ETAT guidance.

2.24. Progress in the treatment of hypovolaemic shock in children

Globally, the recognition and prompt treatment of circulatory shock in severely ill children has resulted in reduced mortality. In the USA, Carcillo and colleagues report a reduction in mortality from hypovolaemic shock from 120 deaths/100,000 infants in the 1960s to <10 deaths/100,000 infants in 2001 (greater than tenfold)[14]. In the UK, early treatment of shock initiated before transfer to tertiary centres reduced mortality in children with meningococcal sepsis from 22.5% to 2.5%[230 232]. However, there is no data to show progress in the treatment of shock in children from developing countries but oral rehydration and targeted use of intravenous fluid resuscitation to treat shock in diarrhoea, widely used in Africa, has led to a global reduction in deaths secondary to diarrhoea from 4.6 million annually in 1980 to 1.9 million reported in 2003[1 273]. Diarrhoea, instead of pneumonia as currently reported, had been the leading cause of childhood under-five mortality before 1980. In the USA, deaths secondary to septic shock decreased from 32 to 8 per 100,000 infants between 1960s to 2001[14]. Europe has recorded a similar decline in childhood morality but the burden and outcome of severe sepsis/septic shock in African hospitals is largely unknown. The gains in the resource rich countries have come with concurrent introduction of other interventions as part of emergency care and success cannot be attributed solely to fluids.

2.25. Summary of what research needs to be done

A number of questions remain in the field of septic shock and hypovolaemic shock in paediatric febrile illnesses. Firstly, there is need to identify appropriate clinical signs for diagnosis of shock. Secondly appropriate fluids for use in resuscitation of shock in children with shock need to be identified. Thirdly, haemodynamic and cardiac function is children with severe illnesses should be described. Finally, investigation on whether a generic approach to fluid resuscitation for shock in children with various illnesses can be adopted needs to be done.

2.26. Scope of thesis

This thesis will focus on two main themes; firstly, the investigation of the haemodynamic status of children admitted with severe illnesses in at Kilifi District Hospital, Kenya, a typical rural district hospital in sub-Saharan Africa. To achieve this, non-invasive haemodynamic monitoring has been included to supplement clinical diagnosis of shock. Secondly, clinical trials to establish the safety and efficacy of volume expansion in two conditions where fluid resuscitation is controversial, severe

malaria and severe malnutrition are presented. Two trials investigate the safety and efficacy of various colloids for resuscitation in children in shock with severe malaria and one trial investigates the safety of isotonic fluid resuscitation to treat shock in children with severe malnutrition. Finally, a systematic review and meta-analysis summarising the evidence behind the current fluid resuscitation guidelines is presented.

CHAPTER 3 : STUDY DESIGN AND METHODS

This chapter describes methodologies for studies presented in chapters 4, 5 and 6. There are 5 cohorts described; data on prospective clinical surveillance collected at Kilifi District Hospital (KDH) during the years 2002-2004 that is used to derived clinical definitions of shock; prospective observational study on haemodynamic status of children with severe febrile illnesses; two clinical trials comparing HAS versus gelofusine (a gelatin) and dextran versus starch for the management of shock in severe malaria; and a trial investigating the safety of isotonic fluids for treatment of shock in severe malnutrition.

3.1. STUDY AREA AND GENERAL PROCEDURES

3.1.1. Study area

The studies were conducted within the children wards of the Kilifi District Hospital, located at the coast of Kenya within Kilifi County. The Kenya Medical Research Institute (KEMRI) has a research centre situated at the hospital, KEMRI-Centre for Geographic Medicine Research-Coast (KEMRI-CGMRC). The centre is currently run as a collaborative programme between KEMRI and the Wellcome Trust of the United Kingdom, under the KEMRI-Wellcome Trust Programme (KWTP). The centre is located 60 km north of Mombasa town, latitude 03°40'S, and longitude 39°48'E. The hospital serves mainly a rural population and the research programme runs a demographic surveillance site (Kilifi Health and Demographic Surveillance System- KHDSS) with approximately 250,000 persons and census is done four times per year. Malaria is endemic in this area and follows the long rains that occur from April to June and the short rains in October to November. This area has however experienced a reduction in malaria transmission with subsequent reduction in malaria admissions from 18.43 per 1000 children in 2003 to 3.42 per 1000 children in 2007[274]. Malnutrition , defined as mid-upper arm circumference (MUAC) <11.5cm, is common among children admitted to the hospital, present in up to 41% of all paediatric admissions, which is above the national prevalence of 35%[275], and complicating about 50% of in-hospital deaths[276].

The KWTP runs the paediatric services within the hospital which admits children from birth to 13 years. Most children are admitted to a 35-bed general ward but those who are severely ill are managed in 6-bed high dependency unit (HDU). Both wards have a number of on-going observational and interventional studies on a number of childhood illnesses. Children in interventional studies that require monitoring are admitted to the HDU and it is well equipped to enable haemodynamic monitoring and the personnel are appropriately trained and get regular refresher training.

3.1.2. Routine procedures

All children admitted to KDH undergo comprehensive history taking and clinical examination using a standard proforma, which was initially paper-based but has been running on Filemaker Pro® database since 2002. Clinicians enter their findings before any samples are taken. Most of the variables entered have dichotomous values only and numerical values or non-dichotomous variables are selected from a drop-down list. There is also provision for a brief free text narrative. Oxygen saturations are measured by pulse oximeter (Nellcor). The database is programmed with logical range checks and flags for errors. Between 2002 and 2004, routine samples at admission included full blood count (MDII, Beckman Coulter, Fullerton, CA), thick and thin blood smear for malaria parasites, blood sugar (GM7, Analox Instruments, London, UK), venous blood gas (IL1620, Instrumentation Laboratory, Warrington, UK), lactate (GM 7 analyser, Analox Instruments Ltd, Hammersmith, London, UK and Lactate Pro®), electrolytes (sodium and potassium) (Chiron Diagnostics Limited, Halstead, UK), creatinine (Creatinine analyser 2, Beckman Coulter), and blood culture (BACTEC 9050, Becton Dickinson).

From the beginning of 2005 routine bloods done for all admissions included full blood count, thick and thin blood smear for malaria parasites, and blood culture. Children admitted to HDU however continue to get measurements of electrolytes, venous blood gas, electrolytes and creatinine. Children admitted to the general ward are reviewed at least once daily by a dedicated clinical team and a standard proforma is also completed at discharge or in case of death.

Children admitted also have anthropometrics measurements which include left mid upper arm circumference (MUAC), weight, and height/length. MUAC is measured using non-stretchable tape, weight with an electronic scale (Soehnle model 7300, CMS Instruments, UK), and length using a measuring board of standard design. The database automatically calculates certain variables such as weight for height Z-score (WHZ) and weight for age Z-score (WAZ).

3.1.3. Criteria for admission to the HDU

Children with impaired consciousness (prostration or coma), respiratory distress (chest indrawing or deep/Kussmaul breathing) if malaria slide is positive, clinical features of shock, hypoxia (oxygen saturations less than 90%) requiring high flow oxygen at ≥10litres /minute, meningitis, burns≥1 5% of body surface area, or extreme low birth weight infants (≤1kg body weight) are admitted to the HDU. Prostration is defined as inability to feed if aged ≤8 months or inability to sit in child who was previously sitting if aged >8 months[277]. Coma is defined as Blantyre coma score (BCS) ≤2[277] or inability to localise painful stimuli. Clinical features of shock are defined as any of capillary refill time

> 2 seconds, palpable temperature gradient (determined by running the back of the hand up shin to the core till a demarcation line is reached), weak pulse, or hypotension (systolic blood pressure <70mmHg in children aged <1 year and <80mmHg if aged ≥1 year old).

Assessment using a standard proforma that is entered real time into the database is also done during admission and discharge at the HDU. Continuous monitoring of heart rate, respiratory rate, oxygen saturations, and electrocardiograph activity is done using Siemens® multi-channel recorder in children admitted to HDU. Monitoring using the monitor is done as long the child remains in coma but clinical and nursing monitoring continue till the patient is discharged from the HDU. Blood pressure and axillary temperature are also measured 4 hourly. The readings obtained by the recorder are also recorded in the nursing notes 4 hourly. Patients are routinely re-assessed by the clinicians at 4 hours post admission or earlier for those receiving resuscitation treatments such as fluid resuscitation, glucose correction, or anticonvulsant medication. Further clinical reviews are done daily and whenever there is clinical deterioration. The nurses also perform routine 4 hourly observations and these are recorded in standard paper-based proforma. Children also have routine repeat full blood count, blood glucose, electrolytes, venous blood gas, and creatinine at 4 hours post-admission and at 24 hours. Malaria slide is done 8 hourly till 3 negative slides are obtained. Mechanical ventilation facilities are not available at the HDU but children with apnoea are usually ventilated using bag valve mask (BVM) device until they resume breathing or otherwise for a reasonable duration before cessation dependent on clinical judgement.

3.2. STUDY 1: EVALUATION OF CLINICAL DEFINITION OF SHOCK AND DEVELOPMENT OF SHOCK SCORE

This was a retrospective analysis based on prospectively collected admission data of an unselected (all admissions) population of children admitted to KDH. In this section, the predictive values of various clinical features commonly used to diagnose shock are assessed against objective measurements of tissue hypoperfusion (elevated lactate and elevated base deficit). Surviving Sepsis Campaign (SSC) defines tissue hypoperfusion as elevated lactate (≥4mmol/L)[137] while consensus definition adopted at the International Paediatric Sepsis Consensus Conference (IPSCC) defines septic shock as the presence any two signs, which include base deficit >5mEq/L or lactate level >2 standard deviations[178], after bolus infusion of 40ml/kg of isotonic fluid in the presence of sepsis. The aim was to derive a clinical definition of shock using acidosis (presence of both elevated serum lactate and base deficit) as a marker of the tissue hypoperfusion. Results for this section are presented in chapter 4.

3.2.1. Objectives

a) The main aim of this study was to develop a predictive model for diagnosis of shock based on biochemical markers of shock.

3.3. The secondary aim was to compare sensitivities and specificities of existing clinical definitions of shock and compare with the derived predictive model for shock.

3.4. STUDY 2: EVALUATION OF HAEMODYNAMIC AND CARDIAC MEASURES OF PERFUSION STATUS IN CHILDREN WITH SEVERE AND NON-SEVERE DISEASE

This was a prospective study conducted between 2009 and 2010 and involved non-invasive measurements of cardiac output and other haemodynamic parameters in children with various disease severities using a non-invasive device, ultrasonic cardiac output monitor, USCOM (USCOM Pty. Ltd., Sydney, NSW, Australia) and echocardiography. Results from this section are presented in chapter 5.

3.4.1. Objectives

a) To describe the haemodynamic status of children admitted with severe illness and/or impaired perfusion

b) To prospectively evaluate the clinical definition of shock derived from Kilifi data using non-invasive measurement of central circulation and haemodynamic status.

c) To describe the haemodynamic and myocardial function changes in children receiving fluid expansion

d) To assess the validity of a non-invasive measuring of cardiac output (USCOM) by comparing the agreement in measurements obtained using USCOM and echocardiography

3.4.2. Participants

This study involved children aged >2 months and ≤12 years with a history of febrile illness and/or admission axillary temperature ≥37.5°C. Eligible children were divided into two major groups (each with two sub groups): **Severe disease group (SeD)**, defined by impaired consciousness (coma or prostration) and/or respiratory distress (deep breathing or chest indrawing); and **Non-severe illness group (NSeD)**, defined as children without impaired consciousness and/or respiratory distress. The two groups were further subdivided in subgroups depending on the presence or absence of clinical signs of shock and disease severity used in the FEAST trial[41]. The trial used a broad definition of

shock where shock was defined as the presence of severe disease, abnormal temperature (history of fever or axillary temperature ≥37.5 or <36.0), and any feature of impaired perfusion as below (Table 3.1). Children admitted with trauma, burns, poisoning/envenomation/intoxication and whose parental/guardian consent could not be obtained were excluded.

Table 3-1: Study groups in the Haemodynamics study

- **Severe disease group**
  - With features of impaired perfusion as defined in the FEAST trial (SIMP)
  - Without features of impaired perfusion as defined in the FEAST trial (S)
- **Non-severe illness group**
  - With features of impaired perfusion as defined in the FEAST trial (NSIMP)
  - Without features of impaired perfusion as defined in the FEAST trial (NS)

Definitions:

- ***Signs of impaired perfusion as defined in FEAST trial:*** Any of the following clinical features; capillary refill > 2seconds, lower limb temperature gradient, weak radial pulse volume, and severe tachycardia (<12months: heart rate >180bpm; 12 months to 5years: heart rate >160bpm; or >5years: heart rate >140bpm).
- ***Impaired consciousness:*** Prostration (inability to sit if aged >8months or inability to breastfeed if ≤8 months); coma(inability to localise painful stimulus or Blantyre coma score (BCS) ≤2)

3.4.3. Sample size

Formal sample sizes were not calculated for the evaluation of cardiac and haemodynamic functions. The numbers in the various groups were deliberately chosen to avoid having large number of children with limited information on shock. Sample sizes for various groups were as follows; SIMP=50, S=50, NSIMP=50, and NS=25 participants.

3.4.4. Screening and enrolment

Eligible children were flagged at admission by the online real-time database management system. Those eligible were enrolled consecutively (unselected) until the desired sample size was achieved for each of the four groups. Recruitment was done between 8am and 8pm, was restricted to weekdays, and a maximum of 4 patients per day. The four recruited for any given day were those that were flagged first.

3.4.5. Clinical examination

All children eligible for this study underwent the standard admission process which includes history taking, clinical examination and routine clinical blood sampling. The admission database was configured to flag eligible children once history and examination details were entered and any

additional clinical data are collected systematically. Clinical examination was done at admission, 1 hour, 8hours, and 24 hours after admission and thereafter daily assessment was conducted until discharge or death. Enrolled children had the following clinical examination at admission and at each clinical review: assessment of conscious level and Blantyre coma score; degree of respiratory distress; need for supplemental oxygen; capillary refill time, lower limb temperature gradient; radial pulse volume assessment; heart rate; respiratory rate; and blood pressure; and daily weight. Clinical review was not done by those performing the haemodynamic measurements. The clinical review data was extracted from the patient notes using a specially designed standard proforma.

3.4.6. Haemodynamic monitoring

Echocardiography (GE Logiq Book Ultrasound Echocardiography (GE Healthcare UK Ltd., St. Giles, UK)) and USCOM (USCOM Pty. Ltd., Sydney, NSW, Australia) were used for haemodynamic monitoring. All children enrolled had USCOM reading at admission, 1 hour, 8 hours and 24 hours. Two readings were taken from each valve (aortic and pulmonary) and the final reading used was the average of the four readings. All the four readings were done within 2 minutes. For haemodynamic measurement of shock, cardiac index (CI), stroke volume index (SVI), systemic vascular resistance(SVR), inotropy index, and systemic vascular resistance index (SVRI) readings were used[179]. In emergency cases which required fluid resuscitation, USCOM measurement was done and consent obtained later (deferred) once the patient was stable. If parents/guardians declined to give consent then the observations were not included in the analysis and further haemodynamic monitoring was not done.

Every fourth consecutive patient enrolled into the two arms with severe disease had an echocardiogram done within 10 minutes of an USCOM measurement. Stroke volume, cardiac index, and cardiac output were determined using echocardiogram. Two different specially trained clinicians performed echocardiogram and USCOM measurement and they did not share their findings. The findings were not used to guide patient management. The following parameters were automatically calculated by the USCOM device using these formulae [168] shown in section 2.11; cardiac output (CO),Cardiac index (CI), stroke volume (SV), stroke volume index (SVI), systemic vascular resistance (SVR) and index (SVRI), and contractility (inotropy) measured as Smith-Madigan Inotropy Index (SMII). USCOM device stores its results the data was downloaded into a spreadsheet and stored.

3.4.7. Study sampling

Plasma remaining from the clinical samples was used to test for measurement of serum lactate, creatinine, and urea. For participants with severe illness, stored samples of 2 millilitres of urine taken at admission and at 24 hours was used for the measurement of urine osmolality.

3.5. PHASE II TRIALS OF VOLUME EXPANSION USING COLLOIDS IN CHILDREN WITH SEVERE MALARIA AND SHOCK

Previous trials conducted in Kilifi showed that treatment of shock using bolus infusion of 5% human albumin solution (HAS) resulted in better survival when compared to 0.9% saline[19-21]. Because HAS is expensive and not easily available in Africa, these trials were designed to investigate the safety of other colloids. They also explored whether the benefits seen with HAS, attributed to its colloidal properties, could be replicated with other cheaper synthetic colloids. Two separate Phase II trials investigating the full range of synthetic colloids were conducted; the first compared the safety and efficacy of fluid resuscitation for shock using gelofusine (a gelatin) and HAS in children with severe malaria; and the second study compared dextran 70 to hydroxyethyl starch 130/0.4(HES). The results of the two trials are presented in chapter 5.

Hypotheses:

Study 3: Phase II trial of volume expansion with albumin compared to Gelofusine in children with severe malaria and shock

a) HAS and Gelofusine have similar safety and efficacy when used for fluid resuscitation for shock in children with severe malaria

Study 4: Phase II trial on the use of Dextran 70 or starch for supportive therapy in children with severe malaria and shock

b) Fluid resuscitation for shock in severe childhood malaria using dextran and starch result in similar efficacy and both have similar safety profile.

3.5.1. Participants

Both studies (3 and 4) enrolled children aged ≥3 months with clinical features of severe malaria. Screening was done both at the general ward and the HDU. Children who were potentially eligible were transferred to the HDU where randomisation was done. Some children were also admitted directly to the HDU on arrival to hospital. Severe malaria was defined as the presence of impaired consciousness (coma or prostration) and/or deep breathing in child positive for *Plasmodium*

falciparum on thick/thin film. Children were eligible if they had all the following; severe malaria, metabolic acidosis with base deficit ≥8 mmol/L, haemoglobin >5g/dL, and at least one clinical feature of shock. Clinical features indicative of shock included a positive temperature gradient (determined by running the back of the hand up the shin detecting a line of demarcation), capillary refill time >2 seconds, weak radial pulse, OR hypotension (systolic blood pressure <70mmHg if aged <1 year and <80mmHg if aged >1 year). Children with conditions where volume expansion was considered potentially harmful were excluded. These included oedematous malnutrition, children known to have renal disease or heart disease, those presenting with pulmonary oedema (defined as the presence of bilateral fine basal crepitations plus pulse oxygen saturations in air <90%), and those with clinical features of raised intra-cranial pressure (unequal pupil size, papilloedema, or systolic blood pressure of >90th centile for age in association with a falling heart rate). Written parental/guardian consent was required for inclusion into the study. However, in the study comparing HAS to Gelofusine®, but not dextran versus starch trial, ethical approval was obtained to defer consent in emergency situations (mainly decompensated shock). Cases who presented as emergency were excluded in the dextran versus starch trial. The studies obtained ethical approval from KEMRI/National Ethics committee.

Standard management for severe malaria included intravenous (quinine 15mg/kg loading dose followed by 10mg/kg twice daily), dextrose for hypoglycaemia (5mls/kg of 10% dextrose), antibiotics (chloramphenical and benzylpenicillin) antipyretics, and anticonvulsants. All children received maintenance fluids (4mls/kg/hour of 5% dextrose/0.18% saline). Antibiotics were administered till blood cultures were reported negative at 48 hours and lumbar puncture was performed at the earliest opportunity to rule out meningitis in those with impaired consciousness. Diazepam (0.3mg/kg given once) was the first-line anticonvulsant and second-line was phenobarbitone (15mg/kg loading then 5mg/kg once daily maintenance). Those with further uncontrolled convulsions received phenytoin or sodium valproate. Whole blood transfusion (20mls/kg) was given if haemoglobin fell below 4g/dl, or for haemoglobin < 5g/dL if associated with respiratory distress.

3.5.2. Sample size

The trials were designed to generate new information on the safety and efficacy of these colloids in severe malaria. Formal sample sizes were not calculated since there was no previous experience with these colloids in children with severe malaria. A sample size of 40 children for each intervention fluid was considered sufficient to provide adequate safety information to inform design of future randomised trials involving these fluids. Eighty children were recruited into the study comparing HAS

to Gelofusine®, 40 to HAS and 40 to Gelofusine® study, and 80 children were also recruited to the study comparing dextran to starch, 40 to dextran and 40 to starch.

3.5.3. Randomisation

For children recruited to HAS versus Gelofusine® study (study 3) blocks of 10 patients were recruited sequentially to either HAS or Gelofusine. Only one of the study fluids was available in the ward at any time during the study to reduce risk of bias that may be introduced a clinician who may prefer a particular fluid.

In study comparing dextran to starch (study 4), fluids to be administered was indicated in pre-prepared sealed envelopes that were prepared using a random list was generated using a computer programme by a statistician who was not involved in the recruitment process. Randomisation was done in blocks, with unequal sizes and the sequence was only known by the statistician. There was no masking of the study interventions in both studies.

3.5.4. Interventions

a) Study 3: HAS versus Gelofusine

Children received 20ml/kg (or 40ml/kg if hypotensive) over 1 hour of intervention fluid (Gelofusine (Braun, Sheffield UK) or 4.5% human albumin solution (BPL, Elstree, UK)) at enrolment. Participants were reassessed clinically at 1 hour and a further 20ml/kg of fluid (or 40ml/kg if hypotensive) over 1 hour was given if the child still had any of the following features; capillary refill time >2 seconds, heart rate or systolic blood pressure outside threshold rates (Table 3.2). After 2 hours, further boluses were only given if the there was decompensated shock (hypotension plus a clinical feature of shock).

b) Study 4: Dextran versus Starch

Children in this study also received 20-40ml/kg of study fluid-either 6% Dextran 70 (Gentran® 70, Baxter Healthcare Pty Ltd, UK) or 6% hydroxyethyl starch (HES 130/0.4) (Voluven®, Fresenius Kabi Ltd, UK) –following the same criteria as used in study 1. Children were also reassessed at 1 hour and further boluses given as per criteria used in study 1.

In both studies all those enrolled were continuously monitored for blood pressure, electrocardiography, oxygen saturations, heart and respiratory rate using a Siemens® multi-channel recorder.

Table 3-2: Threshold heart rates and mean blood pressure at various ages

Age (years)	Heart rate (beats/min)	Systolic BP (cm Hg)
Newborn	120–180	70
≤1	120-180	75
≤2	120-160	80
≤7	100-140	85
≤5	90-120	85

3.5.5. Outcome measures

In the comparison of HAS versus Gelofusine® (study 3) the primary outcome was in-hospital mortality and secondary endpoints included resolution of acidosis (percentage reduction of base deficit at 8 hours following enrolment), potential complications of volume resuscitation (pulmonary oedema, raised intra-cranial pressure and allergic reaction) and neurological sequelae determined at one month following post-discharge using standardised neurological assessment. Secondary endpoints included in-hospital mortality, potential complications of fluid resuscitation as listed above and neurological sequelae at discharge and at one month post-discharge.

The Dextran versus starch trial (study 4) enrolled participants at lower risk of death since emergencies were excluded owing to the need to obtain consent prior to enrolment. Thus the primary outcome measure was attainment of resuscitation goals (resolution of shock) defined as absence of all of the following features; severe tachycardia (>180 beats/minute if aged <12months, > 160 beats/minute if aged 1-5years or >140 beats/minute if aged ≥ 5 years); hypoxia (oxygen saturation <95%); hypotension: systolic blood pressure (SBP) (<70mmHg for <12 months and <80mmHg for > 1 year) or delayed capillary refill time (CRT) (≥3seconds). These goals were adapted from American College of Critical Care Medicine/Paediatric Advanced Life Support (ACCM/PALS)[136 220].

3.5.6. Study monitoring and adverse event reporting

The two studies each had had an external monitoring committee. All adverse events and deaths were reported to the committee and KEMRI/National ethics board. KWTRP has a dedicated Clinical Trials Facility (CTF) who provided independent monitors for the studies.

3.6. PHASE II TRIAL OF ISOTONIC FLUID RESUSCITATION IN CHILDREN WITH SEVERE MALNUTRITION AND HYPOVOLAEMIA

3.6.1. Hypothesis and objectives

Current WHO guidelines on the management of shock in children with severe malnutrition recommend low-sodium solutions given at low volumes and slower rates for fluid resuscitation[8 10]. This practice is markedly different from the management of shock in well-nourished children were rapid infusions of large volumes of isotonic solutions are recommended[137 220 278]. In-hospital mortality in children with severe malnutrition remains high despite strict adherence to WHO guidelines including that on fluid management[4]. These deaths occur early and in many who display signs of shock. This study investigated the safety of two isotonic solutions for treatment of shock in severe malnutrition. The aim was to examine the safety and tolerability of current WHO fluid management regime and compare these to more standard resuscitation treatments used in current paediatric emergency care. The null hypothesis was that there would be no difference between these protocols in correction of shock. The main objective was to provide pilot data on the tolerability of a number of different regimes for treating hypovolaemia compared with the current WHO recommended schedule. Results are presented in chapter 6.

3.6.2. Participants

Children aged ≥6 months with severe malnutrition, defined as any of: weight for height z-score <-3 or weight for height percentile 70%; or mid-upper arm circumference (MUAC) < 11.0cm; or bilateral oedema (kwashiorkor). The study had two phases; a pilot phase and a randomised controlled trial (RCT) phase. The two phases are presented separately below because enrolment criteria and management were different.

3.6.3. Pilot phase

An initial pilot study was conducted to provide baseline data on the safety and efficacy of the WHO fluid resuscitation guidelines for malnourished children with shock. Children were enrolled if they fulfilled WHO definition of shock which defines shock as the presence of all the following; cold hands, capillary refill time >3 seconds, weak and fast pulse. A sample size of 20 children was chosen and successively admitted children received fluid resuscitation as recommended by WHO while under continuous monitoring of heart rate, respiratory rate, systolic blood pressure, and electrocardiogram using Siemens® Multi-Channel recorder. All children also had urine catheter fixed for monitoring urine output.

They received half-strength Darrow's with 5% dextrose (HSD/5D) at 15ml/kg over 1 hour. A second bolus of 15ml/kg over the next 1 hour was given if the child showed clinical signs of improvement and no signs of fluid overload (increasing respiratory rate or heart rate). If there was no improvement at 1 hour, the child received blood transfusion (10ml/kg over 3 hours). The child received maintenance HSD/5D at 4ml/kg/hour while awaiting blood transfusion.

3.6.4. Phase II trial comparing isotonic fluids to WHO fluid (RCT phase)

This phase incorporated two important changes which were different from WHO recommendations because few children fulfilled WHO definition of shock and their poor outcome in the pilot study suggested that shock treatment was being given at a late or pre-terminal stage. The definition of shock was made less stringent (shown below) to include children in earlier stages of shock. Early nasogastric feeding, recommended by the guideline immediately after resuscitation, was withheld and children placed on maintenance intravenous dextrose fluids until children were stabilised, intestinal ileus excluded and tolerance of oral feeds established. Shock was defined as any of the following features: capillary refill time > 2 seconds, lower limb temperature gradient, weak radial pulse volume, deep 'acidotic' or 'Kussmaul' breathing, creatinine >80 µmol/L, or impaired consciousness (if persisting after correction of hypoglycaemia). Written consent from parent/guardian was obtained prior to enrolment except in emergency (specifically decompensated shock), when a verbal assent was obtained from parent/guardian. In such cases, a full written consent obtained once the child stabilised.

3.6.5. Exclusion criteria

Participants with severe anaemia (haemoglobin ≤5g/dL), pulmonary oedema, raised intra-cranial pressure, known renal disease, known congenital heart disease, or no parental/guardian consent were excluded.

3.6.6. Randomisation

Two subgroups were considered; Severe dehydration/shock (Group A) – children with shock and severe dehydrating diarrhoea defined as ≥6 watery stools per day, and presumptive septic shock (Group B) (non diarrhoeal shock) – defined as children with shock but with <6 watery stools[279] in previous 24 hours. Patients were assigned to intervention fluids using cards, which indicated the fluid to be infused, in sealed envelopes that were randomly generated using a computer program. This was done by a statistician who was not involved in the recruitment of patients. However there was no masking of interventions.

3.6.7. Interventions

Participants in Group A were randomly assigned to receive either WHO fluid resuscitation regime HSD/5D or Ringers Lactate (RL). Participants in Group B were randomised to one of three fluid resuscitation intervention arms: WHO fluid resuscitation regime, Ringers Lactate or 5% human albumin solution (HAS).

Those randomised to the WHO fluid resuscitation regime (HSD/5D) received bolus fluid as per pilot phase (see section 3.5.3). Children randomised to Ringers Lactate or albumin resuscitation received an initial bolus of 10ml/kg over 30 minutes, repeated only twice over one hour (i.e. up to 30ml/kg in total) if clinical reassessment demonstrated any of the following features of shock: CRT > 3s, weak pulse volume, temperature gradient, or hypotension (systolic blood pressure <80mmHg plus clinical features of shock). Additional boluses of 10mls/kg over one hour were only permitted if oliguria (< 0.5mls/kg/hour) or 20mls/kg over one hour if there was hypotension. Maximum boluses given were 40ml/kg. Children were assessed after each bolus and hourly clinical resolution of shock and signs of fluid overload (pulmonary oedema or raised intracranial pressure). Pulmonary oedema was defined as bilateral crepitations plus pulse oxygen saturations <90% in air and raised intracranial pressure defined as unequal pupillary size/reaction to light. There was no invasive monitoring and participants did not receive inotropes, vasopressors, or hydrocortisone. Further fluid beyond resuscitation were given by nasogastric tube in both groups except in cases where the child had feeding intolerance, such as having increased volumes of watery diarrhoea and coma, when low volume maintenance (4ml/kg/hour of HSD/5D) was provided.

3.6.8. Safety monitoring

All adverse events and deaths were reported within 24 hours to the KEMRI/National ethics committee. The safety committee received summary reports of all serious adverse events (SAEs) and advised on the safety and conduct of the trial. Ethical approval for the study was obtained from the KEMRI/National ethics committee and OXTREC (Oxford Research Ethics Committee). The trial was monitored three times by an independent monitoring team from Clinical Trials Facility (CTF) for protocol adherence.

3.6.9. Outcomes

Primary outcome measurement was the resolution of features of shock at 8 and 24 hours. Resolution of shock was defined as the absence of all of the following: severe tachycardia (heart rate >160 beats per minute), CRT > 2s or oliguria (urine output<1ml/kg/hr). Secondary outcomes included

incidence of adverse events (such as pulmonary oedema or raised intracranial pressure) and mortality.

3.6.10. Sample size

We aimed to recruit 90 children; 40 to Group A (20 for each fluid) and 50 to group B (25 for each fluid). In summary 45 children were to receive Ringer's Lactate, 45 to receive HSD/5D, and 20 to receive HAS.

We did not calculate sample size calculation but chose a number of patients considered adequate to provide sufficient information on haemodynamic response and adverse events to the two fluid management regimes and to understand potential efficacy based on our previous experience. There were no published data about the interventions used and also aimed to minimised exposure to an untested intervention.

3.6.11. Standard management of severe malnutrition

A nasogastric tube is routinely fixed at admission in all children with severe malnutrition for milk feeding (F75 or F100 formulae). F75 is started as soon as possible (in conscious children). Initially the children receive 130mls/kg/day of F75 given every 3-4 hours and this is replaced by F100 as soon as the child's appetite returns or oedema improves. Malnutrition oral rehydration solution (Re-So-Mal) is given to children with persistence of significant diarrhoea (> 6 loose stools/day). Intravenous ampicillin (50mg/kg four times daily) and intramuscular gentamicin (7.5mg/kg once daily) are routinely prescribed for 7 days. Intravenous ceftriaxone at 50mg/kg is used as second line antibiotic or when directed by microbiological results. Children also receive oral mebendazole at 100mg twice daily for three days and metronidazole 5mg/kg thrice daily for five days to treat giardiasis. Hypoglycaemia (blood glucose <3mmols/L) is treated with 5mls/kg of 10% dextrose.

Mineral and electrolyte supplements are also given once the child is able to tolerate feeds. These include: oral Vitamin A 100,000IU once if < 1 year or two doses of 200,000 IU if >1year; Mineral-Electrolyte mix[10] (1ml/kg/day) & multi-vitamin supplements (1ml/kg/day) until discharge; and oral Folate supplements at 5mg once daily. Iron supplements were given to children when the clinical condition had improved, oedema resolved and the child was gaining weight.

Children with clinical features of shock transferred to the HDU are continuously and non-invasively monitored for heart and respiratory rate, oxygen saturation using a multi channel Siemens® monitor and systolic blood pressure. Children on IV fluids have urinary catheterisation. At admission blood

gases, plasma electrolytes and creatinine, full blood count, and blood glucose were measured and reassessed at 8- and 24-hours post-admission. Blood and urine were cultured at admission on all children and lumbar puncture, where indicated.

3.7. STATISTICAL METHODS

3.7.1. Study 1: evaluation of clinical definition of shock and development of shock score

3.7.1.1. Development of predictive clinical model

Participants

Children admitted to KDH between 2002 and 2004 have comprehensive clinical assessment and data recorded on a standard proforma and blood chemistry including blood gas analysis and lactate were measured in all children admitted during this time. Thus, the data for analysis was collected prospectively, in standardised format and participants were unselected. A sub-population of the above cohort, patients admitted during 2002 and 2003 (7673 children), were used as the derivation (training) set and that for 2004 (3812 children) as validation (test) set.

3.7.1.1.1. Association between base excess and lactate with mortality: Derivation set

Base excess and lactate data for participants collected in the year 2002 and 2003 (derivation set) was analysed to determine levels that were associated with increased risk of mortality. The association between base excess and mortality was examined by comparing the odds of death in children who died with base excess above a given cut-off compared to odds of death among those below the cut-off. Respective odds ratios and 95% confidence intervals were calculated in stepwise manner starting from the lowest base excess in the dataset, -35 (minus 35), and increasing by intervals of 5. A given cut-off level of bases excess of lactate was deemed to be associated with increased risk of death if the crude odds ratio was ≥2.0. However likelihood ratios (LR) were also used in the determination of cut-off.

Likelihood ratio (LR) summarises the degree to which a positive or negative result increases or decreases, respectively, the odds of having the particular disease (tissue hypoperfusion in this case)[280]. LR >1 indicates a given result is associated with the presence of disease (LR>10 provide strong evidence to rule in diagnosis) and LR <1 indicates that the result is associated with disease's absence (LR<0.1 strong evidence to rule out diagnoses)[280]. When tests report results as being either positive or negative, the two likelihood ratios are called the positive likelihood ratio (LR+) and the negative likelihood ratio (LR-) respectively. LRs are not dependent on disease prevalence unlike sensitivity and specificity, and can be calculated for multi-category tests without dichotomisation [281] [282]. Dichotomisation has the disadvantage that it may discard useful diagnostic information[280]. Base excess ranges with odds ratios ≥2 and LR+≥2 or LR- ≤0.5 were taken as important predictors of in-hospital death.

A similar analysis assessed the association between lactate levels and mortality. Levels of lactate ranged from 0 to 27.5 mmol/L and stepwise incremental cut-off levels of 2.5mmo/L were investigated. A definition of impaired perfusion was defined as consisting of a composite measurement of both lactate and base excess above certain cut-off thresholds (as determined through above methodology), which are components of proxy measures for tissue hypoperfusion in various existing definitions of shock[137 178].

3.7.1.1.2. Clinical signs to define shock: Derivation set (year 2002-2003)

Using the base excess and lactate cut-offs derived above (year 2002-2003 dataset), the odds ratios and 95% confidence intervals of various clinical features to identity children with tissue hypoperfusion (meeting the above threshold base excess and lactate cut-off) were calculated. The clinical parameters or signs that were tested in the model were selected from those that are recommended in the various paediatric shock definitions[7 8 136 137 181 220]. Crude odds ratios of an association between the parameter with the presence of acidosis (either bases excess or lactic acidosis) were initially calculated and then adjusted for severity of illness. Sensitivity, specificity, positive, and negative predictive values for the various clinical signs were then calculated.

A predictive model for tissue hypoperfusion (elevated lactate plus elevated base deficit) was developed through a number of steps by use of likelihood ratios (LRs) as follows; For each clinical sign of shock, crude LR for a positive result (LR+), indicating an increased probability of having acidosis or a negative result (LR-), indicating a decreased probability of having acidosis, were calculated. Signs with LR ≥2.0 or ≤0.5 were chosen as clinically useful and included in a multivariable model to determine a clinical definition of shock that predicts acidosis[2]. Confounding variables were adjusted for in the multivariable model. Final signs chosen as independent predictors of tissue hypoperfusion were those which had LR ≥2.0 or ≤ 0.5 in the multivariable model.

A predictive score for tissue hypoperfusion was developed by approximating the natural logs for the individual crude likelihood ratios for various clinical signs of shock. A constant was added in cases where the natural log was negative to get a value of zero[2 283 284]. Predictive scores were calculated for the overall group, and separately for cases with severe disease and non-severe disease. Severe disease was defined as the presence of impaired consciousness and/or respiratory distress since they are two are relatively common, non-specific and readily determined signs which define a sub-group of children with increased the risk of mortality, irrespective of underlying disease[3 17 18 285 286].

3.7.1.1.3. Validation set (year 2004)

The data collected during the years 2004 (3812 children) was used as the validation set. Sensitivity, specificity, area under receiver operating characteristics curves (ROC) were calculated for the clinical signs found predictive of acidosis (presence of both elevated serum lactate and base deficit) in the derivation set.

3.7.2. Study 2: evaluation of haemodynamic and cardiac measures of perfusion status in children with severe and non-severe disease

Baseline characteristics for children in the various groups of disease severity were presented as proportions and compared using chi square or Fisher's exact tests as appropriate.

Objective 2a: Description of haemodynamic status in children with severe illness

Means and standard deviations (SD) for haemodynamic measurements (CI, SVI, SVRI, and SMII) obtained using USCOM for participants in the various groups were calculated. Mean haemodynamic measurements obtained in the four groups were compared using analysis of variance (ANOVA). Paired t-test was used to compare the mean admission haemodynamic measurements for normally distributed data and Mann-Whitney (Wilcoxon ranksum) test to compare medians of non-normally distributed data. Comparison was done between the following groups: severe illness versus non severe illness, signs of impaired perfusion versus no signs of impaired perfusion, those fulfilling FEAST criteria versus those not fulfilling FEAST criteria.

Objective 2b: Assessment of association between clinical signs of shock and haemodynamic features of central circulation.

Assessment of correlations between haemodynamic parameters indicative of central circulation (CI and SVI), total vascular resistance (SVRI), and contractility (SMII) were done against individual clinical signs and various shock definitions (criteria). Assessment against the shock definition derived in chapter 4 was also done. Only USCOM measurements were used.

Objective 2c: Haemodynamic and myocardial function changes with bolus infusion

The mean change in SVI and CI at 1 hour post admission was compared between those receiving fluid bolus and those not receiving fluid bolus using t-test. Multilevel mixed modelling was used to compare compared changes on SVI and CI following bolus treatment in the group with severe disease and features of impaired perfusion (SIMP).

Objective 2d: Validity of USCOM for measurement of cardiac output

Bland-Altman analysis[287] [288] and Pitman's test of difference in variance [289] were used to assess agreement between USCOM and echocardiography measurements for CO, CI and SVI –details of interpretation shown in results section.

3.7.3. Phase II trials of volume expansion using colloids in children with severe malaria and shock

To minimise bias, analysis was first done on an intention-to-treat (ITT) basis before a subsequent secondary analysis on those complying with the trial protocol (per-protocol (PP) analysis). Baseline and outcome variables were compared within each study arm using *chi-square* or Fisher's exact tests, as appropriate, for categorical variables and ANOVA for continuous variables. A sub-group analysis of children presenting in coma (BCS≤2), who have increased risk of mortality, was done. The unadjusted relative risk of was compared between albumin and Gelofusine.

Methods of summary measures were used to compare repeated measures in the study comparing dextran versus starch by calculating area under curve (AUC) and maximum value (MV) Matthews *et al* [290] [291]. These included variables such as heart rate, base excess, systolic blood pressure and respiratory rate. Summary measures were used to avoid potential biases that would arise because of missing observations at any time point.

3.7.4. Phase II trial of isotonic fluid resuscitation in children with severe malnutrition and hypovolaemia

The efficacy of various fluid interventions was compared using categorical outcomes. Categorical outcomes were generated using cut-values for normal indicated in various resuscitation guidelines (PALS[11] , ACCM[220], and EPLS[12]). Categorical outcome for laboratory variables were also generated indicating normal and abnormal values. The following outcome were generated using the process stated: severe tachycardia (>160 beats/minute); bradycardia (<60 beats/min); hypoxia (oxygen saturation <95% on air or unable to record by pulse oximeter); tachypnoea (respiratory rate>60 breaths/minute at any age); hypothermia (axillary temperature < 35^0C); capillary refill ≥3 seconds; hypotension (systolic blood pressure <70 mmHg or unrecordable); acidosis (base deficit >8); elevated creatinine (>80 µmol/l); hypoglycaemia (<3.0 mmol/l); hyperglycaemia (>10mmols/l); hypokalaemia (<3mmols/l); hyperkalaemia (>5.5 mmol/l) or hyponatraemia (<125 mmol/l).

Means and standard deviations were calculated for continuous variables using the student t-tests. Non–normally distributed data were compared using Sign-rank test and Kruskal-Wallis. Proportions were compared using chi-square and Fisher's exact tests as appropriate. We also used Kaplan Meier survival analysis to compared time to event (death). The area under curve (AUC) was calculated for

serial measurements and their medians compared using Wilcoxon-Ranksum and Kruskal-Wallis tests. We employed AUC in order to compensate for confounding effect of early mortality, hence missing observations, leading to biases in the highest risk group and resulting imbalance within the survivors[291]. All analyses were by intention to treat.

CHAPTER 4 : DEFINITIONS OF SHOCK AND HAEMODYNAMIC PROFILES IN SEVERE ILLNESS

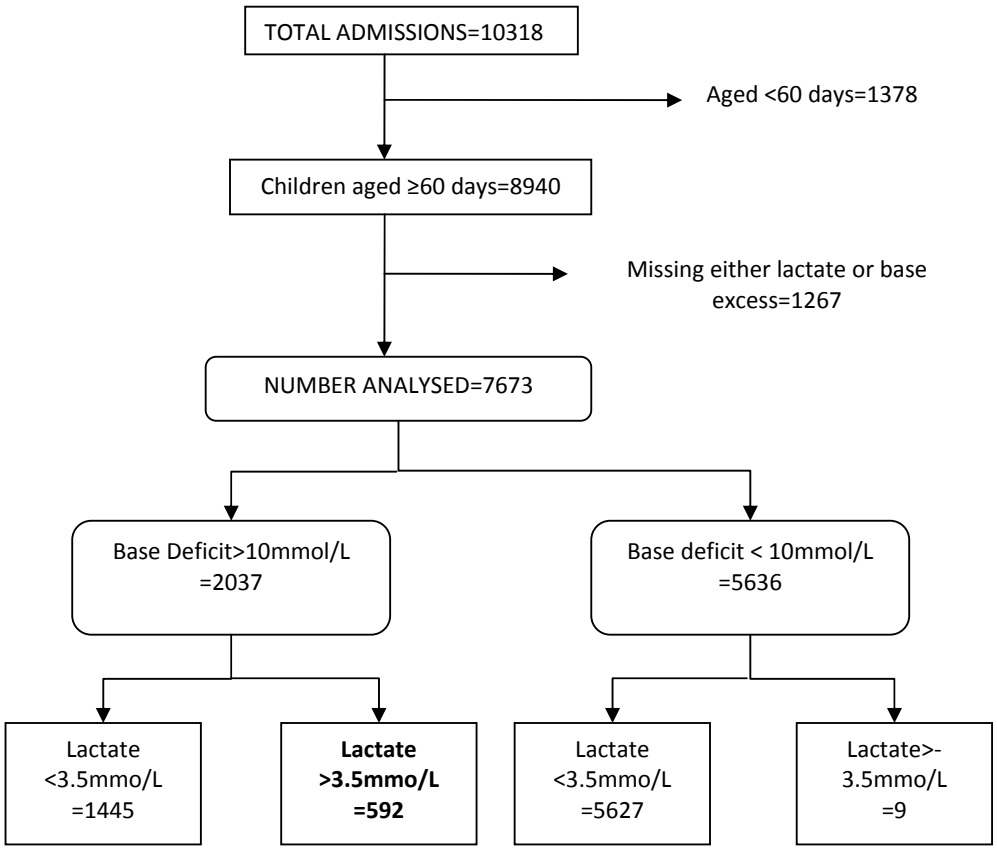
4.1. DEVELOPMENT OF CLINICAL CRITERIA FOR DIAGNOSIS OF SHOCK

Clinical definitions of shock vary widely and few have been evaluated against physiological measurements of shock or other non-observer dependent outcome (Table 2.4) and most have been arrived at through consensus or expert opinions[7 8 11 12 137 178]. This sections presents an evaluation these different signs and clinical definitions of shock against two biochemical markers of tissue hypoperfusion, serum lactate and base deficit[137 159 178]. Data prospectively collected in years 2002 and 2003 was used to derive predictive signs (derivation/training set) and that collected in year 2004 used to validate the signs (validation/test set).

4.1.1. Results

A total of 10318 infants and children aged 0-13 years were admitted in the years 2002 and 2003. For this analysis young infants aged ≤60 days (n=1378) were excluded. Those without either admission lactate or base excess measurement were also excluded (n=1267) leaving a total of 7673 participants for analysis (Figure 4.1). Overall in-hospital mortality among the children retained within the analysis dataset was 7% (546/7673). Mortality among participants without either lactate or base excess measurement was also 6% (80/1267). Overall 2037 (27%) children had base deficit >10mmol/L; nearly all the children with lactate >3.5mmol/L (592/601, 99%) also had raised base deficit (>10mmol/L).

Figure 4-1: Study flow: Children admitted during years 2002 and 2003

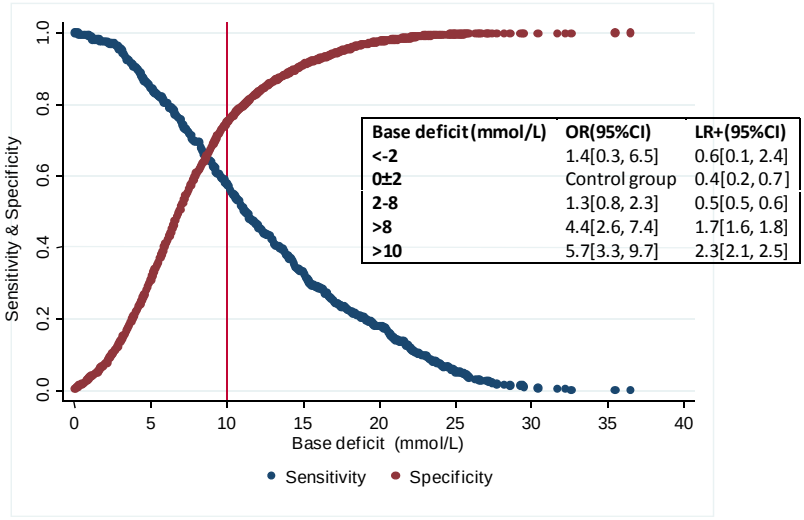


4.1.2. Risk of death with respect to lactate and base deficit

Base deficit

The risk of mortality increased steadily with increase in base deficit (Figure 4.2). A graph of sensitivity versus specificity for base deficit in predicting children at risk of death demonstrated a crossover point for sensitivity and specificity curves at 65%, which corresponded to base deficit level of 8.6mmo/l (LR+ 1.8, LR-=0.5)-Figure 4.2. The optimal point of the smallest sum of residual sensitivity and specificity was however at base deficit level of 9.8mmol/L. This was rounded up to a base deficit >10mmol/L and this was found to be associated with an increased risk for in-hospital death (crude odds ratio=5.7; 95% confidence interval, 3.3 to 9.7) and likelihood ratio of 2.3 [95% confidence interval; 2.1 to 2.5]. Base deficit >10mmol/L, since it fulfilled the preset criteria for prediction of fatality (both OR and LR≥2.0), was therefore selected as a criterion to prospectively examine the datasets for clinically relevant surrogates predicting impaired perfusion.

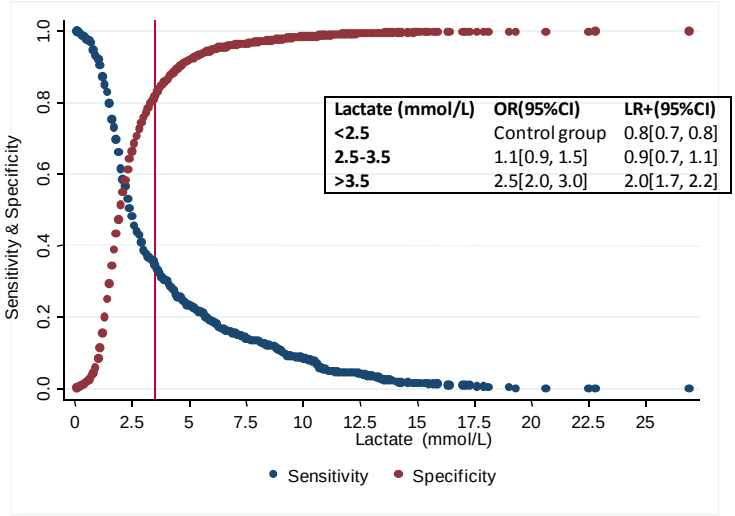
Figure 4-2: Sensitivity and specificity of base deficit for predicting mortality



Lactate

The crossover point for sensitivity and specificity curves for the prediction of death using lactate was at 57%, which corresponded to a lactate level of 2.2mmol/L-Figure 4.3. The optimal point of the smallest sum of residual sensitivity and specificity however corresponded to a serum lactate level of 3.4mmol/L. This was rounded up to a lactate level >3.5mmo/L and was found to be associated with increased risk of death (crude odds ratio=2.5; 95% confidence interval, 2.0 to 3.0) and was also predictive of death (LR+=2.0, LR-=0.9). Lactate level >3.5mmol/L therefore fulfilled the preset criterion for prediction of mortality and was selected as a criterion to prospectively examine the dataset for clinically relevant surrogates for predicting impaired perfusion.

Figure 4-3: Sensitivity and specificity of lactate for predicting mortality



4.1.3. Definition of tissue hypoperfusion using lactate and base deficit

Biochemical measures of tissue hypoperfusion which were prognostically relevant were therefore defined as a composite measure of both serum lactate level >3.5mmol/L **plus** base deficit >10mmol/L. The term '**tissue hypoperfusion'** refers to metabolic acidosis, a term consistent with surviving sepsis guidelines[137 220], and will be used for the rest of the chapter as a laboratory marker of shock (lactate level >3.5mmol/L **plus** base deficit >10mmol/L).

4.1.4. Clinical predictors of tissue hypoperfusion

Baseline characteristics

In the 2002-2003 cohort, a total of 592 (7.7%) children had lactate level >3.5mmol/L plus base deficit>10mmol/L (tissue hypoperfusion). There were no differences in age or sex between patients with tissue hypoperfusion and those without. Children with tissue hypoperfusion had significantly more features of disease severity including proportions with severe malnutrition (determined by MUAC), hypoxia (oxygen saturation <90% in air on pulse oximetry), respiratory distress (deep breathing or chest indrawing), prostration, coma, severe anaemia, bradycardia, and clinical features of shock (delayed capillary refill time, weak pulse volume, temperature gradient, and tachycardia). Baseline characteristics and comparisons are presented in table 4.1.

Association between baseline characteristics and tissue hypoperfusion

Using simple logistic regression, the following variables were found to be significantly associated with tissue hypoperfusion (OR≥2.0); abnormal temperature (defined axillary temperature >38.5°C or <36.0°C), hypoxia, deep (Kussmaul or acidotic) breathing, chest indrawing, delayed capillary refill time, weak pulse volume, bradycardia, tachycardia, temperature gradient, coma, prostration, presence of malaria infection, bacteraemia, and severe anaemia (Table 4.1). Age, sex, admission weight, and nutrition status were not associated with tissue hypoperfusion and were not included in the multivariable model.

A multivariable logistic regression with all the variables that were significant at univariate analysis was done. Tachycardia and temperature gradient were retained in the multivariable model despite being non-significant at univariate analysis because they are signs commonly used in many definitions[12 181 220 292]. The multivariable model was run with and without adjustment for abnormal temperature. This was done because fever/hypothermia is an important sign of sepsis/SIRS[136 137 178 220] and temperature may affect heart rate, respiratory rate and other signs of shock independent of tissue perfusion. Using a multivariable logistic regression model (with or without adjustment for abnormal temperature), tachycardia and temperature gradient were not significantly associated

with tissue hypoperfusion (Table 4.1). The other variables that were significant at univariate remained significantly associated with tissue hypoperfusion in the multivariable model. Chest indrawing was however non-significantly associated with tissue hypoperfusion when stratification by temperature was done.

Table 4-1: Baseline characteristics

Characteristic	Baseline characteristics		
	No tissue hypoperfusion (N=7081)	Tissue hypoperfusion (N=592)	p-value
Age, median[IQR]	23[11,42]	21[10,36]	0.10
Male Sex ,n[%]	3913[55]	315[53]	0.34
MUAC, mean[SD]	13.7[2.0]	13.4[1.9]	<0.001
Malnutrition (MUAC<11.5)	767[11]	79[13]	0.04
Admission weight	10.5[5.0]	9.5[4.1]	<0.001
Abnormal temperature	6148[87]	537[91]	0.007
Airway			
Hypoxia (<90% in air)	307[4]	95[16]	<0.001
Breathing			
Deep breathing	697[10]	200[34]	<0.001
Chest indrawing	1588[22]	193[33]	<0.001
Circulation			
Capillary refill time>2s	393[6]	150[25]	<0.001
Capillary refill time>3s	69[1]	45[8]	<0.001
Weak pulse volume	283[4]	107[18]	<0.001
Bradycardia[a]	24[0.3]	13[2.2]	<0.001
Tachycardia[b]	2767[39]	267[45]	0.003
Temperature gradient	1918[27]	211[36]	<0.001
Conscious level			
Coma	221[3]	91[15]	<0.001
Prostration	408[6]	110[19]	<0.001
Others			
Malaria slide positive	3116[44]	364[61]	<0.001
Bacteraemia	361[5]	48[8]	0.002
Severe anaemia (Hb<5g/dL)	654[9]	176[30]	<0.001

[a]Bradycardia(<3m=<80bpm, 3m-2y=<75, >2y=<60);[b]Tachycardia (<12m=>180bpm, 1y-5y=>160, >5y=<14)

It was not surprising that deep breathing was associated with tissue hypoperfusion because studies have shown that it is a good proxy measure for acidosis[285 286]. The same was expected for chest indrawing because it is an indicator of respiratory acidosis and there is some overlap with deep breathing since the two signs are difficult to differentiate[293]. Only children with complicated severe malnutrition are usually admitted[279] and a study from Kilifi has shown shock as a common complication in the admitted cases[4]. Therefore predominance of acidosis (tissue hypoperfusion) in participants with severe malnutrition seen in this study was not surprising.

Association between clinical signs of shock and tissue hypoperfusion

Delayed capillary refill time and bradycardia were independently associated with tissue hypoperfusion at multivariable analysis (adjusted OR ≥2.0) but weak pulse volume was weakly associated (adjusted OR >1.5). Tachycardia and temperature gradient still showed no association at multivariable analysis (Table 4.2). It was notable that various clinical signs (CRT, bradycardia, and weak pulse volume) showed strong associations at univariate analysis but markedly lowered associations at multivariable analysis (Table 4.2). This highlights the reality that a complex disease process such as acidosis manifests with a large number of highly related, rather than independent clinical signs and symptoms. Various clinical signs are usually a manifestation of some compensatory mechanism during tissue hypoperfusion and the lack of direct relationship may explain the weakening of association.

Table 4-2: Association between baseline characteristics and tissue hypoperfusion

	Association with tissue hypoperfusion			
Characteristic	**Crude OR**	**p-value**	**Adjusted OR**	**p-value**
Airway				
Hypoxia (<90% in air)	4.2[3.3,5.4]	<0.001	2.0[1.5,2.7]	<0.001
Breathing				
Deep breathing	4.7[3.9,5.6]	<0.001	2.2[1.7,2.8]	<0.001
Chest indrawing	1.7[1.4,2.0]	<0.001	1.3[1.1,1.7]	0.007
Circulation				
Capillary refill time>2s	5.8[4.7,7.2]	<0.001	2.1[1.6,2.8]	<0.001
Capillary refill time>3s	8.4[5.7,12.4]	<0.001	2.0[1.2,3.3]	0.008
Weak pulse volume	5.3[4.2,6.7]	<0.001	1.6[1.1,2.2]	0.008
Bradycardia	6.6[3.4,13.1]	<0.001	2.1[0.8,5.0]	0.11
Tachycardia	1.3[1.1,1.5]	0.003	1.2[1.0,1.4]	0.09
Temperature gradient	1.5[1.3,1.8]	<0.001	1.0[0.8,1.2]	0.90
Conscious level				
Coma	5.6[4.3,7.3]	<0.001	2.9[2.1,3.9]	<0.001
Prostration	3.7[3.0,4.7]	<0.001	1.7[1.3,2.3]	<0.001
Others				
Malaria slide positive	2.0[1.7,2.4]	<0.001	1.7[1.4,2.1]	<0.001
Bacteraemia	1.6[1.2,2.2]	0.002	1.4[1.0,1.9]	0.08
Severe anaemia (Hb<5g/dL)	4.2[3.4,5.4]	<0.002	2.8[2.2,3.5]	<0.001

4.1.5. Effect of body temperature on clinical signs of tissue hypoperfusion

Clinical signs independently associated with tissue hypoperfusion were rare when temperature was normal (Table 4.3). Delayed capillary refill time was associated with tissue hypoperfusion when temperature was abnormal but not in normal temperature (Table 4.3). Bradycardia was associated with tissue hypoperfusion both in normal and abnormal temperatures but association seen with normal temperature requires cautious interpretation due to the small numbers of bradycardic

patients with normal temperature. Weak pulse volume was weakly associated both in normal and abnormal temperatures. Like bradycardia, the association seen with normal temperatures should also be interpreted cautiously. Both tachycardia and temperature gradient were not associated with tissue hypoperfusion with either temperature category (Table 4.3).

Table 4-3: Association between baseline characteristics and tissue hypoperfusion stratified by fever

Characteristic	Abnormal temperature (axillary temperature >38.5°C or <36.0°C)		Normal temperature (axillary temperature ≤38.5°C or ≥36.0°C)	
Airway	**n/N[%]**	Adjusted OR	**n/N[%]**	Adjusted OR
Hypoxia (<90% in air)	86/350[25]	2.0[1.4,2.7]	9/52[17]	2.1[0.9,5.3]
Breathing				
Deep breathing	184/798[23]	2.1[1.7,2.7]	16/99[16]	2.2[1.0,5.0]
Chest indrawing	366/5099[7]	1.3[1.0,1.6]	32/791[4]	2.2[1.1,4.4]
Circulation				
Capillary refill time>2s	146/486[30]	2.3[1.7,3.1]	4/57[7]	0.5[0.1,1.8]
Capillary refill time>3s	44/106[42]	2.0[1.2,3.4]	1/8[13]	1.7[0.2,19.2]
Weak pulse volume	99/329[30]	1.6[1.1,2.3]	8/61[13]	1.9[0.7,5.3]
Bradycardia	11/32[34]	2.0[0.7,5.1]	2/5[40]	4.7[0.6,36.5]
Tachycardia	257/2826[9]	1.2[1.0,1.5]	10/208[5]	0.7[0.3,1.5]
Temperature gradient	201/1978[10]	1.0[0.8,1.3]	10/151[7]	0.8[0.4,1.9]
Conscious level				
Coma	88/283[31]	3.0[2.1,4.1]	3/29[10]	1.8[0.5,7.0]
Prostration	104/482[22]	1.7[1.2,2.3]	6/36[17]	2.4[0.8,6.9]
Others				
Malaria slide positive	350/3259[11]	1.8[1.5,2.2]	14/221[6]	1.3[0.7,2.4]
Bacteraemia	47/381[12]	1.4[1.0,2.0]	1/28[4]	0.5[0.1,3.9]
Severe anaemia (Hb<5g/dL)	172/786[22]	2.9[2.3,3.6]	4/44[9]	1.4[0.4,4.5]

4.1.6. Predictive ability of clinical signs for tissue hypoperfusion

Derivation set (2002-03) was again used to calculate LRs for various clinical signs to predict tissue hypoperfusion. LRs were calculated to enable determination of signs that would rule in or rule out tissue hypoperfusion. Capillary refill time >2 seconds, weak pulse volume and bradycardia had adjusted LR+≥2 and therefore represent clinical signs whose presence are predictive of tissue hypoperfusion (Table 4.4). However, CRT >2 seconds and weak pulse volume were only predictive in abnormal temperature (LR+≥2.0) but not in normal temperature (LR+<2.0) (Table 4.4). Bradycardia was predictive in both normal and abnormal temperatures but the caveats mentioned above should be considered in its interpretation The absence of any of these signs did not rule out tissue hypoperfusion (adjusted LR- >0.5) in both normal and abnormal temperatures.

Table 4-4: Likelihood ratios of signs of shock for predicting tissue hypoperfusion

	N=7673									
Clinical Feature	**Crude LR**		**Adjusted LR[1] for clinical signs of shock**		**Adjusted LR[2] for disease, severity and signs of shock**		**Adjusted LR[3] in participants with abnormal temperature**		**Adjusted LR[3] in participants with normal temperature**	
	LR+	LR-	LR+	LR-	LR+	LR-	LR+	LR-	LR+	LR-
Bradycardia	6.5[3.3, 12.7]	1.0[0.9, 1.0]	3.5	1.0	2.3	1.0	2.0	1.0	8.2	1.0
Capillary refill time >2 seconds	4.6[3.9, 5.4]	0.8[0.7, 0.8]	3.4	0.8	2.2	0.9	2.1	0.9	1.5	1.0
Tachycardia	1.2[1.1, 1.3]	0.9[0.8, 1.0]	1.2	0.9	1.1	0.9	1.1	0.9	0.9	1.0
Temperature gradient	1.3[1.2, 1.5]	0.9[0.8, 0.9]	1.1	0.9	1.0	0.9	1.0	1.0	1.0	1.0
Weak pulse volume	4.5[3.7, 5.6]	0.9[0.8, 0.9]	2.2	0.9	2.0	0.9	2.2	0.9	1.0	1.0

[1]adjusted for bradycardia, capillary refill time >2seconds, tachycardia, temperature gradient, weak pulse volume;
[2,3]adjusted as 1 and for severe anaemia, coma, prostration, deep breathing, chest indrawing, malaria parasitaemia, and bacteraemia; LR=likelihood ratio, LR+=positive LR, LR-=negative LR

4.1.7. Derived clinical definition of shock

A criterion for shock was derived from the above analysis of clinical parameters which had an increased odds and likelihood of having tissue hypoperfusion (acidosis). This was defined as presence of abnormal temperature (>38.5°C or <36.0°C) plus a capillary refill time >2 seconds or weak pulse volume or bradycardia (3months=<80 beats per minute, 3months-2years=<75 beats per minute, >2yeard=<60 beats per minute). This is referred to as '**derived shock**'. This was present in 8% (749/8940) of children in the 2002-2003 cohort with a case fatality of 23% (169/749).

4.1.8. Performance of various definitions of shock for predicting tissue hypoperfusion

All three signs (capillary refill time >2 seconds, weak pulse volume and bradycardia) were independently examined for predictive ability and found to have very low sensitivities but high specificities (Table 4.6). The clinical signs may therefore identify only children with advanced stages of tissue hypoperfusion. However tissue hypoperfusion is unlikely in the absence of these signs (high specificities).

Various shock criteria had low sensitivities but high specificities for predicting tissue hypoperfusion (acidosis), therefore tissue hypoperfusion would be unlikely in their absence. ACCM definition has the highest proportion of children fulfilling criteria (34%) but mortality among those identified was 10% (Table 4.7). Less than 1% fulfilled the WHO criteria for shock but mortality for those identified was 46%. FEAST shock criteria were fulfilled by 20% of children and the mortality for that sub-group was 13%. Eight percent fulfilled the derived shock definition and mortality for the group was 23%.

The predictive ability of various definitions that are used in various clinical settings to identify children in shock was also assessed (Table 4.5). The WHO criteria, the derived shock definition, ACCM/PALS definition, and FEAST shock definition all identified children with increased risk of mortality. All these definitions also identified children at increased risk of having tissue hypoperfusion (adjusted likelihood ratio ≥2) except for ACCM (adjusted positive likelihood ratio=1.7).

Table 4-5: Predictive values of various definitions of shock for tissue hypoperfusion

8940	Mortality	Tissue hypoperfusion		Adjusted LRs[1]	
	Crude OR	Crude OR	Adjusted OR[1]	LR+	LR-
Derived shock (n=754, 8%)	6.1[5.0,7.4]	6.1[5.0, 7.4]	4.7[3.8,5.8]	3.7	0.8
FEAST shock (n=1770, 20%)	3.2[2.7,3.8]	3.5[3.0,4.2]	3.3[2.8,3.9]	2.3	0.7
WHO shock (n=24, 0.3%)	13.5[6.0,30.4]	15.8[5.9, 42.6]	14.0[4.9,40.1]	13.8	1.0
ACCM shock (n=3157, 35%)	2.5[2.1,2.9]	2.8[2.4,3.4]	2.6[2.2,3.1]	1.7	0.7

[1]Odds/likelihood ratios adjusted for severe anaemia (Hb<5g/dL)

Clinical signs (delayed capillary refill time, weak pulse volume, or bradycardia) and various shock definitions have poor sensitivities for predicting tissue hypoperfusion (Tables 4.6 and 4.7). The signs and various shock criteria have high specificities therefore tissue hypoperfusion is unlikely in their absence. Abnormal signs and shock by various definitions were rare in non severe disease

Table 4-6: Sensitivity, specificity and predictive values of various signs of shock for tissue hypoperfusion

N=7673	All participants					Severe disease					Non-severe disease			
Clinical Feature	**n[%]**	**Sn(%)**	**Sp(%)**	**PPV (%)**	**NPV (%)**	**n[%]**	**Sn (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**	**Sn (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**
Bradycardia	37[0.5]	2[2,3]	100[99,100]	35[34,36]	92[92,93]	28[76]	3[3,4]	99[99,100]	43[41,45]	87[86,88]	0[0,1]	100[99,100]	11[10,12]	95[95,96]
Capillary refill time >2 seconds	543[7]	26[25,27]	94[94,95]	28[27,29]	94[93,94]	343[63]	36[35,38]	91[89,92]	38[36,39]	90[89,91]	9[8,10]	96[96,97]	11[10,11]	96[95,96]
Capillary refill time >3 seconds	114[1.5]	8[7,8]	99[99,99]	39[38,41]	93[92,93]	88[79]	12[11,13]	98[97,96]	48[46,50]	88[86,89]	1[1,2]	100[99,100]	12[11,12]	95[95,96]
Weak pulse volume	390[5]	18[17,19]	96[95,96]	27[26,28]	93[93,94]	274[70]	26[25,28]	92[91,93]	34[32,36]	89[88,90]	6[5,6]	98[97,98]	11[10,12]	96[95,96]

Table 4-7: Sensitivity, specificity and predictive values of various signs of shock for tissue hypoperfusion

N=7673	All participants					Severe disease					Non-severe disease			
Clinical Feature	**n[%]**	**Sn(%)**	**Sp(%)**	**PPV (%)**	**NPV (%)**	**n[%]**	**Sn (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**	**Sn (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**
Derived shock	647[8]	30[29,31]	93[93,94]	28[27,29]	94[94,95]	419[65]	42[41,44]	88[87,89]	36[34,38]	91[90,92]	11[10,12]	96[95,96]	11[11,12]	95[95,96]
FEAST shock	1543[20]	44[43,45]	82[81,83]	17[16,18]	95[94,95]	1543[100]	73[71,74]	44[42,45]	17[15,18]	91[90,92]	-	-	-	-
WHO shock	16[0.2]	2[1,2]	100[99,100]	56[55,57]	92[92,93]	16[100]	3[2,3]	100[99,100]	56[54,58]	87[86,88]	-	-	-	-
ACCM shock	2769[36]	59[58,61]	66[65,67]	13[12,13]	95[95,96]	1376[50]	77[75,78]	52[50,53]	20[18,22]	93[92,94]	33[32,34]	73[71,74]	6[5,6]	96[95,96]

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4.1.9. Predictive scores for shock

A simplified predictive score was constructed from the derivation set (years 2002 and 2003) by assigning points approximating to the natural logarithm of the crude likelihood ratio for each clinical sign[2]. When potential for a negative score existed a constant was added.

Table 4-8: Likelihood ratios and simplified predictive scores for various clinical signs of tissue hypoperfusion

Clinical Feature	Likelihood ratio		Simplified score	
	Sign Present	Sign absent	Sign present	Sign absent
Bradycardia	6.5[3.3,12.7]	1.0[0.9,1.0]	+2	0
Capillary refill time >2 seconds	4.6[3.9,5.4]	0.8[0.7,0.8]	+1	0
Weak pulse volume	4.5[3.7,5.6]	0.9[0.8,0.9]	+1	0

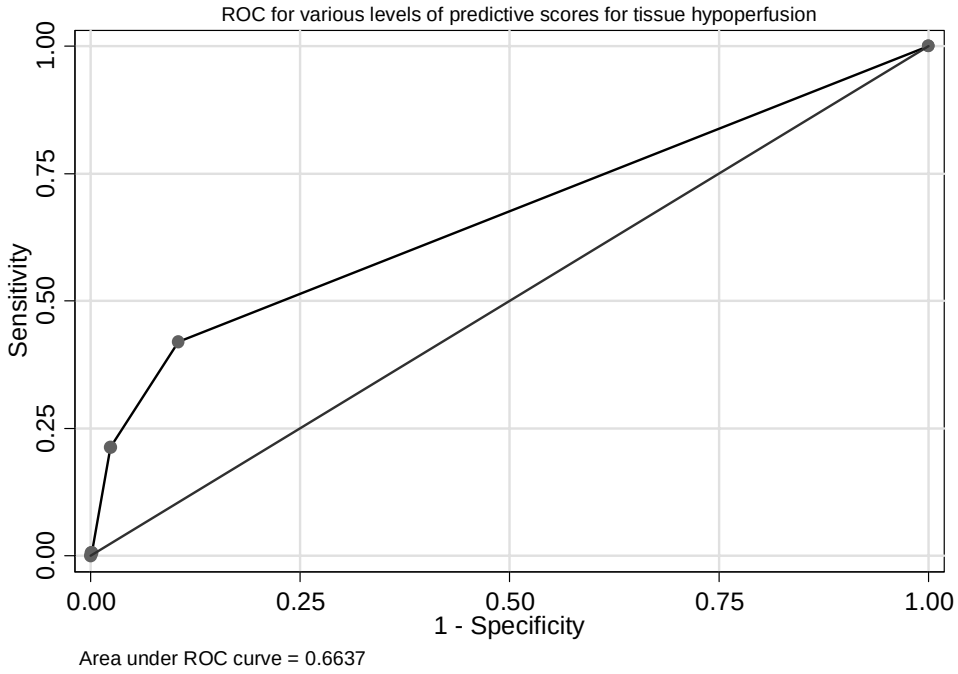
4.1.10. Performance of diagnostic score for shock on validation set

Validation set comprised of children admitted in the 2004. A total of 4991 children were admitted and after excluding 728 children aged <60 days and a further 451 children who were missing either base deficit or lactate, 3812 participants were available for validation of the derived shock definition. The derived shock definition (abnormal temperature plus capillary refill time >2 seconds or weak pulse volume or bradycardia) was applied to the year 2004 dataset and the area under receiver operating characteristics curve (ROC) calculated. Thirteen percent (505/3812) of participants had derived shock and case fatality was 15%. Fifty-seven percent (286/505) of children with derived shock had severe disease (impaired consciousness and/or respiratory distress) and case fatality was 20%; forty-three percent (219/ 505) had no signs of severe disease with case fatality of 8% (17/219).

Area under receiver operating characteristics curve in validation set

The derived shock definition was useful for predicting tissue hypoperfusion in the overall population and in those with severe disease (Figure 4.4) but performed poorly in those without severe disease (Figure 4.6). The area under ROC for the definition in all participants was 0.66 (95% confidence interval 0.62, 0.70). In participants with an abnormal temperature, derived shock definition had a sensitivity of 49% and specificity of 86%, positive likelihood ratio=3.5[2.9, 4.1], negative likelihood ratio=0.6[0.5, 0.7].

Figure 4-4: ROC curves for various levels of predictive score for tissue hypoperfusion

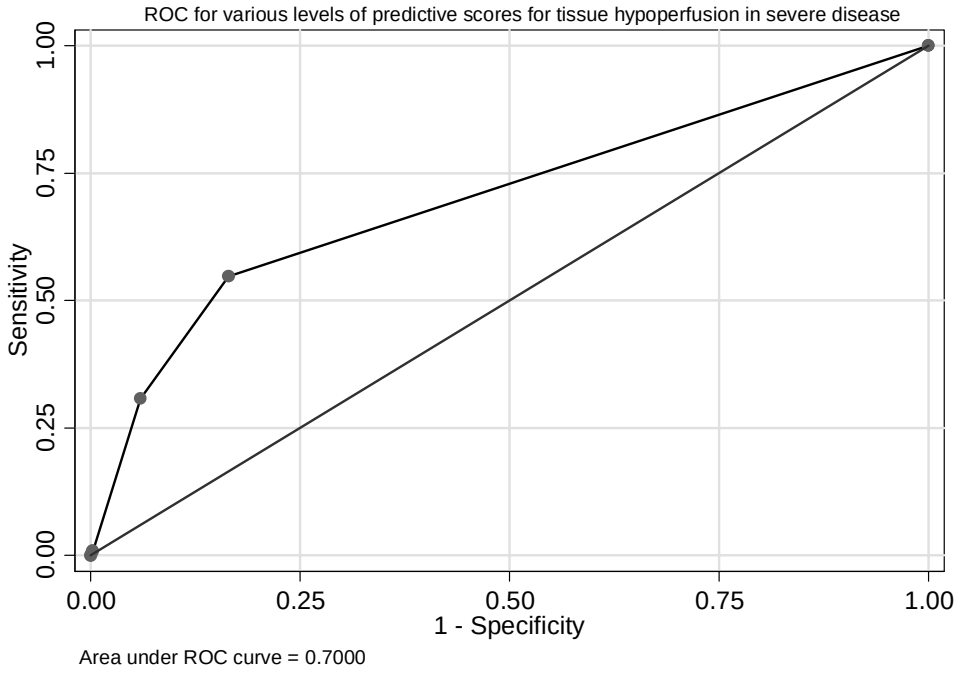


The figure above (Figure 4.4) shows the ROC for all participants fulfilling the derived shock definition in the validation dataset. The graph illustrates that even the derived shock definition is not sufficiently sensitive.

Area under receiver operating characteristics curve in participants with severe disease

In children with severe disease, the ROC was 0.70 (95% confidence interval 0.65, 0.75). The definition had a sensitivity of 55%, specificity of 83%, positive likelihood ratio=3.40, and negative likelihood ratio=0.5 in severe disease.

Figure 4-5: ROC curves for various levels of predictive score for tissue hypoperfusion in severe disease

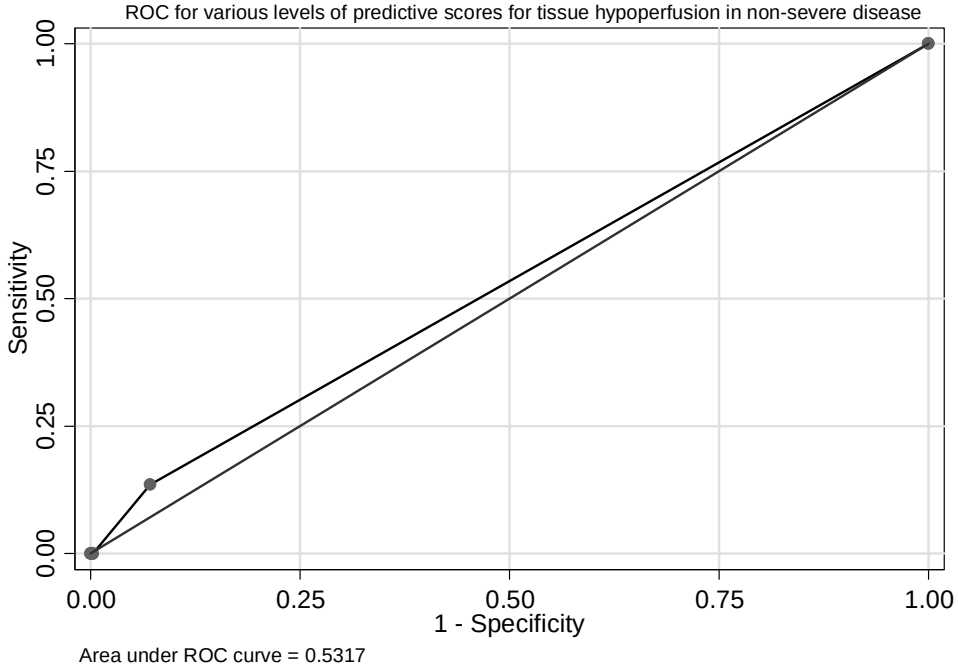


The figure above (Figure 4.5) shows the ROC for participants with severe disease fulfilling the derived shock definition in the validation dataset. The ROC increased when only this sub-group with severe disease (compared to all participants) was considered.

Area under receiver operating characteristics curve in participants with non-severe disease

In children without severe disease the ROC was 0.53 (95% confidence interval 0.48, 0.58). The definition had a sensitivity of 17%, specificity of 91%, positive likelihood ratio=1.9, and negative likelihood ratio=0.9 in non-severe disease.

Figure 4-6: ROC curves for various levels of predictive score for tissue hypoperfusion in non-severe disease for the validation set



The figure above (Figure 4.6) shows the ROC for participants without severe disease fulfilling the derived shock definition in the validation dataset. The derived shock definition did not perform much better than chance in non-severe disease and therefore was not useful in non-severe disease.

Further sub-group analyses for area under receiver operating characteristics curves

The definition of severe disease includes impaired consciousness (prostration or coma) and/or respiratory distress (deep breathing or chest indrawing). From the models presented earlier in this chapter, the odds of deep breathing (adjusted OR=2.2[1.7, 2.8]) and chest indrawing (adjusted OR=1.3[1.1, 1.7]) being associated with tissue hypoperfusion were different. Further sub-grouping of the severe disease was based on the nature of respiratory distress, that is, deep breathing or chest indrawing. For those with severe disease which included impaired consciousness or deep breathing, the ROC was 0.67 (95% CI 0.62, 0.72); 60% sensitivity, 73% specificity, positive likelihood ratio=2.2, negative likelihood ratio=0.5. In those with severe disease which included impaired consciousness or chest indrawing, the ROC was 0.70 (95% CI 0.64, 0.75); 52% sensitivity, 86% specificity, positive likelihood ratio=3.8, negative likelihood ratio=0.6.

4.1.11. Distribution of predictive scores and association with mortality in validation dataset

The predictive scores that were derived in section 4.1.8 were used to classify patients in the validation set (Tables 4.9 and 4.10). The risk of both tissue hypoperfusion and death increased (worsened) with increasing values of predictive scores in all participants and in sub-group with severe disease. Risk of death also increased with rise in predictive scores for non-severe disease but derived shock was rare in non-severe disease and its practical utility is in severe disease.

Table 4-9: Distribution of various predictive scores for tissue hypoperfusion in children admitted to Kilifi District Hospital in the year 2004

	All participants (N=3812)				Severe disease(N=1448)				Non-severe disease(N=2363)			
Predictive score	**No admitted**	**No (%) with tissue hypoperfusion**	**Odds ratio**	**LR+**	**No admitted**	**No (%) with tissue hypoperfusion**	**Odds ratio**	**LR+**	**No admitted**	**No (%) with tissue hypoperfusion**	**Odds ratio**	**LR+**
0	3351	98(3)	-	0.6[0.6,0.7]	1159	53[5]	-	0.5[0.4,0.7]	2192	45[2]	-	0.9[0.8,1.0]
1	332	35(11)	3.8[2.6,5.9]	2.5[1.9,3.5]	167	28[17]	4.2[2.6,6.9]	2.3[1.6,3.3]	165	7[4]	2.1[0.9,4.8]	2.0[1.0,4.0]
2	116	35(30)	14.3[9.2,22.4]	9.3[6.5,13.4]	110	35[32]	9.7[6.0,15.8]	5.3[3.7,7.5]	6	0	-	-
3	1	0	n/a	n/a	1	0	n/a	n/a	0	0	-	-
4	4	1(25)	11.1[1.1,107.3]	7.2[0.8,68.6]	4	1[25]	7.0[0.7,68.0]	3.8[0.4,36.0]	0	0	-	-

Numbers presented in the table above excludes 451 children without lactate and/or blood gas measurement & 8 missing score.

Table 4.8 shows increased (worsened) risk of tissues hypoperfusion with increasing values of predictive scores in all participants and in sub-group with severe disease. Derived shock was rare in non-severe disease

Table 4-10: The distribution of various predictive scores for mortality in children admitted to Kilifi District Hospital in the year 2004

	All participants (N=3812)				Severe disease(N=1595)				Non-severe disease(N=2657)			
Predictive score	No admitted	No (%) died	Odds ratio	LR+	No admitted	No (%) died	Odds ratio	LR+	No admitted	No (%) died	Odds ratio	LR+
0	3748	144[3.84]	-	0.7[0.7,0.8]	1286	72[5.6]	-	0.6[0.5,0.7]	2462	72[2.9]	-	0.9[0.8,1.0]
1	368	37[10]	2.8[1.9,4.1]	2.0[1.5,2.8]	182	24[13.2]	2.6[1.6,4.2]	1.6[1.1,2.4]	186	13[7.0]	2.5[1.4,4.6]	2.2[1.3,3.7]
2	130	39[30]	10.7[7.1,16.2]	7.7[5.5,11.0]	122	38[31.2]	7.6[4.9,12.0]	4.9[3.5,6.8]	8	1[12.5]	4.7[0.6,39.0]	4.2[0.5,33.9]
3	2	1[50]	25.0[1.6,402.1]	18.1[1.1,287.9]	1	0	-	-	1	1[100]		
4	4	2[50]	25.0[3.5,178.9]	18.1[2.6,127.7]	4	2[50]	16.9[2.3,121.4]	10.7[1.5,75.6]	0	0		

Table 4.9 shows increased (worsened) risk of death with increasing values of predictive scores in all participants and in sub-groups with/out severe disease.

4.1.12. Summary of findings

1. Risk of death increases with increased base deficit. Base deficit >10mmol/L is associated with increased risk of mortality and its presence is a good predictor of death (LR≥2). However base deficit ≤10mmol/L is not good predictor of survival (LR- >0.5).

2. Like with case of base deficit, risk of death increases with increased levels of serum lactate. Serum lactate >3.5mmol/L is associated with increased risk of death and its presence is a good predictor of mortality (LR+ ≥2) but lactate level ≤3.5mmol/L is not a good predictor of survival (LR- >0.5).

3. In the whole study population, CRT>2 seconds, weak pulse volume, and bradycardia are associated with increased risk of having serum lactate >3.5mmol/L plus base deficit >10mmol/L (referred to as '**tissue hypoperfusion'**). Presence of any of the three clinical signs was also predictive of tissue hypoperfusion. However the absence of any of the three signs does not predict absence of tissue hypoperfusion. Commonly used signs of shock such as tachycardia and temperature gradient were not associated with tissue hypoperfusion and the signs were also not predictive of mortality.

   Similar findings were seen when only those with severe disease (impaired consciousness and/or respiratory distress) were considered. In the sub-group without severe disease, bradycardia and CRT>2 seconds were predictive of tissue hypoperfusion and death but weak pulse volume was not. However these signs were uncommon in non-severe disease and any associations should be cautiously interpreted.

4. CRT>2 seconds, weak pulse volume, and bradycardia all had high specificities and NPV (>90%) but low sensitivities in the overall study population and when categorised into severe and non-severe disease groups. Sensitivities were even lower in non-severe disease. The three signs indicative of tissue hypoperfusion (acidosis) are rare in non-severe disease and their practical utility is in patients with severe disease.

5. The presence of abnormal temperature (>38.5°C or <36.0°C) plus any of capillary refill time > 2 seconds, weak pulse volume, or bradycardia (called **'derived shock'**) was found to be associated with increased risk of tissue hypoperfusion. Presence of derived shock was predictive of tissue hypoperfusion (adjusted LR+ =3.7) but the absence was not a good predictor of absence of tissue hypoperfusion (adjusted LR-=0.8)

6. WHO [LR+=13.8], derived shock [LR+=3.7], and FEAST definitions of shock [LR+=2.3] were predictive of tissue hypoperfusion but ACCM/PALS [LR+=1.7] was not in the validation set.

7. All the shock definitions significantly identified children at increased risk of death; WHO definition has the highest odds ratios followed by derived shock, then FEAST, and lastly ACCM definition.

8. Derived shock definition was still not a perfect predictor in the validation set, ROC=0.66; severe disease sub-group ROC=0.70, non-severe disease, ROC=0.53. Derived shock definition should therefore be applied only to those with severe disease in clinical practice. All clinical signs and various criteria however compared poorly to direct measurement of lactate and blood gas.

CHAPTER 5 : INVESTIGATION OF HAEMODYNAMIC STATUS OF CHILDREN WITH SEVERE FEBRILE ILLNESSES

5.1. AGREEMENT BETWEEN ECHOCARDIOGRAPHY AND USCOM MEASUREMENTS

Validation of cardiac output measurements obtained using USCOM device has been done against pulmonary artery catheter thermodilution (PATD)[186 294-296] and echocardiography[194 297]. Validation against PATD has been in surgical cases and against echocardiography in neonates. While most studies have found good agreement between USCOM and the other methods[186 298 299], Knirsch and colleagues did not show good correlation of USCOM cardiac output measurements with ones obtained by thermodilution [186]. USCOM validation against echocardiography has not been done in emergency care settings in patients with suspected sepsis who do not necessarily require intensive care admission. Echocardiography is now considered valid and reliable technique for measuring cardiac function like gold-standard method, PATD [179 186-190], but it is technically difficult, expensive and need specialist training and this limits its application. USCOM in a new technology, less technically challenging, has internal quality control for parameters assessed, and requires less training[179]. The initial phase of this study involved a validation of the USCOM measurements against measurements obtained by echocardiography. The purpose of this phase was to ascertain the validity of the haemodynamic measurements obtained by USCOM device and which are used subsequently.

5.1.1. Results

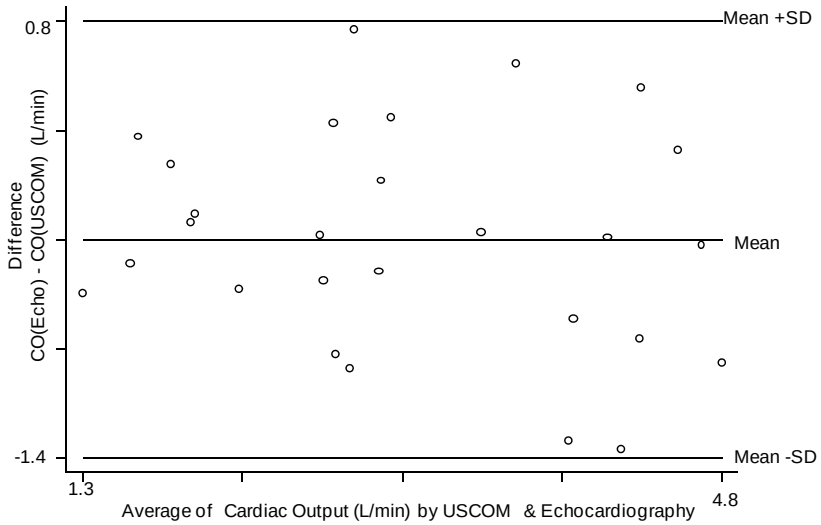
There were 27 paired echocardiography and USCOM measurements obtained from 27 patients. Variables that were compared between the two devices/methods included cardiac output (CO), cardiac index (CI), and stroke volume index (SVI). Agreement between the two instruments was assessed using Bland-Altman plot and Pitman's test of difference in variance. Bland-Altman plot is the difference of paired variables versus their average, and horizontal lines show the reference range (±2 standard deviations or 95% confidence interval) for the difference. In this case, the x axis shows the mean of the parameters (CO, CI or SV) measured by the two methods (echocardiography + USCOM)/2), whereas the y axis represents the absolute difference between the two methods ([Echo-USCOM]). For the purposes of this investigation if the USCOM agrees sufficiently well with the established method (echocardiography), this could be used reliably to estimate the parameters under investigation. Pitman's test examines equality and a significant correlation (r) is based on calculating the correlation between the difference and the mean (of the two measurements using two different devices). If one exists ($p<0.05$), this is evidence that the variances are not the same and

indicates poor agreement. Correlation may be positive or negative. A coefficient near zero implies concordance.

5.1.1.1. Cardiac output

There was good agreement in measurement of CO using echocardiogram and USCOM devices. Bland-Altman plot showed all the differences in measurements obtained using the two devices lay within ±2 standard deviations from the mean (Figure 5.1). CO by USCOM was higher than that by echocardiography on average; mean difference (CO_{echo} minus CO_{USCOM}) between the two measurements was -0.3L/min (95% CI; -0.5 to -0.1 L/min). Limits of agreement (± 2 standard deviations) were -1.4 and 0.8 L/min, respectively. Pitman's test of difference in variance showed a negative correlation (r = -0.181) and good agreement between the two instruments (p = 0.381), i.e., non-significant p-value.

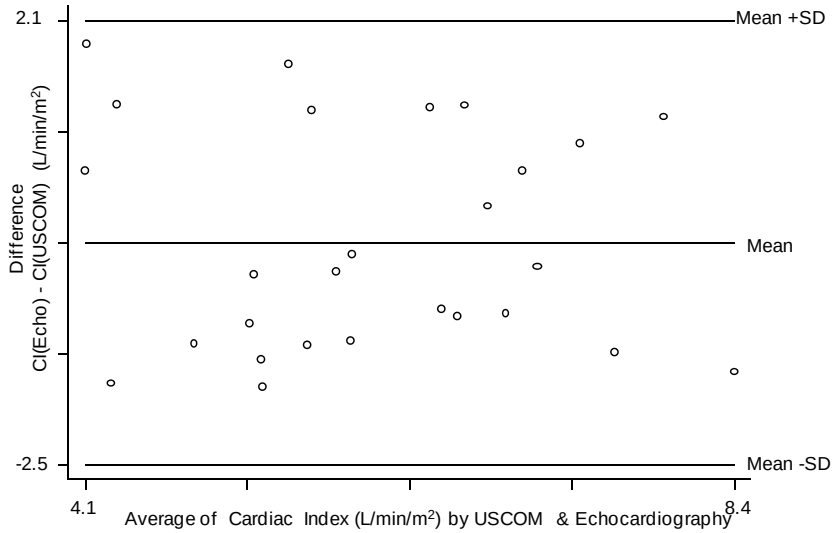
Figure 5-1: Bland-Altman plot comparing cardiac output readings obtained by echocardiography and USCOM



5.1.1.1. Cardiac index

All differences in cardiac index (CI) measurements obtained by the two devices fell within ±2 standard deviations (Figure 5.2). On average, CI measurements obtained by USCOM were higher than those obtained by echocardiography (mean difference-(CI_{echo} minus CI_{USCOM}) - was -0.2L/min/m^2 (95% CI; -0.7 to 0.2 /min/m^2). Limits of agreement (±2SD) were -2.5 to 2.1L/min/m^2. Pitman's test showed minimal difference with a moderately negative correlation (r = -0.065) suggesting a very good agreement between measurements obtained by the two device (p = 0.748).

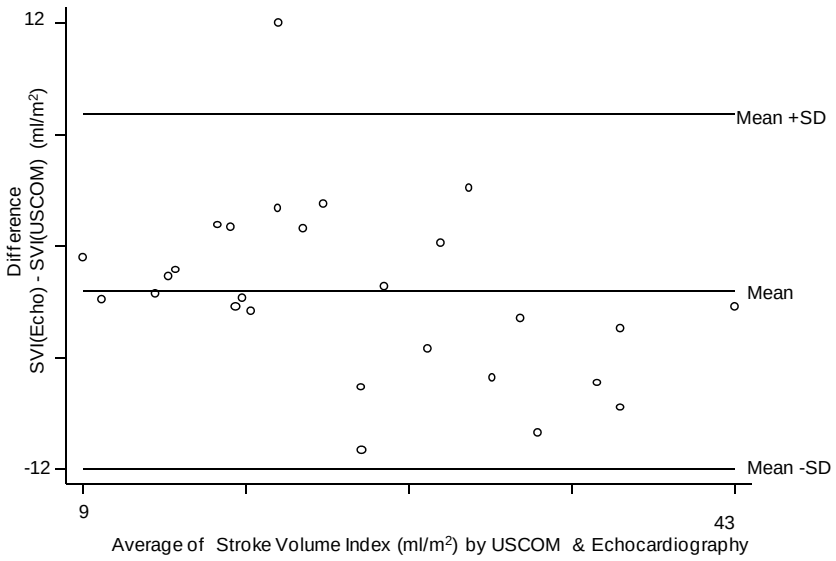
Figure 5-2: Bland-Altman plot analysis comparing cardiac index readings obtained by echocardiography and USCOM



5.1.1.2. Stroke volume index

At lower values SVI, USCOM measurements tended to be higher than echocardiography measurements but the reverse pattern was seen at high SVI values (Figure 5.3). There was one measurement at lower SVI value that was an outlier and tended to skew the overall relationship. All the rest of the measures the differences lay within ±2 standard deviations. The reference range for the difference (±2SD) was from 12 to 7ml/min. The mean difference-(SVI_{echo} minus SVI_{USCOM}) -was -2.7ml/min (95% CI; -4.6 to -0.8), demonstrating higher SVI values obtained by USCOM compared to echocardiography. Pitman's test of difference in variance also showed a negative correlation (r = -0.399) and only moderate agreement (p = 0.076).

Figure 5-3: Bland-Altman plot analysis comparing cardiac output readings obtained by echocardiography and USCOM



5.1.1.3. Conclusion

USCOM and echocardiography techniques showed good agreement in measurement of cardiac output and cardiac index but SVI measurement by the two methods showed moderate to poor correlation (agreement). Therefore caution should be exercised in interpretation of absolute SVI values obtained using USCOM.

5.2. HAEMODYNAMIC PROFILES IN SEVERE ILLNESS

A total of 166 children were enrolled: 24 were non-severe without impaired perfusion (NS), 35 were non-severe with impaired perfusion (NSIMP), 53 were severe without impaired perfusion (S), and 54 had severe disease with impaired perfusion (SIMP)-Table 5.1. Although the intention was to recruit 175 children (NS-25, NSIMP-50, S=50, and SIMP-50), some of the participants who were flagged in the non-severe group resisted attempts to conduct USCOM measurements since they were wide awake hence the procedure was abandoned.

Table 5-1: Definitions of disease severity

- **Severe disease group**
  - With features of impaired perfusion as defined in the FEAST trial (SIMP)
  - Without features of impaired perfusion as defined in the FEAST trial (S)
- **Non-severe illness group**
  - With features of impaired perfusion as defined in the FEAST trial(NSIMP)
  - Without features of impaired perfusion as defined in the FEAST trial (NS)

Definitions:

- *Signs of impaired perfusion as defined in FEAST trial:* Any of the following clinical features; capillary refill > 2seconds, lower limb temperature gradient, weak radial pulse volume, and severe tachycardia (<12months: heart rate >180bpm; 12 months to 5years: heart rate >160bpm; or >5years: heart rate >140bpm).
- *Impaired consciousness:* Prostration (inability to sit if aged ≥9 months or inability to breastfeed if <9 months); coma(inability to localise painful stimulus or Blantyre coma score (BCS) ≤2)

Abnormal values of various parameters were defined using the upper and lower cut-offs for normal values as provided by Smith[300] (Table 5.2); for example, low CI was defined as a value below the lower limit for normal and high CI defined as value above upper limit of normal. A study by Cattermole *et al*[193] in schools and Kindergarten in Hong Kong to establish normal ranges for USCOM has recently been published and reported slightly different normal ranges. However generalisability of the findings by Cattermole will only be known after similar studies are conducted in other populations.

Haemodynamic indices obtained are described as high or low if they fall above upper limit or below lower limit of normal, respectively (Table 5.2). High or low values are both classified as abnormal.

Table 5-2: Normal values of USCOM haemodynamic measurements

Age (in years)	0-2	2-5	5-10	10-16
SV(ml/kg)	1.5-2.25	1.5-2.4	1.25-2.2	1.25-1.75
SVI(ml/m^2)	36-45	40-55	40-60	40-60
CO(L/min)	2.5-3.5	2.5-4	2.8-5	3.5-7.5
CI(L/min/m^2)	4.2-5.5	3.5-5	3.5-5	3.2-4.8
SVR(d.s.cm^{-5})	1500-2000	1500-2000	1200-1800	900-1500
SVR(d.s.$cm^{-5}m^2$)	800-1200	1000-1600	1000-2000	1100-2300
Inotropy index/SMII(W/m^2)	1.1-1.5	1.3-1.8	1.5-2.0	1.7-2.3

SV=stroke volume; SVI= stroke volume index; CO=cardiac output; SVR=systemic vascular resistance; SVRI= systemic vascular resistance index; SMII=Smith-Madigan Inotropy Index. References[300]; W/m^2=Watts per m^2; d.s.=dynes per second

5.2.1. Baseline characteristics

5.2.1.1. Clinical features

Overall, 50% [83/166] of the participants were female, median age was 19 months [IQR 7,38], median MUAC was 13.5cm[IQR 12, 14.6], 14% had malnutrition (MUAC<11.5cm), 69% had fever (axillary temperature ≥37.5°C), and 2%[4] had hypothermia (axillary temperature <36.0°C). Over 50% of participants had chest indrawing or deep breathing and 47% had severe tachycardia. Hypoxia (pulse oximetry <95% on air), tachypnoea (>60breaths/minute), sunken eyes, and coma were present in over 10% of the participants and prostration was present in 8% of participants. Nine (5.4%) participants had capillary refill time > 2 seconds, seven (4.2%) had weak pulse volume and none had bounding pulse or bradycardia. Overall mortality was 9% [15/166]. Six percent (10/166) of participants had shock defined by derived shock definition, 32% (53/166) by FEAST definition, 22% (36/166) by ACCM/PALS definition, and 0.6% (1/166) by WHO definition. Clinical features of shock (delayed capillary refill time, severe tachycardia, weak pulse volume, and temperature gradient) were only present in the subgroups with features of shock (NSIMP and SIMP) (Table 5.3).

Severe disease subgroup

Subgroup analysis of participants with severe disease (S and SIMP groups) comparing S and SIMP groups showed no differences in sex, age, nutritional status, or severity features of hypothermia, respiratory distress (indrawing/deep breathing), dehydration (reduced skin turgor or sunken eyes), or coma (BCS≤2) between the two groups (Table 5.3). However, participants with features of shock (SIMP) had significantly higher respiratory rates, proportions with hypoxia and prostration (inability to sit unsupported if previously sitting and aged >8 months, or inability to feed if aged ≤8months).

Non-severe disease group

There were significantly more females and a higher proportion with tachypnoea in participants with features of shock (NSIMP) compared to those without features of shock (NS). Participants in the two groups otherwise had similar age, nutritional status, oxygen saturations, and hydration status. All three deaths in the non-severe sub-group were in those with features of shock. The NS group had significantly less females as compared to the other groups.

Severe versus non-severe disease groups

As expected, the study groups were imbalanced in terms of disease severity as participants with severe disease (S and SIMP) had more severe features compared to non-severe group (NS and NSIMP). Participants with severe disease were significantly younger, had more females (due to the few females in NS group) than those without (NS and NSIMP).

5.2.1.2. Clinical diagnoses

Clinical diagnoses indicated by admitting clinicians are outlines in Table 5.4. Majority of the participants had a syndromic diagnosis of lower respiratory tract infection (LRTI) followed by malaria (P. falciparum slide positive), gastroenteritis (>3 loose motions/day), and malnutrition (MUAC<11.5cm or oedema) respectively. LRTI diagnosis was non-specific as it was defined as cough plus tachypnoea (LRTI), plus chest indrawing (severe LRTI), or plus any of coma, prostration, cyanosis, cyanosis (very severe LRTI)[8]. Therefore many participants with other diagnoses were probably classified as having LRTI.

Table 5-3: Baseline clinical features for participants

Feature	Overall (N=166)	Non-severe n[%]	N) (n=22)	NSIMP (n=36)	p-value	Severe n[%]	S (n=50)	SIMP (n=58)	p-value	Overall Chi^2 test for trend/ F-value	p-Value
Female sex , n[%]	83[50]	20[34]	4[18]	16[44]	0.05	45[42]	26[52]	37[63]	0.22	12.4	0.0004
Age (months), median [IQR]	19[7,38]	25[15,42]	30[15,39]	23[14,34]	0.17	13[5,36]	12[5,36]	13[6,32]	0.82	6.8	0.08
MUAC(cm), mean[SD]	13.5[1.9]	13.7[2.0]	14.3[1.9]	13.4[1.9]	0.08	13.3[1.9]	13.2[1.6]	13.5[2.1]	0.42	1.9	0.14
MUAC <11.5cm	23[14]	6[10]	2[9]	4[11]	1.00	17[16]	7[14]	10[17]	0.79	1.2	0.28
Median MUAC [IQR]	13.5[12,14.6]	13.9[12,15]	14.5[13,15.2]	13.5[12,14.8]	0.08	13.5[12,14.2]	13.5[12.2,14]	13.5[12,14.8]	0.45	0.6	0.45
Fever (≥37.5°C)	114[69]	43[74]	13[59]	30[83]	0.03	71[66]	27[54]	44[76]	0.01	0.3	0.59
Hypothermia(<36.0°C)	4[2]	2[3]	1[5]	1[3]	1.00	2[2]	0[0]	2[3]	0.50	0.1	0.82
History of fever	153[92]	55[95]	20[91]	35[97]	0.55	98[91]	46[92]	52[90]	1.00	0.2	0.63
Airway											
Oxygen saturations <95% in air, n[%]	25[15]	3[5]	0	3[8]	0.28	22[20]	6[12]	16[28]	0.06	11.6	0.0007
Breathing											
Indrawing, n[%]	106[64]	0	0	0	-	106[98]	50[100]	56[97]	1.00	121.9	<0.001
Deep breathing ,n[%]	106[64]	0	0	0	-	106[98]	50[100]	56[97]	1.00	121.9	<0.001
Respiratory rate, mean[SD]	49[15]	44[15]	36[11]	49[14]	0.0008	51[14]	48[13]	55[15]	0.01	9.9	<0.001
Severe tachypnoea (>60bpm), n[%]	34[20]	9[16]	0	9[25]	0.01	25[23]	8[16]	17[29]	0.12	5.3	0.02
Circulation											
Capillary refill time>2s	9[5]	2[3]	0	2[6]	0.52	7[6]	0	7[12]	0.01	4.2	0.04
Capillary refill time>3s	1[0.6]	0	0	0	-	1[1]	0	1	1.00	1.2	0.28
Severe tachycardia	77[47]	29[50]	0	29[85]	<0.001	48[44]	0	48[84]	<0.001	18.9	<0.001
Bradycardia	0[0]		-	-	-		-	-	-	-	-
Temperature gradient	14[9]	2[3]	0	2[6]	0.53	11[12]	0	12[21]	<0.001	10.0	0.001
Weak radial pulse volume	7[4]	1[2]	0	1[3]	1.00	6[6]	0	6[10]	0.03	4.9	0.03
Bounding pulse	0										
Dehydration											
Reduced skin turgor	12[7]	2[3]	1[5]	1[3]	1.00	10[9]	2[4]	8[14]	0.10	3.7	0.05
Sunken eyes	18[11]	5[9]	2[9]	3[8]	1.00	13[12]	4[8]	9[16]	0.25	1.2	0.28
Disability											

Prostration	14[8]		0	0	-	14[13]	3[6]	11[19]	0.05	12.1	0.0005
Coma	18[11]		0	0	-	18[17]	8[16]	10[18]	1.00	9.0	0.003
Death	15[9]	3[5]	0	3[8]	0.29	12[11]	6[12]	6[10]	1.00	1.6	0.21
Shock Definitions											
WHO shock	1[0.6]	0	0	0	-	1[1]	0	1[2]	1.00	1.2	0.28
Derived shock	10[6]	2[3]	0	2[6]	0.52	8[7]	0	8[14]	0.007	5.3	0.02
FEAST shock*	53[32]	0	0	0	-	58[100]	0	58[100]	-	-	-
ACCM/PALS shock	36[22]	2[3]	0	2[6]	0.52	34[31]	10[20]	24[41]	0.02	23.4	<0.001
No participant had bradycardia (<60bpm) or bounding pulse											

Table 5-4: Clinical syndromic diagnoses in study participants

Clinical diagnosis at diagnosis	Study group				
	NS	**NSIMP**	**S**	**SIMP**	**Total**
LRTI[1] syndrome	2	12	23	29	66
Malaria	2	8	6	12	28
Gastroenteritis	4	4	3	6	17
Malnutrition	2	6	4	4	16
Febrile convulsions	3	0	3	0	6
Anaemia	0	1	3	1	5
Cellulitis/pyomyositis	2	1	0	0	3
Meningitis	0	0	2	1	3
Septicaemia/sepsis	0	0	3	0	3
URTI	0	2	0	0	2
Asthma	0	0	1	1	2
Encephalopathy	0	0	1	1	2
Osteomyelitis	0	1	1	0	2
Unknown aetiology	3	0	0	0	2
Bronchiolitis	0	0	0	1	1
Congenital abnormalities	0	0	0	1	1
Epilepsy	1	0	0	0	1
Fever of unknown origin	1	0	0	0	1
Immunosuppression	0	0	0	1	1
Nephrotic syndrome	1	0	0	0	1
Sickle cell disease	0	1	0	0	1
Viral infection	1	0	0	0	1
Total	**22**	**36**	**50**	**58**	**166**

[1]lower respiratory tract infection

5.2.1.3. Laboratory measurements

Overall, 47% of participants had severe metabolic acidosis (base deficit >10mmol/L) and 30% had admission lactate>3.5mmol/L, two features of global tissue hypoperfusion. Renal perfusion was assessed using serum creatinine, urine osmolality and urea. Twelve percent of all participants had creatinine>80µmol/L, 33% had urine osmolality <400mOsm/L (an indicator of reduced renal urine concentration ability), and 21% had urea >6.5mmol/L (an indicator of reduced renal excretion of nitrogenous waste). One child had creatinine level >1000µmol/L (urea=5.92mg/dL, urine osmolality=237mOsm/L) and likely had chronic renal failure. Other markers of severity included hypoglycaemia (<3.0mmol/L) in 6% of participants, 19% had hyponatraemia (<130mmol/L), 7% had acidaemia (pH<7.2), and 5% had severe anaemia (Hb<5g/dL). No participant had urine osmolality >800mOsm/L, a sign of increased urine concentration. Details of the laboratory characteristics are presented in table 5.5.

Severe disease subgroup

In the severe disease subgroup 46% had base deficit >10mmol/L and 28% had lactate >3.5mmol/L. Markers of renal impairment were as follows; elevated creatinine (>80µmol/L) in 15%, reduced osmolality in 34%, and elevated urea in 24% of participants. Other markers of disease severity were also not much different from that of the overall group; hypoglycaemia in 6%, hyponatraemia in 15%, hypokalaemia in 15%, acidaemia in 9% and severe anaemia in 8% of participants. Although there higher proportions of participants with hypoglycaemia and elevated urea among participants without features of shock (S group) compared to those with features of shock (SIMP group), these were not significant. Other markers of disease severity, renal function, and global tissue perfusion were similar between the two subgroups.

Non-severe disease sub-group

Proportions with markers of tissue hypoperfusion, renal impairment, and disease severity were comparable to the severe disease category; base deficit >10mmol/L (49%), lactate >3.5mmol/L (35%), elevated creatinine (2%), reduced urine osmolality (30%), elevated urea (16%), hypoglycaemia (6%), hyponatraemia (26%), hypokalaemia (18%), acidaemia (2%), and severe anaemia (5%). Participants in the subgroup with features of shock (NSIMP) were more acidaemic, had larger base deficit, higher proportion had elevated lactate or hypoglycaemia compared to those without features of shock but these differences were not significant. Markers of renal function and electrolyte abnormalities were similar between the two groups.

Severe disease versus non severe disease

Surprisingly, there were no significant differences in the proportions with markers of tissue hypoperfusion (acidosis), renal impairment, electrolyte disturbances, or other features of disease severity between participants with severe disease and those with non-severe disease. Severe disease sub-group though had higher proportions with elevated urea, elevated creatinine, and acidaemia (reduced pH). The lack of differences in the two subgroups is attributable to two possible reasons; the presence of the subgroups with features of shock in the non-severe disease category, and the small number of participants. For example, no patient in NS group had hypoglycaemia but the overall comparison showed no difference because of those with hypoglycaemia in the NSIMP subgroup. Paradoxically, hyponatraemia was more common in participants with non-severe disease compared to severe disease with the difference mainly due to the high proportions in the NSIMP group. Hyponatraemia could be a result of inappropriate anti-diuretic hormone (ADH) release in cases with LRTI syndrome. Hyponatraemia is relatively common in children admitted to hospital in tropical countries and it has been suggested that the commonest cause is ADH release[301], however studies in India[302] and Kilifi[303 304] suggest that moderate hyponatraemia were associated with signs of hypovolaemia rather than dilution secondary to water overload.

Table 5-5: Baseline laboratory measurements for participants

Feature	Overall (N=166)	Non-severe NS (n=22)	NSIMP (n=36)	p-value	Severe S (n=50)	SIMP (n=58)	p-value	Overall Chi^2 test for trend/ F-value	p-Value
Acid/Base									
pH	7.35[0.09]	7.38[0.07]	7.35[0.09]	0.26	7.34[0.09]	7.35[0.11]	0.64	0.5	0.70
pH<7.2	9/128[7]	0/14[0]	1/27[4]	1.00	3/38[8]	5/49[10]	1.00	2.3	0.13
Base deficit (mmol/L)	11[6]	10[5]	11[7]	0.72	11[6]	11[6]	0.70	0.1	0.94
Base deficit >10mmol/L	60/128[47]	5/14[36]	15/27[56]	0.23	16/38[42]	24/49[49]	0.52	0.1	0.75
Lactate (mmol/L)	3.3[2.3]	2.8[1.4]	4.1[3.2]	0.14	2.9[1.9]	3.2[2.1]	0.44	1.8	0.14
Lactate >3.5mmol/L	40/142[30]	5/17[29]	12/31[39]	0.52	11/42[26]	15/52[29]	0.78	0.3	0.59
Bicarbonate (mmol/L)	15[5]	15[4]	14[4]	0.58	15[5]	14[5]	0.47	0.3	0.84
Renal function									
Creatinine (µmol/L)	81[132]	47[13]	75[112]	0.37	83[94]	95[182]	0.74	0.4	0.72
Creatinine >80µmol/L	13/109[12]	0/13[0]	2/14[8]	0.53	6/13[19]	5/41[12]	0.40	1.4	0.25
Urine osmolality (mmol/L)	528[270]	519[331]	622[252]	0.30	478[274]	510[252]	0.62	1.4	0.26
Urine osmolality <400 mOsm/L	35/107[33]	6/13[46]	5/24[21]	0.14	12/30[40]	12[30]	0.45	0.1	0.73
Urine osmolality >1200 mOsm/L	0/107[0]								
Urea (mmol/L)	5.6[5.0]	4.3[2.6]	6.2[6.5]	0.32	6.4[5.1]	5.0[4.5]	0.27	0.8	0.51
Urea >6.5 mmol/L	22/104[21]	3/13[23]	3/24[13]	0.64	10/29[34]	6/38[16]	0.09	0.01	0.92
Electrolytes									
Serum sodium (mmol/L)	133[10]	133[7]	132[5]	0.81	132[17]	135[5]	0.27	0.6	0.60
Hyponatraemia (<130mmol/L)	19/101[19]	1/11[9]	8/23[35]	0.21	6/30[20]	4/37[19]	0.32	1.3	0.26
Serum potassium (mmol/L)	3.6[0.8]	3.6[0.6]	3.5[0.8]	0.91	3.6[0.9]	3.5[0.9]	0.48	0.2	0.91
Hypokalaemia (<3.0mmo/L)	16/100[16]	2/11[18]	4/23[17]	1.00	4/29[14]	6/37[16]	1.00	0.1	0.85
Severity features									
Blood sugar (mmol)	5.8[2.2]	5.3[1.8]	5.1[2.1]	0.76	6.4[2.7]	5.7[2.1]	0.12	2.4	0.07
Hypoglycaemia (<3.0mmol/L)	9/150[6]	0/18[0]	3/31[10]	0.29	5/47[11]	1/54[2]	0.09	0.2	0.68
Haemoglobin (g/dL)	8.8[2.3]	9.3[2.2]	8.5[2.5]	0.35	8.7[2.6]	8.9[1.9]	0.67	0.4	0.75
Severe anaemia (Hb<5g/dL)	8/116[7]	0/12[0]	2/26[8]	1.00	4/34[12]	2/44[5]	0.40	0.02	0.88

No child ha urine osmolality >1200mOsm/L

5.2.1.4. Haemodynamic indices

Mean cardiac index in all participants was 5.8[±1.4]L/min/m^2 with 69% (101/146) of participants who had a measurement at baseline having an abnormal cardiac index; 10% with low cardiac index and 60% with high cardiac index. Participants with clinical features of shock (SIMP and NSIMP) had significantly higher cardiac indices compared to participants without features of shock (NS and S). The clinical picture was one that principally displayed a pattern of a hyperdynamic circulation (Table 5.6). In the severe disease subgroup, children with features of shock had significantly higher mean cardiac index (p=0.04) and a higher proportion with high cardiac index compared to those without shock (67% versus 47%; odds ratio=2.2; p=0.04). A similar picture of hyperdynamic circulation was seen in participants with non-severe disease who had features of shock.

Mean stroke volume index (SVI) in all participants was 40[±12]ml/m^2 and 60% had SVI out of normal range, predominantly low SVI (46%). The proportion with low SVI was higher in those with severe disease when compared to those without (53% versus 32%; odds ratio=2.1[1.0, 4.4]; p=0.06). There was no difference in proportions with high SVI between those with and without severe disease (10% versus 12%; odds ratio=0.6[0.2, 1.6]; p=0.27). Comparing children with shock to non-shocked individuals, within the sub-groups of severity, the mean SVI and proportions with low or high SVI were similar for both groups.

Admission inotropy and SVRI

Low inotropy index (contractility) was found in 11% of participants at admission while 60% had high inotropy index. There were no differences in mean admission inotropy index between various disease severe groups (Table 5.6). Thirty-five percent of participants (52/149) had low SVRI (vasodilatation) and 18% had increased SVRI (vasoconstriction).

Table 5-6: Baseline haemodynamic indices for participants

Feature	Overall (N=166)	Non-severe NS (n=22)	NSIMP (n=36)	Odds ratio	p-value	Severe S (n=50)	SIMP (n=58)	Odd ratio	p-value	Overall Chi^2 test for trend	p-Value
Cardiac index											
Mean CI ($L/min/m^2$)	5.8[1.4]	5.7[1.7]	6.2[1.3]	-	0.25	5.4[1.3]	6.0[1.4]	-	0.04	2.6	0.06
Abnormal CI, n [%]	101/146[69]	11/20[55]	22/31[71]	2.0[0.6,6.6]	0.25	28/43[65]	40/52[77]	1.8[0.7,4.4]	0.21	2.4	0.12
Low CI, n [%]	14/146[10]	1/20[5]	0/31[0]	0.0	0.34	8/43[19]	5/52[10]	0.7[0.2,3.1]	0.72		
High CI, n [%]	87/146[60]	10/20[50]	22/31[71]	2.1[0.6,7.5]	0.19	20/43[47]	35/52[67]	2.2[0.8,5.7]	0.04		
Stroke volume index											
Mean SVI (ml/m^2)	40[12]	45[14]	43[12]		0.68	38[11]	38[10]		0.96	3.0	0.03
Abnormal SVI, n [%]	90/149[60]	13/20[65]	16/33[48]	0.5[0.2,1.6]	0.25	28/43[65]	33/53[62]	0.9[0.4,2.1]	0.77	0.2	0.62
Low SVI, n [%]	68/149[46]	7/20[35]	10/30[30]	0.6[0.2,2.2]	0.43	22/43[51]	29/53[55]	1.0[0.4,2.4]	0.98		
High SVI, n [%]	22[15]	6/20[39]	6/33[18]	0.4[0.1,1.8]	0.23	6/43[14]	4/53[8]	0.5[0.1,2.2]	0.34		
Inotropy index (INI)											
Mean INI (W/m^2)	1.83[0.65]	1.86[0.83]	1.99[0.61]		0.51	1.67[0.43]	1.84[0.72]		0.18	1.5	0.21
Abnormal INI, n [%]	108/150[72]	12/20[60]	22/33[67]	1.3[0.4,4.3]	0.63	34/43[79]	40/54[74]	0.8[0.3,2.0]	0.57	1.8	0.18
Low INI, n [%]	17/149[11]	3/20[15]	0/33[0]	0.0	0.07	7/43[16]	7/53[13]	0.6[0.2,2.5]	0.52		
High INI, n [%]	90/149[60]	9/20[45]	22/33[67]	1.8[0.5,6.0]	0.35	27/43[63]	32/53[60]	0.8[0.3,2.0]	0.59		
SVRI											
Mean SVRI ($d.s.cm^{-5}m^2$)	1031[383]	1032[309]	914[257]		0.14	1155[512]	1004[331]		0.08	2.7	0.05
Abnormal SVRI, n [%]	80/150[53]	11/20[55]	19/33[58]	1.1[0.4,3.4]	0.86	27/43[63]	23/54[43]	0.4[0.2,1.0]	0.05	1.5	0.22
Low SVRI, n [%]	52/149[35]	7/20[35]	16/33[48]	1.5[0.4,5.1]	0.54	12/43[28]	17/53[32]	0.7[0.3,1.9]	0.52		
High SVRI, n [%]	27/149[18]	4/20[20]	3/33[9]	0.5[0.1,2.8]	0.41	15/43[35]	5/53[9]	0.2[0.1,0.6]	0.002		

Odds ratios adjusted for sex and age

Effect of dehydration on haemodynamic indices

Ten percent (17/166) of participants had a diagnosis of gastroenteritis; 4(18%) in NS, 4(11%) in NSIMP, 3(6%) in S, and 6(10%) in SIMP groups. Overall mean cardiac index in participants with gastroenteritis (5.3±1.8 L/min/m^2) was lower than in those with without (5.9±1.4 L/min/m^2), (p=0.10) as was heart rate (141±23bpm versus 152±24bpm, p=0.07). However, the SVI was similar in participants with gastroenteritis (39±15 ml/m^2) when compared to those without (40±11 ml/m^2), p=0.54. Proportions with axillary temperature >38.5°C were also similar between the two groups, 24% in participants with gastroenteritis and in 26% in those without (p=0.52). Sixty percent (10/17) of participants with gastroenteritis had low SVI at admission. Eighteen percent (3/17) had low CI at admission while 35% (6/17) had high CI. One child with gastroenteritis died and the child had low SVI and low CI.

In the sub-group with severe disease (S and SIMP combined), both CI and SVI were significantly lower in participants with gastroenteritis when compared to those without; CI (4.6±1.0 versus 5.8 ±1.4 L/min/m^2, p=0.02, respectively) and SVI (33±7 versus 39±11 ml/m^2, p=0.14, respectively). Mean heart rates were lower for those with gastroenteritis (143±25bpm versus 155±24bpm, p=0.18). Both SVI and CI were also lower for participants with gastroenteritis compared to those without in both S and SIMP sub-groups (not shown).

However in the sub-group without severe disease (NS and NSIMP combined) CI and SVI were similar between participants with gastroenteritis when compared to those without; mean cardiac index were 5.9±2.3 L/min/m^2 in participants with gastroenteritis and 6.1 ±1.3 L/min/m^2 in those without, p=0.77.

Participants with dehydration and features of severe disease with or without clinical features of shock therefore have reduced stroke volume which is consistent with hypovolaemia. This is however not seen in those without severe disease. The lower mean cardiac index and lower mean heart rates in those with severe disease and dehydration (gastroenteritis) indicated inadequate compensation for the reduced preload in these patients.

Haemodynamic indices in participants with malaria

Seventeen percent (28/166) of participants had malaria; 2(8%) in NS, 8(23%) in NSIMP, 8(15%) in S, and 10 (19%) in SIMP groups. The overall mean cardiac index at admission in malaria patients was 6.9±1.3L/min/m^2, and was significantly higher compared to those without malaria, 5.6±1.4L/min/m^2, p<0.001. Mean cardiac index was still significantly higher

in the subgroup of malaria patients with severe disease and in the SIMP sub-group compared to non-malaria patients in those two sub-groups. Similar pattern was seen in mean admission SVI, 45±11ml/m^2 in malaria patients versus 37±10ml/m^2 in non-malaria patients, p=0.004. Mean SVI was similarly significantly higher in malaria patients with severe disease and SIMP groups compared to non-malaria patients.

Six (21%) participants with malaria died out of which 5(83%) had a combination of elevated cardiac index and low SVRI. However, only 2 (33%) of the deaths were in those with concurrent low SVI. Four (67%) of the deaths were in those categorised as S or SIMP groups while 2(33%) were in the NSIMP group.

When malaria patients were further divided into subgroups based on acidosis, participants with acidosis (base deficit>10mmol/L) and those without (base deficit≤10mmol/L) had similar cardiac indices, 6.8±1.4L/min/m^2 versus 6.8±1.3L/min/m^2, p=0.99. However participants with acidosis had lower mean SVI, 41±9ml/m^2, compared to those without, 48±12ml/m^2, p=0.13. The similarity in cardiac indices seen in this study suggests compensation by tachycardia for acidotic cases with reduced SVI. This compensatory tachycardia was confirmed by a higher mean heart rates in malaria patients with acidosis, 170±27 beats/minute, compared to 143±19 beats/minute in non-acidotic cases (p=0.02). Similar findings were reported in adults with severe malaria[305].

Although non-significant, the finding of low SVI in acidotic patients is in agreement with earlier findings of low cardiac output in children with malaria and severe acidosis[21]. However, hypovolaemia is not the only mechanism for tissue hypoperfusion in severe malaria because sequestration of infected red blood cells which plays a major role in the pathogenesis of malaria. Sequestration in capillaries and post-capillary venules results from interaction between molecules expressed on the surface of infected red cells and vascular endothelial receptors. Sequestered has been observed in vital organs such as brain during severe malaria and the proportion of capillaries with sequestration has been shown to correlate with base deficit and lactate in adult malaria[306]. Reduced red cell deformability and rosetting may also contribute to impairment of microcirculation in severe malaria[307]. These other mechanisms do not contribute to tissue hypoperfusion in sepsis and are unique to malaria. The finding of reduced SVI (hypovolaemia) in this study should therefore be seen as additional to the mechanisms unique to malaria. Furthermore hypovolaemia may augment these mechanisms.

Summary of haemodynamic findings at admission

In summary the majority of children with clinical features of impaired perfusion had evidence of hyperdynamic circulation, with a higher proportion having a high cardiac index compared to those without, irrespective of severity. Participants with severe disease generally had lower stroke volume index compared to non-severe disease, irrespective of features of shock. The origin of the lower SVI may be due to any of four causes; reduced preload (venous return), increased afterload, impaired myocardial function (reduced contractility), or reduced compliance. Reduced preload may be caused by hypovolaemia secondary to gastroenteritis. The finding that participants with clinical features of shock (SIMP) have higher cardiac indices suggests compensation by increasing heart rates (tachycardia) which is one of the components of the calculation for cardiac index. Afterload (net force opposing left ventricular fibre shortening during ventricular ejection) can be inferred from clinical signs suggestive of centralisation of blood volume and reduced flow to the peripheries through increased vascular tone. Alternatively, afterload can be measured by SVRI which calculates vasoconstriction (elevated SVRI) in case of increased afterload and vasodilatation (reduced SVRI) in case of reduced decreased afterload.

This study also found low prevalence of clinical signs supportive of increased afterload such as prolonged capillary refill time and temperature gradient. Additionally, although imperfect, prevalence of high systemic vascular resistance (SVRI) at admission was 9% (5/53) in SIMP group compared to 35% (15/43) of the S group, odds ratio 0.2[0.1, 06.0, p=0.002. Reduced SVRI point to vasodilatation and reduced rather than increased afterload. The SVRI measurements should be cautiously interpreted because the algorithm for its calculation assumes a default central venous pressure (CVP) reading of zero when CVP value is not entered. The design of present study did not allow for CVP measurement. The USCOM device does not measure compliance and the recently introduced measure for contractility (inotropy index) requires CVP measurement for accurate reading and has also not been validated. However, since there was a systemic bias to all measurement at admission only limited inference can be made from the findings between the groups. The findings of lower SVI and the absence of clear alternative explanations suggest that myocardial dysfunction (contractility) cannot be ruled out in those with severe disease without gastroenteritis. An alternative explanation for reduced SVI could be dehydration but the proportions with gastroenteritis were similar in the different study groups (Table 5.6). Myocardial dysfunction is however more usually accompanied by low CI and the high values in patients with features of shock make this unlikely. Low prevalence of low inotropy index also supports this finding.

5.2.2. Haemodynamic indices in participants with various shock features

Derived shock and delayed capillary refill time

Only 10 (6%) and 9 (5%) of participants had derived shock definition and delayed capillary refill time (dCRT) (>2 seconds), respectively, therefore no definitive conclusions or assertions can be made from the haemodynamic findings due to the small numbers. There were no differences in the mean cardiac indices or SVIs between participants with normal capillary refill time (nCRT) and dCRT (Table 5.7). Mean CIs were 5.8±1.8L/min/m^2 and 5.8±1.4L/min/m^2, mean SVIs were 41±11ml/m^2 and 40±12 ml/m^2, for participants with and without derived shock respectively.

There was no association between dCRT and high CI (crude OR=0.8[0.1, 4.9]) but there was trend towards increased odds of having dCRT in participants with low CI (crude OR=1.7[0.1, 20.0]). This is consistent with reduced CI accompanied by compensatory vasoconstriction which also results in increased afterload leading to fall in stroke volume and consequent fall cardiac output/index. There was also no association between derived shock and high CI (crude OR=1.0[0.1, 5.9]) but a trend towards increased odds of derived shock in participants with low CI (crude OR=1.7[0.1, 20.0]). The main component of derived shock definition is dCRT and similar explanations advanced above apply. There was also a trend towards increased odds of dCRT or derived shock in participants with cold shock (low CI + high SVRI) (Table 5.8).

Severe tachycardia

Forty sex percent (77/166) of participants had severe tachycardia. Mean CI as expected was higher among participants with severe tachycardia (6.1±1.3L/min/m^2 versus 5.5 L/min/m^2, p=0.004) but the mean SVI were similar in the two groups, 40±11ml/m^2 and 40±12ml/m^2, for tachycardic and non-tachycardic groups respectively. It was also non-significantly associated with low SVRI (vasodilatation), odds ratio=3.3[0.5, 22]. Forty three percent (33/77) of participants with tachycardia had axillary temperature >38.5°C compared to 11% (10/89) in those with axillary temperature ≤38.5°C (risk ratio=2.1, chi^2=21.5, p<0.001). The association of tachycardia with fever may explain why it is a poor indicator of haemodynamics.

Temperature gradient

Only 8% (14/166) had a palpable temperature gradient. Mean CI was higher in participants with palpable temperature gradient than those without, 6.5±1.5L/min/m^2 versus 5.7±1.4, p=0.08. Mean SVI was however similar in the two groups, 42±10ml/m^2 versus 40ml/m^2 in

participants with temperature gradient than those without, respectively. Positive temperature gradient was non-significantly associated with both low and high CI (Table 5.7).

Weak pulse volume

Was present in 4% (7/166) of participants and all of them had delayed CRT therefore the findings are essentially line those of delayed CRT.

5.2.3. Haemodynamic indices at admission in participants with various shock definitions

Haemodynamic indices in participants with FEAST signs of shock

Participants fulfilling the FEAST definition of shock demonstrated a pattern of hyperdynamic circulation (high cardiac indices) and were more likely to have high cardiac indices when compared to those without FEAST shock (crude odds ratio=2.2[1.0, 5.2]; adjusted odds ratio=2.8[1.0, 7.4], 0.04). Those with FEAST signs of shock were also less likely to have elevated SVRI, therefore unlikely to have increased afterload (Table 5.6).

Table 5-7: Association between haemodynamic indices and FEAST shock

	FEAST shock				Adjusted OR	
	Present [n=54]	**Absent [n=112]**	**p-value**	**Crude OR**	**Adjusted OR**	**p-value**
Cardiac index						
Mean	6.1[1.3]	5.7[1.5]	0.07			
Abnormal CI	38/48[79]	63/98[64]		2.1[0.9,4.8]	2.2[0.8,5.5]	0.10
Low CI, n [%]	4/48[8]	10/98[10]		1.4[0.4,5.5]	0.8[0.1,3.2]	0.70
High CI, n [%]	34/48[71]	53/98[54]		2.2[1.0,5.2]	2.8[1.0, 7.4]	0.04
SVI						
Mean	39[10]	41[12]	0.26			
Abnormal SVI	31/49[63]	59/100[59]		1.2[0.6,2.4]	1.0[0.4,2.3]	0.95
Low SVI	27/49[55]	41/100[41]		1.5[0.7,3.2]	1.1[0.4,2.5]	0.89
High SVI	4/49[8]	18/100[18]		0.5[0.1,1.7]	0.6[0.1,2.6]	0.53
Inotropy index						
Mean	1.86[0.74]	1.81[0.60]	0.62			
Abnormal INI	39/50[78]	69/100[69]		1.6[0.7,3.5]	1.2[0.5,3.1]	0.68
Low INI	6/49[12]	11/100[11]		1.5[0.5,5.2]	0.8[0.2,3.2]	0.77
High INI	32/49[65]	58/100[58]		1.6[0.7,3.5]	1.3[0.5,3.4]	0.60
SVRI						
Mean	958[286]	1068[420]	0.10			
Abnormal SVRI	22/50[44]	58/100[58]		0.6[0.3,1.1]	0.5[0.2,1.2]	0.13
Low SVRI	17/49[35]	35/100[35]		0.7[0.3,1.6]	1.0[0.3,2.5]	0.93
High SVRI	4/49[8]	23/100[23]		0.3[0.1,0.9]	0.2[0.1,0.6]	0.003

Adjusted for disease severity

ACCM shock

Only 22% (36/166) had ACCM shock. Mean CI at admission in participants with ACCM shock was 6.3±1.6L/min/m^2 compared to 5.7±1.4 L/min/m^2 in those without (p=0.05) and mean SVIs at admission were 42±14mil/min and 40±11 mil/min, respectively (p=0.31). The risk of ACCM shock in participants with abnormal of CI was as follows; low CI, adjusted OR=1.8[0.3,

10.1] and high CI, adjusted OR=2.1[0.7, 6.1]. ACCM shock was however significantly associated with elevated SVI, adjusted OR=3.9[0.9, 16.9] but not with low SVI, adjusted OR=1.0[0.4, 2.7]. Elevated SVI seen in participants with shock according to ACCM guidelines could be secondary to reduced afterload (reduced vascular resistance). Diagnosis of shock in accordance with ACCM guidelines was also more likely in participants with a combination of high CI plus low SVRI (vasodilatation), adjusted OR=5.7[2.0, 16.3] but not in those with low CI plus elevated SVRI (vasoconstriction), adjusted OR=1.6[0.3, 8.0].

Inotropy index

Abnormal inotropy index (low or high) was not associated with derived shock, delayed CRT, or ACCM shock. Participants with FEAST shock had non-significant increased risk of having high inotropy index, OR=2.1[0.9, 4.8; p=0.07], but there was no association with low inotropy index, OR=1.5[0.5, 5.2; p=0.49].

5.2.4. Haemodynamic indices in participants in survivors and non-survivors

Fifteen (9%) participants died during the course of hospital admission; one (5%) in NS group, 3(8%) in NSIMP, 6(12%) in S, and 6 in SIMP groups. Mean CI, SVI and heart rates were similar in survivors and non-survivors (Table 5.7). Although the numbers were small, there was a trend to an increased risk of death in participants with low cardiac index (2/14, 14%), adjusted OR=4.3[0.4, 51.0]. Only six percent (5/86, 6%) of children with high CI died, adjusted OR=1.3[0.2, 7.5]. These findings suggest that inability to maintain cardiac output for any reason increase the risk factor for death. These include determinants of stroke volume (reduced preload, impaired contractility, reduced or increased afterload, or impaired compliance) or inability to increase heart rate. Abnormal cardiac index at any time in the course of admission was also weakly associated with increased risk of death; low CI, OR=3.3[0.8, 12.9; p=0.09], and high CI, OR=2.2[0.8, 6.0; p=0.12]. Low SVI at admission was also non-significantly associated with increased risk of death, adjusted OR=2.3[0.5, 11] which implies impairment of a determinant of stroke volume rather than heart rate. Vascular resistance at admission, as measured by SVRI which had doubtful accuracy, was not associated with risk of death. However, low SVRI at any time during the course of admission significantly increased the risk of death, OR=2.4[1.0, 5.7; p=0.05], but high SVRI was only weakly associated, OR=2.7[1.0, 7.6; p=0.07].

Table 5-8: Admission haemodynamic indices in participants with various shock features and outcomes

Haemodynamic parameter	Severe tachycardia			Temperature gradient			Delayed capillary refill time			Died		
	Yes =77	No =89	p-value	Yes=14	No =152	p-value	Yes=9	No =157	p-value	Yes =15	No =157	p-value
CO, mean[SD]	3.1[1.7]	2.6[1.3]	0.08	2.6[1.5]	1.9[1.5]	0.49	2.3[1.5]	2.9[1.5]	0.30	2.6[1.5]	1.9[1.5]	0.54
CI, mean[SD]	6.1[1.3]	5.5[1.5]	0.004	6.5[1.5]	5.7[1.4]	0.08	5.9[2.0]	5.8[1.4]	0.88	5.6[1.8]	5.8[1.4]	0.62
SVI, mean[SD]	40[11]	40[12]	0.82	42[10]	40[12]	0.66	41[13]	40[12]	0.78	36[11]	40[12]	0.26
Heart rate, mean[SD]	-	-	-	161[28]	164[26]	0.67	155[40]	164[25]	0.30	158[32]	164[26]	0.38
Abnormal indices			**Adjusted OR**			**Adjusted OR**			**Adjusted OR**			**Adjusted OR**
Low CI	3/14[21]	0.4[0.1,1.9]	0.1[0,2.8]	1/14[7]	3.3[0.2,59]	-	1/14[7]	1.7[0.1,20]	-	2/14[14]	3.6[0.4,30]	4.3[0.4,51]
High CI	49/84[58]	2.3[1.1,4.9]	2.3[0.5,9.8]	9/85[11]	5.1[0.4,42]	3.4[0.5,26]	3/86[3]	0.8[0.1,4.9]	-	5/86[6]	1.3[0.2,7.1]	1.3[0.2,7.5]
Low SVI	32/66[48]	0.8[0.4,1.7]	1.0[0.3,3.8]	4/67[6]	0.6[0.2,2.6]	0.5[0.1,2.3]	2/68[3]	0.8[0.1,6.3]	0.8[0.1,7.6]	6/68[9]	2.7[0.5,14]	2.3[0.5,11]
Low SVRI	27/48[56]	1.1[0.5,2.3]	3.3[0.5,22]	4/50[8]	1.1[0.3,4.5]	1.3[0.3,5.6]	2/51[4]	0.9[0.1,5.7]	0.9[0.1,6.2]	3/51[6]	1.0[0.2,4.9]	1.0[0.2,4.7]
High SVRI	6/27[22]	0.2[0.1,0.7]	0.6[0.1,3.2]	2/26[8]	1.1[0.2,6.0]	2.9[0.4,20]	1/27[4]	0.9[0.1,8.7]	2.0[0.2,22]	2/27[7]	1.3[0.2,7.7]	1.1[0.2,5.6]
Haemodynamic patterns												
High CI + Low SVRI	24/69[35]	1.5[0.7,3.2]	2.9[0.5,17]	4/11[36]	1.3[0.4,4.8]	1.4[0.3,5.4]	2/6[33]	1.1[0.2,6.4]	-	3/9[33]	1.1[0.3,4.7]	1.2[0.3,5.1]
Low CI + Low SVRI	-	-	-	-	-	-	-	-	-	-	--	
Low CI + High SVRI	2/69[3]	0.2[0,1.1]	0.2[0,3.3]	1/11[9]	1.2[0.1,11]	2.5[0.1,32]	1/6[17]	2.6[0.3,25]	7.5[0.5,120]	2/9[22]	4.0[0.7,23]	3.4[0.6,19]
Low SVI + Low SVRI	5/71[7]	5.5[0.6,50]	-	1/11[9]	1.8[0.2,17]	0.9[0.1,8.7]	0/6	-	-	1/9[11]	2.4[0.3,22]	3.3[0.3,41]
Low SVI + High SVRI	5/71[7]	0.2[0.1,0.6]	0.3[0.1,2.0]	2/11[18]	1.1[0.2,5.7]	2.9[0.4,20]	1/6[17]	1.0[0.1,8.9]	2.4[0.2,25]	2/9[22]	1.4[0.3,7.4]	1.2[0.2,5.7]
Low SVI + Low SVRI	5/71[7]	5.5[0.6,50]	-	1/11[9]	1.8[0.2,17]	0.9[0.1,8.7]	0/6			1/9[11]	2.4[0.3,22]	3.3[0.3,41]

5.2.5. Haemodynamic indices in participants with biochemical markers of impaired perfusion

Markers of global hypoperfusion (lactate, base deficit, acidaemia)

Abnormal values at admission were found in the following proportions of participants; elevated lactate-30% (43/142), elevated base deficit-47% (60/128), and acidaemia (pH<7.20)-7% (9/128). There were no differences in mean CIs and mean SVIs between participants with elevated markers of global hypoperfusion (elevated lactate, elevated base deficit, or acidaemia) and those without (Table 5.8).

Risk of having elevated lactate was more common in participants with low CI, adjusted OR=8.5[1.0, 72.0], and also with high CI, adjusted OR=2.0[0.7, 5.4], compared to those with normal lactate levels. Lactate levels were however not associated with alterations of SVI. The odds was increased in participants displaying both vasodilatation (low SVRI) and vasoconstriction (high SVRI), but predominantly in those with vasoconstriction (Table 5.8).

Elevated base deficit was not associated with any perturbations of CI or SVI. The few patients with low CI plus vasoconstriction (high SVRI) had some evidence of elevated base deficit, adjusted OR=1.9[0.4, 9.4].

There were very few participants with acidaemia therefore any trends or associations seen here should be interpreted cautiously. No participant with acidaemia had low cardiac index. There were however non-significant associations between high CI and acidaemia, adjusted OR=2.9[0.3, 29], and low SVI and acidaemia, adjusted OR=2.1[0.2, 20]. Both high and low vascular resistances were risk factors.

In general, there was poor relationship between peripheral clinical markers of shock (dCRT and temperature gradient) with either biochemical markers of tissue hypoperfusion or central perturbations. However numbers with abnormal clinical features were small and may have missed potential relationships. Nevertheless the study highlighted poor relationship between clinical signs of shock and the markers of tissue hypoperfusion. A previous study by Pamba *et al*[225] found that dCRT was only a prognostic marker when present in severe disease rather than when seen with single features of severity such as hypoxia and raised creatinine supporting the finding seen here.

Table 5-9: Haemodynamic indices in participants with various markers of impaired perfusion

Haemodynamic parameter	Lactate (N=142)			Base deficit (N=128)			pH(n=128)		
	Lactate >3.5(n=43)	Lactate ≤3.5 (n=99)	p-value	Base deficit >10 (n=60)	Base deficit ≤10 (n=68)	p-value	pH <7.2 (n=9)	pH ≥7.2 (n=119)	p-value
CO, mean[SD]	3.4[1.9]	2.7[1.3]	0.03	2.9[1.6]	2.9[1.4]	0.93	2.7[1.7]	2.9[1.5]	0.77
CI, mean[SD]	5.8[1.5]	5.8[1.3]	0.99	5.9[1.5]	5.7[1.4]	0.41	6.7[1.3]	5.8[1.4]	0.12
SVI, mean[SD]	42[14]	40[10]	0.42	40[12]	40[11]	0.77	44[14]	40[12]	0.38
Heart rate, mean[SD]	163[25]	164[28]	0.80	166[29]	160[25]	0.21	164[30]	162[27]	0.87
Abnormal indices	**n[%]**	**Crude OR**	**Adjusted OR**	**n[%]**	**Crude OR**	**Adjusted OR**	**n[%]**	**Crude OR**	**Adjusted OR**
Low CI	4/10[40]	3.4[0.7,17]	8.5[1,72]	4/9[44]	1.1[0.2,4.7]	1.0[0.2,5.1]	0/9	-	-
High CI	21/75[28]	2.0[0.7,5.6]	2.0[0.7,5.4]	31/67[46]	1.1[0.5,2.6]	1.1[0.5,2.5]	5/67[7]	2.7[0.3,25]	2.9[0.3,29]
Low SVI	14/53[26]	0.9[0.4,2.0]	0.9[0.4,2.3]	21/51[41]	0.8[0.3,1.7]	0.7[0.3,1.7]	3/51[6]	2.9[0.3,29]	2.1[0.2,20]
Low SVRI	16/45[36]	2.0[0.8,4.5]	1.8[0.8,4.2]	18/40[45]	0.9[0.4,2.1]	0.9[0.4,2.0]	3/40[8]	2.2[0.3,14]	2.7[0.3,21]
High SVRI	4/18[22]	1.0[0.3,3.5]	1.1[0.3,3.8]	7/17[41]	0.8[0.3,2.4]	1.2[0.3,4.0]	2/17[12]	3.7[0.5,29]	5.2[0.4,72]
Haemodynamic patterns			**Adjusted OR**			**Adjusted OR**			**Adjusted OR**
High CI + Low SVRI	13/31[42]	1.8[0.8,4.3]	1.7[0.7,4.0]	15/50[30]	0.9[0.4,2.1]	0.9[0.4,2.0]	2/6[33]	1.1[0.2,6.6]	1.4[0.2,8.4]
Low CI + Low SVRI	0/31	-	-	-	-	-	-	-	-
Low CI + High SVRI	3/31[10]	2.3[0.5,11]	2.9[0.6,15]	4/50[8]	1.7[0.4,8.0]	1.9[0.4,9.4]	0/6	-	-
Low SVI + Low SVRI	3/34[9]	2.1[0.4,10]	1.9[0.4,9.3]	2/52[4]	0.5[0.1,2.5]	0.4[0.1,2.2]	0/7	-	-
Low SVI + High SVRI	4/34[12]	0.9[0.3,3.0]	1.1[0.3,3.6]	6/52[12]	0.7[0.2,2.0]	0.8[0.2,2.5]	2/7	2.7[0.5,15]	2.9[0.4,20]

Markers of renal perfusion (creatinine, osmolality)

Only 12% (13/109) of participants had creatinine >80µmol/L and 33% (35/107) had urine osmolality <400mOsm/L (reduced renal urine concentrating ability). No differences in mean CIs or mean SVIs at admission were seen in participants with elevated creatinine compared to those with normal creatinine. There was increased risk of having elevated creatinine in participants with low SVI, adjusted OR=6.3[0.8, 46] but there was no association with abnormal cardiac indices (Table 5.9). Elevation in creatinine was not related to dehydration since 23% (3/13) of children with raised creatinine had gastroenteritis. This lack of association could have been a result of the small numbers of participants with elevated creatinine in this study. Participants with a combination of low stroke volume and vasodilatation were at increased risk of having elevated creatinine. Venous return may be reduce in cases of venous vasodilatation (peripheral pooling) resulting in reduced in stroke volume

Participants with reduced renal concentration of urine (low osmolality) had significantly lower mean cardiac index (and lower mean heart rate) compared to those with normal osmolality (Table 5.9). Hypodynamic circulation (low CI and low SVI) were also a risk factor for low osmolality. Loss of renal concentrating ability may be lost during pre-renal failure secondary to hypovolaemia. Increased renal losses when urine is poorly concentrated may also lead to further reduction in venous return resulting in reduced SVI and CI when there is no compensatory increase in heart rate. Therefore low osmolality may be indicative either a cause or effect of low cardiac output.

Elevated admission serum lactate was significantly associated with increased risk of death, odds ratio=9.6 [2.6, 34.9; p<0.001]. Elevated creatinine level was also associated with increased risk of death (odds ratio=4.0; 95% confidence interval 1.1, 17.0; p=0.03). There was no association between base deficit >10mmol/L and risk of death, odds ratio= 1.1 [0.4, 3.5; p=0.83]. There was also no association between reduced urine osmolality and survival/death.

Table 5-10: Haemodynamic indices in participants with various markers of renal perfusion

Haemodynamic parameter	Creatinine (N=109)			Urine osmolality (N=107)		
	Creatinine >80 (n=13)	Creatinine ≤80 (n=96)	p-value	Urine osmolality <400 (n=35)	Urine osmolality ≥400 (n=72}	p-value
CO, mean[SD]	2.8[1.5]	2.9[1.6]	0.80	2.4[1.6]	3.1[1.6]	0.08
CI, mean[SD]	6.1[1.3]	5.7[1.5]	0.30	5.2[1.7]	6.0[1.3]	0.02
SVI, mean[SD]	43[11]	40[12]	0.48	40[14]	40[10]	0.75
Heart rate, mean[SD]	162[23]	164[28]	0.89	153[28]	167[27]	0.01
Abnormal indices	**n[%]**	**Crude OR**	**Adjusted OR**	**n[%]**	**Crude OR**	**Adjusted, OR**
Low CI	1/9[11]	1.0[0.1,11]	1.0[0.1,14]	7/10[70]	3.8[0.7,20]	3.7[0.7,21]
High CI	9/60[15]	1.4[0.3,5.7]	1.4[0.3,5.5]	12/54[22]	0.5[0.2,1.3]	0.6[0.2,1.8]
Low SVI	7/41[17]	8.4[0.9,78]	6.3[0.8,46]	19/45[42]	2.6[0.2,7.0]	2.2[0.8,6.2]
Low SVRI	5/32[16]	2.0[0.4,8.2]	1.9[0.4,9.3]	10/32[31]	1.2[0.4,3.2]	1.3[0.5,3.5]
High SVRI	4/20[20]	2.7[0.6,12]	2.4[0.6,9.3]	9/17[53]	2.9[0.9,9.7]	2.8[0.8,10]
Haemodynamic patterns			**Adjusted OR**			**Adjusted OR**
High CI + Low SVRI	5/13[29]	1.5[0.5,5.2]	1.5[0.4,5.6]	6/30[20]	0.5[0.2,1.4]	0.6[0.2,1.7]
Low CI + Low SVRI	0/3	-	-	-	-	-
Low CI + High SVRI	1/13[8]	0.9[0.1,8.1]	0.7[0.1,5.5]	6/30[30]	7.6[1.3,44]	5.9[1.1,32]
Low SVI + Low SVRI	1/13[8]	3.5[0.3,43]	4.3[0.3,60]	3/32[9]	2.1[0.4,11]	2.4[0.4,16]
Low SVI + High SVRI	4/13[31]	2.3[0.6,8.6]	1.7[0.5,5.2]	9/32[28]	3.8[1.2,12]	3.5[1.0,13]

5.2.6. Haemodynamic patterns of participants at admission

Haemodynamic indices obtained can be used to give an indication of the particular pathophysiological abnormality during shock: low cardiac index indicates cardiogenic abnormality; low vascular resistance indicates abnormality in vascular tone, while elevation of either (CI or SVRI) demonstrates good compensatory response[181]. Cardiogenic abnormality comprises an abnormality in any of the components of cardiac output, that is, stroke volume and heart rate. Stroke volume is determined by venous return (preload), contractility, afterload (vascular resistance) and compliance (diastolic function). This study could not measure diastolic function. Cardiac index is dependent on compensatory changes in heart rate but stroke volume is independent of heart rate[159 169]. Stroke volume in adults in adults with septic shock is also maintained is some cases by ventricular dilatation which results in increased end-diastolic volume[159]. Studies in adults and an animal model of sepsis has shown better survival in animals that develop cardiac dilatation (increasing end-diastolic volume and preserving stroke volume) compared to those with non-compliant ventricles

(impaired diastolic function)[308-311]. Therefore adults may be able to maintain their stroke volume[309-311]. However, children mainly use compensatory increase in heart to maintain their cardiac output in shock states and are unable to significantly increase contractility due to short myocardial fibres and thinner cardiac musculature.

Proportions of various haemodynamic patterns are presented for participants with the measurements. Ten percent (14/146) had low CI (cardiogenic abnormality), 60% (87/146) had high CI (hyperdynamic circulation), 46% (68/146) had low SVI, and 15% (22/146) had high SVI at admission. Although our measurement of vascular resistance was of doubtful accuracy, 35% (52/146) had low SVRI (abnormal vascular tone, vasodilatation) and 18% (27/146) had high SVRI (vasoconstriction).

Participants with severe disease had some distinct differences in haemodynamic patterns compared to those without severe disease. Cardiogenic abnormality (low cardiac index) was more common in severe disease compared to non-severe disease (14% versus 2%, respectively), as was low SVI (53% versus 32%, respectively) (Table 5.10). The two findings were consistent and are probably indicative of an abnormality in any of the following in severe disease; venous return, myocardial contractility, compliance, or afterload. The higher prevalence of low SVI and CI in severe groups were still present even after excluding participants with gastroenteritis. Indicators of hyperdynamic circulation (high CI or high SVI) were similar in participants with severe disease and those with non-severe disease. There were however higher proportions of participants with non-severe disease who had vasodilatation and vasoconstriction compared to severe disease (Table 5.10).

In the subgroups of participants with severe disease, prevalence of low CI was 10% in participants with features of shock (SIMP) and 19% in participants without shock (S). Hyperdynamic circulation (high CI) was however more prevalent in participants with shock, 67% versus 47% (Table 5.10). There were no differences in the proportions with low SVI between SIMP and S groups, 55% and 51% respectively. Proportions with vascular tone abnormalities (high or low SVRI) were however higher in the group without features of shock compared to those with features. A higher proportion of participants without shock had a combination low cardiac index plus increased SVRI (16% versus 4%) compared to those with shock. This pattern has been referred to as ‘cold shock’ and is reportedly more common in children with septic shock at admission to PICU with community acquired sepsis[179]. Proportions with ‘warm shock’[179], defined as a combination of high cardiac index plus low SVRI were similar in the two groups. Warm shock is reported to be the adult presentation of

septic shock and is also the pattern in paediatric septic shock secondary to hospital acquired infections[179]. When considering a combination of stroke volume index (to remove the influence of hear rate) and vascular resistance to describe 'warm' and 'cold' shock patterns, participants with features of shock (SIMP) were likely to have a combination of low SVI and vasodilatation (6%) compared to zero in the S group (Table 5.6). This was consistent with a hyperdynamic circulation. On the other hand participants without shock (S group) were likely to have a combination of low SVI plus high vascular resistance index, 35% versus 9% (Table 5.10).

Participants with signs of impaired perfusion used in the FEAST trial were less likely to have cold shock but more likely to have warm shock. This was seen both in the overall study population and in the subgroup with severe disease. The association between FEAST signs of impaired perfusion and warm or cold shock patterns were however statistically non-significant but this could be due to small sample sizes.

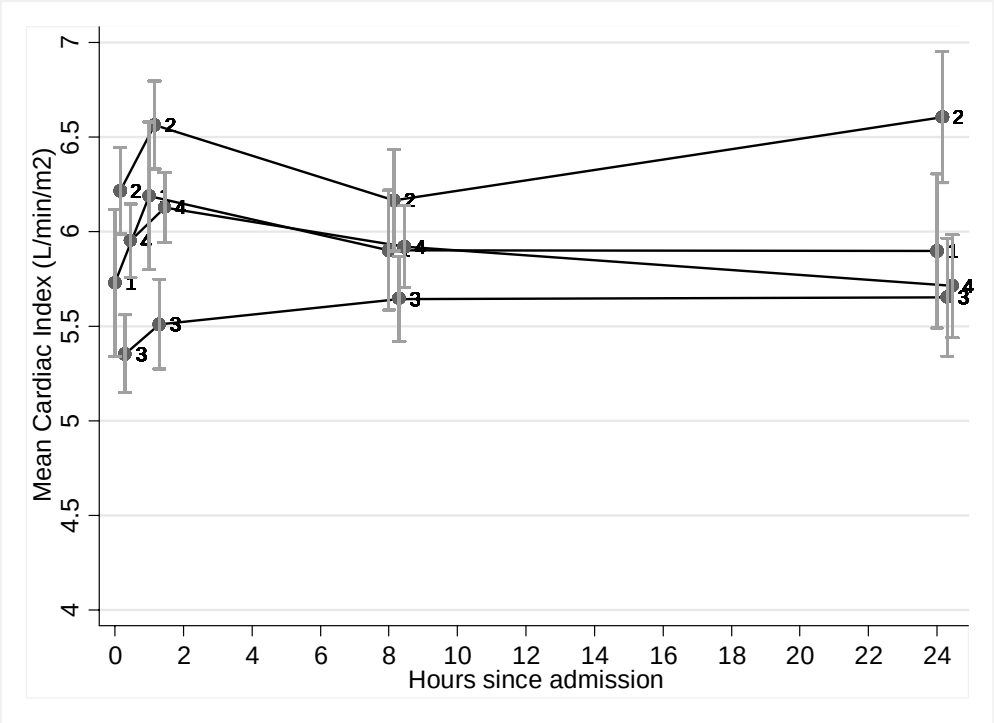
Table 5-11: Patterns of shock in participants with various disease severities

Haemodynamic abnormality	Prevalence in various disease states				
	All participants (N=146)	Severe disease (n=95)	Non severe disease (n=51)	Severe disease with impaired perfusion (n=52)	Severe disease without impaired perfusion (n=43)
Low CI	14[10]	13[14]	1[2]	5[10]	8[19]
High CI	87[60]	55[58]	32[63]	35[67]	20[47]
Low SVI	68[46]	51[53]	17[32]	29[55]	22[51]
High SVI	22[15]	10[10]	12[23]	4[8]	6[14]
Low SVRI	52[35]	29[30]	23[43]	17[32]	22[51]
High SVRI	27[18]	20[21]	7[43]	5[9]	15[35]
Low CI + high SVRI	11[8]	10[11]	1[2]	3[4]	7[16]
Low CI + low SVRI	0	0	0	0	0
High CI + high SVRI	2[1]	1[1]	1[2]	1[2]	0[0]
High CI + low SVRI	46[32]	26[27]	20[39]	15[29]	11[26]
Low SVI + high SVRI	25[17]	20[21]	5[9]	5[9]	15[35]
Low SVI + low SVRI	8[5]	6[6]	2[4]	6[11]	0[0]
High SVI + high SVRI	1[1]	0	1[2]	0	0
High SVI + low SVRI	17[10]	8[7]	9[15]	4[8]	4[9]

5.2.7. Changes in cardiac indices in participants with various disease severities

Participants with FEAST clinical features of shock (SIMP and NSIMP) presented with higher mean cardiac indices at admission when compared to those without shock (NS and S) (Figure 5.4). The subgroup that was clinically diagnosed as having shock (SIMP) showed reduction in CI over 24 hours observation as would have been expected as result of reduced heart rates.

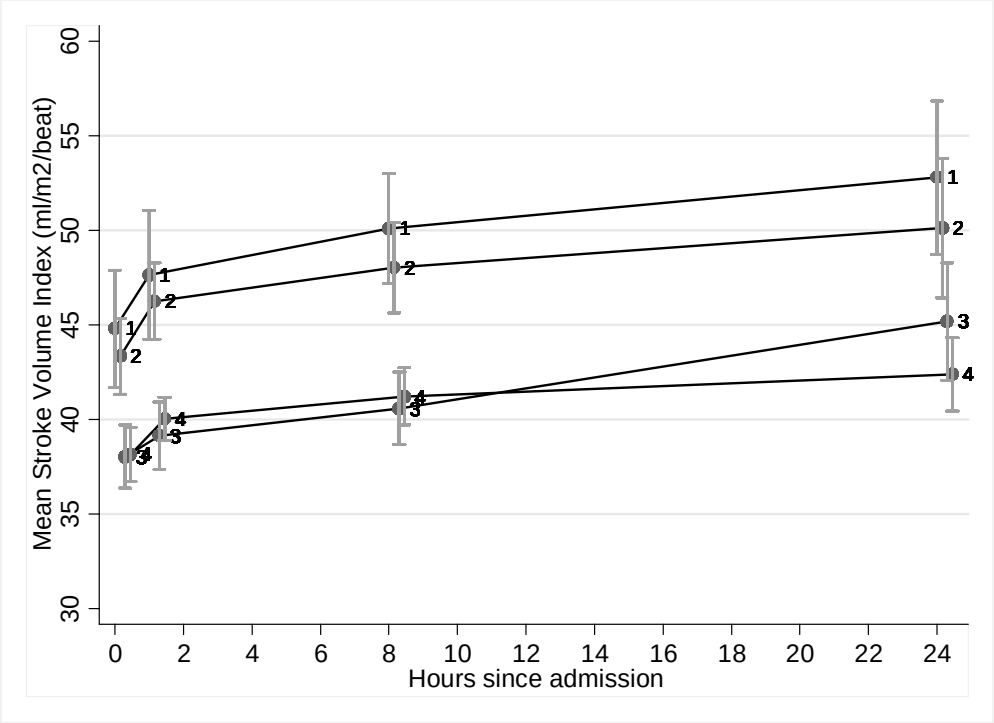
Figure 5-4: Changes in cardiac indices in participants with various disease severities



Key: 1=NS; 2=NSIMP; 3=S; 4=SIMP

Figure 5.5 shows that participants with severe disease had low SVI at admission compared to those without severe disease. Overall, there were increased in SVI in all groups over the course of admission but this has not taken care of missing observations (e.g. due to death).

Figure 5-5: Changes in stroke volume indices in participants with various disease severities



Key: 1=NS; 2=NSIMP; 3=S; 4=SIMP

5.2.8. Haemodynamic changes with fluid bolus infusion

Description in this category was restricted to participants with severe disease and features of impaired perfusion (SIMP subgroup) only. There were 58 children in this subgroup and 24[41%] received a fluid bolus. Decision on bolus admission was made by the attending clinician and was basely solely on clinical judgement.

5.2.8.1. Baseline haemodynamic parameters

Participants with severe disease and features of shock who were prescribed fluid boluses had different baseline characteristics compared to those who did not receive boluses. Significantly higher proportions of bolus recipients had clinical features of shock (temperature gradient, weak pulse volume, delayed capillary refill time), features of dehydration (sunken eyes, reduced skin turgor), markers of tissue hypoperfusion (elevated lactate, increased base deficit), and acidaemia (Table 5.11). Tachycardia was however significantly more common among non-recipients. Sex and age were similar in bolus recipients and non-recipients. Mean serum creatinine and urine osmolality were similar between bolus recipients and non-recipients.

Mean cardiac indices and proportions with high CI (hyperdynamic circulation) were similar between participants who received fluid bolus compared to those who did not. However, 3 (15%) participants who received fluid bolus had low CI and 1 (33%) died compared to 6% (n=2) in non-recipients of which none died. Baseline mean SVI was non-significantly lower amongst participants who received fluid bolus (Table 5.11) but proportions with low SVI were similar between the two subgroups. However, mortality was higher in the subgroups that received fluid bolus (21%) compared to those who did not (3%). All baseline findings taken together indicate a sicker group of children who received fluid bolus even in this subgroup. Therefore differences in mortality, baseline haemodynamic findings, and post-admission haemodynamic profiles between bolus recipients and non-recipients cannot be attributed to bolus infusion alone but may be indicative of underlying disease severity.

Table 5-12: Baseline characteristics of participants with severe disease and shock who received bolus

Characteristic	No bolus (n=34)	Bolus (n=24)	Chi-square	p-value
Demography				
Age [median, IQR]	13[6, 49]	13[5, 25]	0.8	0.46
Female sex [n, %]	12[35]	9[38]	0.0	0.86
Features of shock **[n, %]**				
Tachycardia	33[97]	15[63]	10.5	0.002
Weak pulse volume	1[3]	5[21]	6.5	0.04
Temperature gradient	1[3]	11[48]	16.6	<0.001
Capillary refill time >2seconds	0[0]	7[29]	11.0	0.001
Sunken eyes	1[3]	8[35]	10.5	0.002
Reduces skin turgor	0[0]	8[35]	13.8	<0.001
Markers of impaired perfusion				
Lactate [mean±SD]	2.7[1.7]	3.9[2.4]		0.05
Lactate>3mmol/L[n, %]	4[14]	11[48]	7.2	0.007
Base deficit [mean±SD]	9[4]	13[7]		0.01
Base deficit>10mmol/L[n, %]	9[38]	14[58]	2.1	0.15
pH[mean±SD]	7.39[0.06]	7.31[0.13]		0.01
pH<7.20[n, %]	0[0]	5[21]	5.6	0.05
Markers of renal perfusion				
Creatinine [mean±SD]	85[28]	107[53]		0.71
Creatinine >80 [n, %]	2[9]	3[16]	0.4	0.65
Urine osmolality [mean±SD]	526[257]	487[254]		0.63
Urine osmolality <400[n, %]	4[22]	8[36]	0.9	0.49
Haemodynamic indices				
Cardiac index[mean±SD]	5.9[1.1]	6.0[1.8]		0.82
Low cardiac index [n, %]	2[6]	3[15]	1.1	0.36
High cardiac index[n, %]	22[69]	13[65]	0.0	0.89
Stroke volume index [mean±SD]	39[11]	36[9]		0.37
Low stroke volume index [n, %]	18[55]	11[55]	0.0	0.97
Death [n, %]	1[3]	5[21]	4.9	0.07

Cardiac index=L/min/m^2; stroke volume index=ml/m^2; lactate/base deficit=mmol/L; creatinine=µmol/L; urine osmolality= mOsm/L

5.2.8.2. Changes in haemodynamic indices in patients with shock following bolus infusion

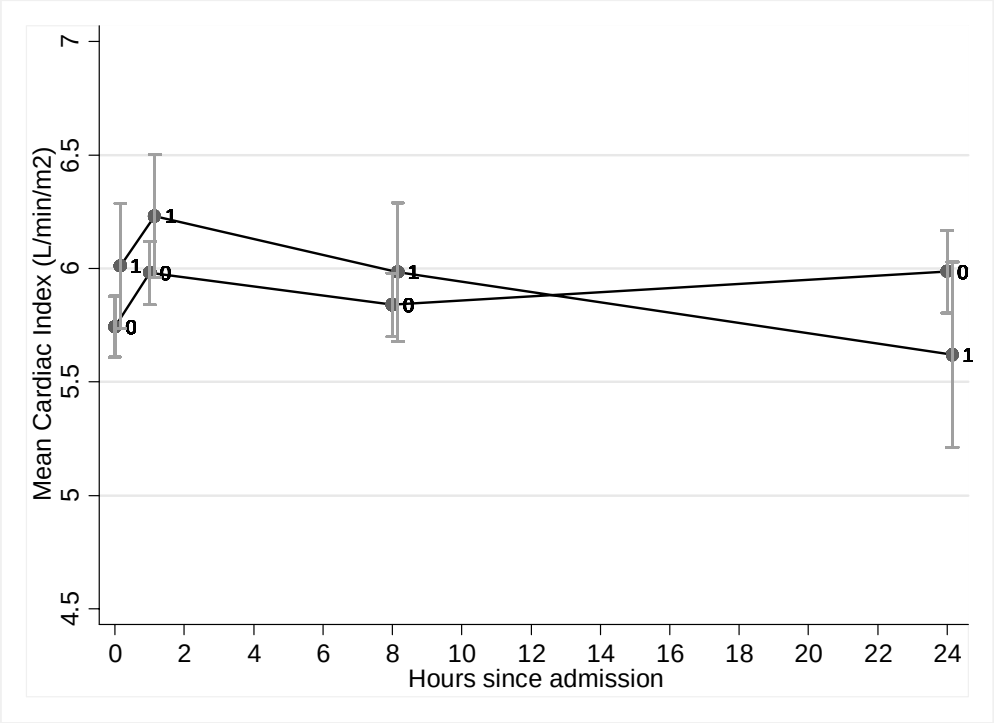
Changes in haemodynamic indices over 24 hours between bolus recipients and non-recipients were monitored. As expected, mean cardiac indices fell over 24 hours' observation both in participants who had received fluid bolus and non-recipients (Fig 5.6). This was probably a result of reduction in heart rate (resolution of tachycardia) following initiation of treatment. The effect of bolus infusion on changes in cardiac indices following admission are however difficult to determine because participants who received fluid bolus were more severely ill as shown above (Table 5.11). Both bolus recipients and non-recipients had an increase in cardiac index at one hour review and a fall at subsequent reviews (8 hours and 24 hours). Mean fall in cardiac index at 24 hours was 0.4L/min/m^2 [95% confidence interval, -1.0 to 1.8; p=0.59] in bolus recipients and 0.1L/min/m^2 [95% confidence interval, -0.5 to 0.8; p=0.68]. These changes should however be interpreted cautiously because they do not take into account the influence of any missing values that may be due to various reasons such as early deaths (3 bolus recipients died within 24 hours compared to 1 non-recipient) who may have had worse profiles.

Participants who received fluid bolus (more severely ill) and non-recipients both increased their SVIs over 24 hours' observation. This was seen even after excluding participants with gastroenteritis. Mean change in SVI for bolus recipients at 24 hours was 4.1ml/m^2 [95% confidence interval, -11.6 to 3.4; p=0.28] and 4.3ml/m^2 [95% confidence interval, -11.0 to 2.4; p=0.20] in non-recipients-see Figure 5.7. Again, changes in SVI presented do not take into account missing values due to mortality and should be interpreted with caution. However, two aspects should be considered; one is that even at admission, the more severely ill group (bolus recipients) had lower SVI and this remained lower during observation; and secondly, there is an increase in SVI following admission in severely ill children with shock even without bolus. Reduction in heart rate in the course of admission improves compliance/diastolic function of the heart because the heart has more time to relax leading to prolonged filling phase, increased end-diastolic volume and resulting in increased strove volume[180 218].

Mixed effects modelling comparison of mean values for haemodynamic indices in participants who received fluid bolus versus those who did not over a period of 24 hours did not show any significant differences. For cardiac index the intercept was 5.8L/min/m^2 and the mean difference from the mean due to fluid bolus (β-coefficient) was 0.3 L/min/m^2, p=0.38. Intercept for SVI was 30.7ml /m^2 and mean difference due to fluid bolus (β-coefficient) was 0.3ml /m^2; p=0.86. Intercepts for inotropy and SVRI indices were 1.59W/m^2

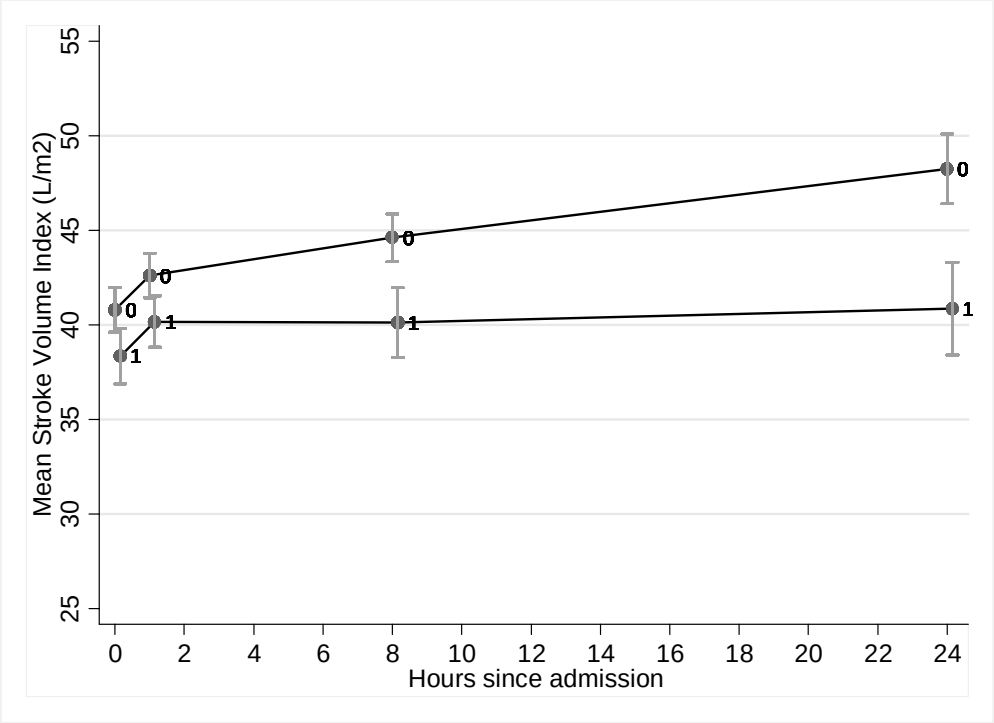
and 947 d.s.cm^{-5}m^2, mean differences due to fluid bolus (β-coefficients) were 0.15 W/m^2 (p=0.26) and -17 d.s.cm^{-5}m^2 (p=0.81), respectively.

Figure 5-6: Changes in cardiac index children with shock following bolus infusion



Key: 0=No bolus; 1=Bolus

Figure 5-7: Changes in SVI children with shock following bolus infusion



Key: 0=No bolus; 1=Bolus

5.2.9. Haemodynamic indices for survivors at 24 hours

When only survivors were considered, mean SVI at 24 hours was significantly lower for bolus recipients compared to non-recipients (p=0.04). There was also a significant increase in the mean SVI in those who did not receive fluid at 24 hours when compared to baseline (mean increase=9.9ml/m^2, p=0.006) but not for bolus recipients (mean increase=2.3ml/m^2, p=0.41). These could have been as a result of having more severely ill patients among recipients. However given that there were no significant differences in SVIs at admission, the differences at 24 hours may also be interpreted to be a consequence of the bolus administration.

There were no differences in the mean cardiac index and SVRI among survivors at 24 hours who received fluid bolus compared to those who did not but the inotropy index was lower (though clinically non-significant) among bolus recipients (p=0.05). The mean changes in cardiac and inotropy indices when compared to the baseline levels were not significant.

5.2.10. Summary of findings

1. There was good agreement in cardiac output and cardiac index measurements obtained using USCOM and echocardiography. This demonstrated validity of cardiac output and

index measurements obtained by USCOM. There was however moderate agreement in SVI measurements obtained by the two devices. A pattern was seen where USCOM readings for SVI were higher than echocardiography readings at low SVI values but were lower at high SVI readings. SVI obtained by USCOM in this study were valid as evidenced by low SVI values in participants with shock secondary to gastroenteritis, a known cause of hypovolaemia.

2. Hyperdynamic circulation (high cardiac index) was the predominant presentation in children with clinical features if impaired perfusion. Low cardiac index (cardiogenic failure) was rare in children with clinical features of shock. Low cardiac index however presents a risk factor for mortality.

3. Abnormal cardiac indices (high or low CI) are associated with elevated lactate (a marker of tissue hypoperfusion, and acidaemia (pH<7.20) but not with base deficit. Reduced urine osmolality (but not elevated creatinine), as a marker of renal concentration of urine, was associated with low cardiac index.

4. Participants with severe disease (S and SIMP) had significantly lower baseline SVI compared to those without severe disease (NS and NSIMP).

5. Elevated lactate and elevated creatinine were associated with increased the risk of death; however, acidosis and low urine osmolality were not associated with mortality.

6. Criteria for bolus administration mainly identified children who were sicker, had higher risk of mortality, and who also had higher proportions of markers for tissue hypoperfusion (elevated lactate, base deficit) and acidaemia.

7. The effect of bolus administration on haemodynamic indices (CI and SVI) is uncertain because the clinical criteria for bolus administration identified more severely ill children and this did allow for comparison with non-recipients.

8. Mortality was associated with low cardiac index and low stroke volume, two indications of inability to compensate for reduced circulating volume.

9. Abnormal cardiac index was associated with elevated lactate (marker of global hypoperfusion). The association was stronger with low as compared to high cardiac index. Abnormal cardiac index as also associated with acidaemia. Elevated creatinine

was associated with low stroke volume. Reduced osmolality was separately associated with low cardiac index and low stroke volume.

10. Severely ill participants with shock (SIMP) who received fluid bolus had worse admission SVI and a modest increase in SVI compared to the less sick participants in same sub-group. The difference was not explained by gastroenteritis explained and may be the result of worse cardiovascular function.

CHAPTER 6 : MANAGEMENT OF SHOCK

6.1. PHASE II TRIALS OF VOLUME EXPANSION USING COLLOIDS IN CHILDREN WITH SEVERE MALARIA AND SHOCK

Studies covered under this section reports the on the safety of synthetic colloids (dextran, hydroxyethyl starch, and gelatin) for treatment of shock in children with severe malaria complicated by metabolic acidosis, a marker of hypovolaemia. Methodology has been described in chapter 2-study 3 and 4.

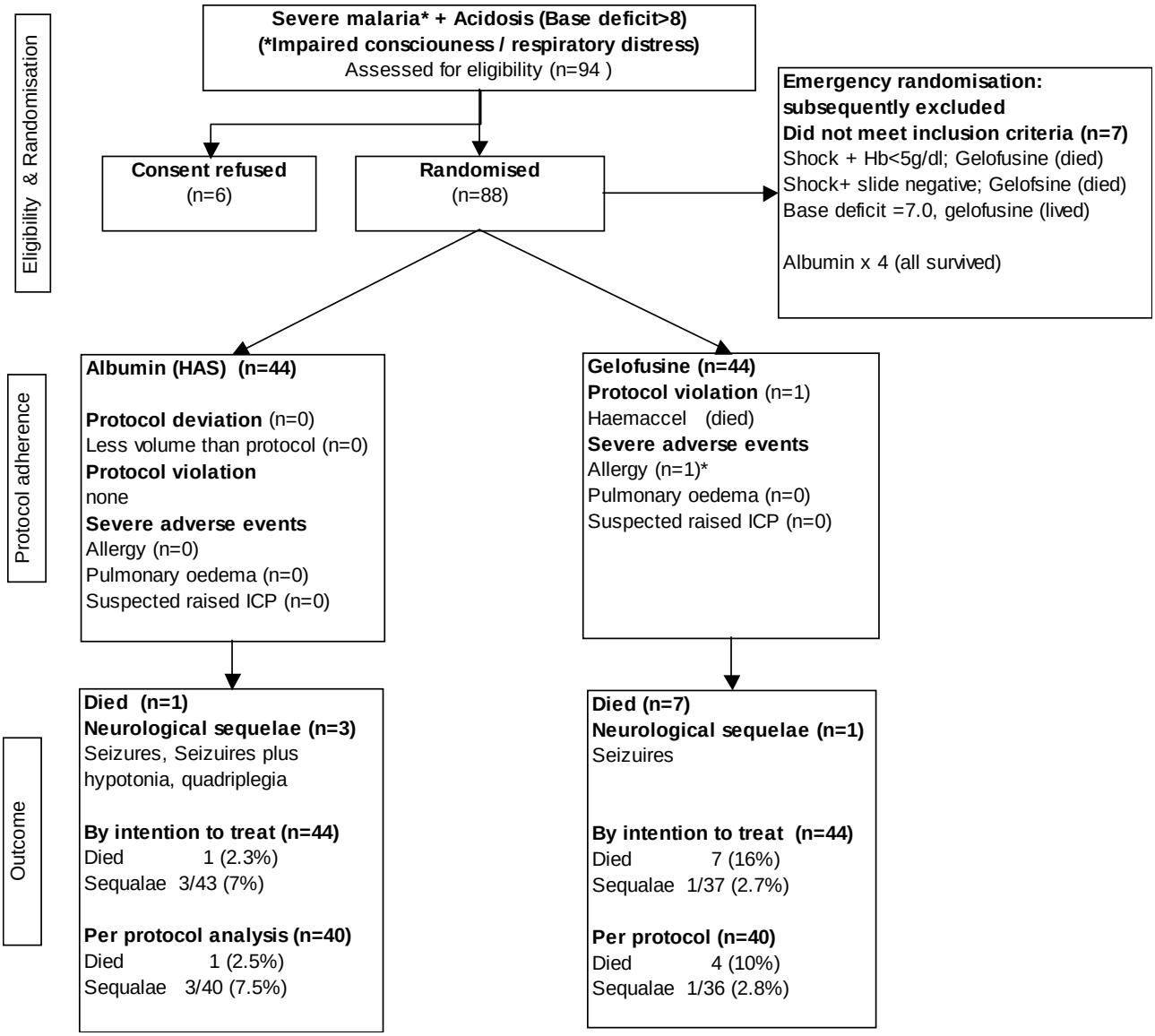
6.1.1. PHASE II TRIAL OF VOLUME EXPANSION WITH ALBUMIN COMPARED TO GELOFUSINE IN CHILDREN WITH SEVERE MALARIA AND SHOCK

Results

6.1.1.1. Participants

Participants were enrolled between December 2004 and January 2006 when the required sample size was achieved. A total of 94 children were assessed for eligibility, there was no parental/guardian consent in 6 participants (88 met criteria) while 7 participants were randomised as emergencies and received study interventions, but were subsequently found not to have met with all the inclusion criteria. Therefore 80 participants met the strict inclusion criteria (Figure 6.1). There were no protocol deviations but there was one protocol violation where a child was allocated to Gelofusine but received Haemaccel® erroneously. No child withdrew from the study and there were no losses to follow-up.

Table 6-1: Trial flow-Gelofusine versus albumin



6.1.1.2. Analysis strategy

Data was analysed by both intention to treat (ITT) and per protocol (PP). The per-protocol analysis included only those fulfilling inclusion criteria and adhering to trial protocol. A total of 88 children were included in the ITT analysis [albumin n=44 and Gelofusine n=44] for both primary and secondary outcomes including 7 children who were randomised following emergency assent and the one child who erroneously received Haemaccel rather than Gelofusine. Participants excluded after emergency assent presented with a clinical picture similar to severe malaria but subsequently found

to have negative plasmodium malaria slide. Hence, 80 children were included in the PP analysis [albumin n=40 and Gelofusine n=40].

6.1.1.3. Baseline characteristics

Participants allocated to Albumin and Gelofusine groups had similar markers of clinical or biochemical of severity at baseline (Table 6.2). All children had one or more clinical features of hypovolaemia including severe tachycardia (heart rate > 160 beats per minute), delayed capillary refill time (≥3 seconds), hypoxia (oxygen saturations <95% on pulse oximetry) or hypotension (systolic blood pressure < 80mmHg or < 70 mmHg if <1year).

Table 6-2: Baseline Characteristics for participants enrolled into Gelofusine versus albumin

Admission features	**Overall (N=80)**	**Albumin (n=40)**	**Gelofusine (n=40)**	**P-value**
Median Age [interquartile range]	33[21,39]	34 [19,41]	27 [15,39]	0.37
Severity feature	n (%)	n (%)	n (%)	
Coma (BSC≤2)	45(56)	25 (63)	20(50)	0.52
Deep breathing	65(81)	35 (88)	30 (75)	0.11
Severe tachycardia (>160 beats per minute)	39(49)	21 (53)	18 (45)	0.57
Severe tachypnoea (>60 breaths per minute)	22(28)	10 (25)	12 (30)	0.57
Hypoxia (saturation <95%)	17(21)	8 (20)	9 (23)	0.83
Hypotension(Systolic blood pressure < 80 mmHg if > 1yr or <70mmHg in ≤1yr)	8(10)	4 (10)	4 (10)	0.97
Delayed capillary refill of >2 s	23(29)	11 (28)	12 (30)	0.74
Status epilepticus	26(33)	14 (35)	12 (30)	0.63
Posturing	21(26)	10 (25)	11 (28)	0.53
Hypoglycaemia (<3mmols/L)	24(30)	14 (35)	10 (25)	0.37
Weight for age Z score < 3	20(25)	11 (28)	9 (23)	0.60
Creatinine >80µmol/L	35(44)	19 (48)	16 (40)	0.97
Lactate > 5mmol/L,	30(38)	18 (45)	12 (30)	0. 30
Potassium >5mmol/L	14(18)	5 (13)	9 (23)	0.18
Laboratory variable:	mean ± SE	mean ± SE	mean ± SE	
Haemoglobin level, g/dL	8.2±0.2	8.1 ± 0.3	8.3 ±0.3	0.55
pH	7.23±0.02	7.22 ±0.02	7.24 ±0.02	0.67
Base deficit, mmol/L	16±0.6	16 ±0.8	16 ±0.8	0.98
Venous PCO_2, kPa	3.86±0.22	3.96 ±0.33	3.68 ±0.27	0.51
Lactate level, mmol/L	6.1±0.5	6.6 ±0.7	5.6 ±0.7	0.31
Sodium level, mmol/L	133±0.7	134 ±0.9	133 ±1	0.68
Creatinine level, µmol/L	89±5	87 ±6	95 ±10	0.50
Potassium level, mmol/L	4.4±0.1	4.4 ±0.1	4.5 ±0.2	0.70
Bicarbonate level, mmol/L	12.0±0.5	12.1±0.7	11.7±0.6	0.65

6.1.1.4. Primary endpoints

Resolution of shock

A review at 8 hours showed that 82% (64/78) had resolution of shock or only had a single feature of the five features and required no further intervention. There were no differences in the resolution of shock between the two intervention fluids (Table 5.3). Volumes of fluids administered as bolus and total amounts infused (bolus plus maintenance) were similar between the two intervention arms (Table 6.3).

Table 6-3: Primary Outcomes by ITT

	Albumin	Gelofusine	P-value
Status at 8hours			
Resolution of shock[β], n/N (%)			
Number with shock at admission	35/42(83)	37/43(86)	0.77
Number with shock at 8 hours	9/41(20)	5/37(14)	0.24
Base deficit reduction, % (95% CI)			
Patients with Moderate acidosis	35 (12-59)	27 (6-48)	0.59
Patients with Severe Acidosis	25 (10-40)	21 (9-33)	0.61
Volume received, ml/kg (95% CI)			
As boluses			
Patients with Moderate acidosis[α]	21(18-23)	21(19-24)	0.54
Patients with Severe acidosis[σ]	27(22-32)	28(23-34)	0.70
Total volume			
Patients with Moderate acidosis	46 (41-51)	44 (40-47)	0.44
Patients with Severe acidosis	50 (44-57)	52 (46-58)	0.69
Safety (solicited events), n/N (%)			
Pulmonary oedema	0	0	
Raised intracranial pressure	0	2/44 (5)	
Possible allergic reaction*	0	1/44 (2.3)	

[α]Moderate acidosis = base deficit > 8 but <15 mmol/L; [σ]Severe acidosis = base deficit ≥ 15 mmol/L

[β]Resolution of shock defined as absence of all of the following features; severe tachycardia (>180 beats/minute if aged <12months, > 160 beats/minute if aged 1-5years or >140 beats/minute if aged ≥ 5 years); hypoxia (oxygen saturation <95%); hypotension: systolic blood pressure (SBP) (<70mmHg for <12 months and <80mmHg for > 1 year) or delayed capillary refill time (CRT) (≥3seconds).

Resolution of acidosis

Overall, resolution of shock and metabolic acidosis were similar between the groups although many patients remained acidotic in both groups (Table 5.3).

Solicited Serious Adverse Events

There was no evidence of pulmonary oedema or fluid overload in any trial participant. Signs suggestive of raised intracranial pressure were suspected in two children (2%) randomised to Gelofusine. These children showed unilateral pupillary dilatation, unresponsive to mannitol infusions, at 4 hours and 3 hours after admission respectively. Both progressed to develop bilateral fixed dilated pupils before a terminal respiratory arrest.

One participant who received Gelofusine developed a generalised red rush one hour of receiving fluid and was suspected to have an allergic reaction. The child received symptomatic treatment with intravenous chlorpheniramine and intravenous hydrocortisone but had no systemic signs of anaphylaxis and the rash resolved within one hour. However concurrent administration of intravenous benzylpenicillin did not allow us to establish a definite causal relationship.

6.1.1.5. Secondary Outcomes

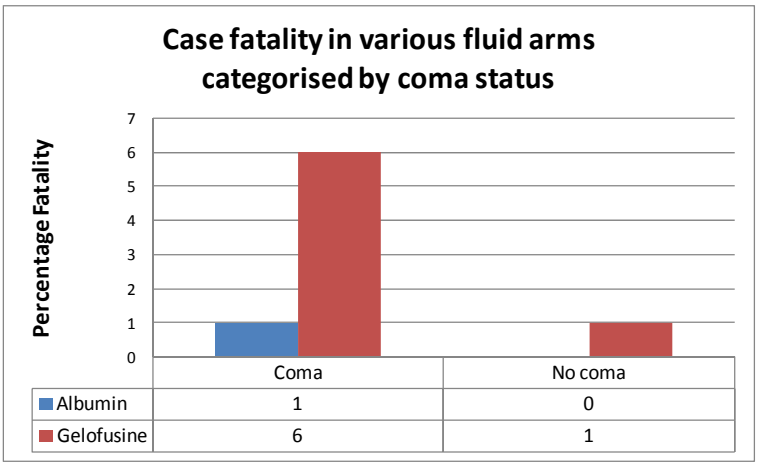
Death

By intention to treat analysis, death occurred in 1/ 44 (2.3%) of the albumin treated patients compared to 7/44 (15.9%) of the Gelofusine treated patients, Fisher's Exact test, P=0.06. Considering only those patients complying with the protocol, fatal outcome occurred in 1/40 (2.5%) of HAS treated children and 4/40 (10%) of Gelofusine recipients; P=0.36. In the subgroup admitted in coma, mortality in the albumin arm was 1/ 25 (4%) for both ITT and PP analysis and 6/23 (26%) or 3/20 (15%) in the Gelofusine group for ITT or PP analysis; P=0.04 and 0.31 respectively. Details are summarised in table 6.4 and figure 6.1. With the differences in mortality seen between HSD/5D and RL, the study only had 53% power to demonstrate a difference in mortality if 10% type I error was allowed.

Table 6-4: Secondary outcomes by ITT

	Albumin	Gelofusine	P-value
Secondary outcomes			
In-hospital death, n/N (%)			
By intention to treat (ITT)	1 (2.3)	7 (16)	0.06
Per protocol	1/40 (2.5)	4/40 (10)	0.36
Safety (unsolicited events), n/N (%)			
Neurological sequelae: ITT	3/43 (7.0)	1/37 (2.7)	0.61
Per protocol	3/39 (7.7)	1/36 (2.8)	0.62

Figure 6-1: Case fatality in various fluid intervention arms by coma status



Unsolicited Serious Adverse Events

Status epilepticus was present in two children who died in Gelofusine group and in the one fatal case who received HAS. In the three cases, optimal seizure control was compromised by respiratory depression. The other three children who died had severe anaemia, hyperkalaemia and wheeze/stridor, respectively.

Neurological sequelae developed in 3/43 survivors receiving albumin (7.0% by ITT) and 1/37 (2.3%) survivor who received Gelofusine (2.7% by ITT), Fisher's Exact test P=0.62; and in 3/39 (7.7%) receiving albumin and 1/36 (2.8%) receiving Gelofusine per protocol P=0.61 (Table 5.3). The four children in the PP analysis all had coma at admission and 3 had evidence of pre-existing neurological impairment (Table 5.3). A participant with pre-existing epilepsy was diagnosed to have neurological sequelae because the carer reported an increased seizure frequency and severity at one month after discharge.

6.1.1.6. Summary of findings

1. 5% Human albumin solution (HAS) and Gelofusine were both equally effective in treating shock, determined by resolution of clinical features of shock, and metabolic acidosis
2. By intention to treat, children with shock and severe malaria who were treated with HAS showed a trends toward reduced mortality when compared to children who received Gelofusine. The two groups however had similar mortality when only those who complied with all aspects of the protocol, per protocol analysis, was done.
3. For the subgroup with coma, mortality in participants who received Gelofusine was significantly higher than for those who received HAS.

4. Fatal neurological events (brain swelling and transtentorial herniation with unilateral papillary dilatation) were more common in recipients of Gelofusine (9%) than HAS (2.4%).
5. Neurological sequelae were more common in survivors who received HAS (7%) than Gelofusine (2.7%) by ITT.
6. No incidences of gross haemorrhage, pulmonary oedema or fluid overload seen in either arm.
7. One incident of suspected allergic reaction, of moderate severity, was seen with Gelofusine and none with HAS.

6.1.2. PHASE II TRIAL ON THE USE OF DEXTRAN 70 OR STARCH FOR SUPPORTIVE THERAPY IN CHILDREN WITH SEVERE MALARIA AND SHOCK

RESULTS

The trial was conducted from June 2006 to December 2008 and screened 133 children. A total of 101 children were eligible, 16 (16%) refused consent, and 6 children were excluded due to various reasons as shown in the trial flow diagram (Figure 6.2). Eight children presented with emergencies (hypotensive shock) therefore did not qualify for the trial because it was unethical for the trial team to wait for informed consent before treatment. Mortality in those with emergencies was 28.5% (2/7) and six were managed with 0.9% saline bolus while one child died before infusion could be started. Seventy nine children were enrolled; 39 to Dextran arm and 40 to with HES arm. One envelope for the Dextran arm was accidentally opened prematurely before parental consent was obtained therefore this was not used when carer declined participation into the study.

6.1.2.1. Baseline Variables

The median age of the trial participants was 40 months [IQR; 28,53)] and participants in the two arms had similar baseline clinical and laboratory features except for hypoglycaemia which was slightly more common (though non-significant) in the HES arm - 12(30%) - compared to 5 (13%) in the Dextran arm (P =0.09), see Table 6.5. A total of 20/79 (25%) children received blood transfusion in accordance with the WHO guidelines during the course of admission, 11 (28%) in the Dextran arm and 9 (23%) in the HES arm (p=0.71). One who received HES had both *Streptococcus pneumoniae* bacteraemia and meningitis. No other cases of sepsis from any source were noted in the participants.

Figure 6-2: Trial flow

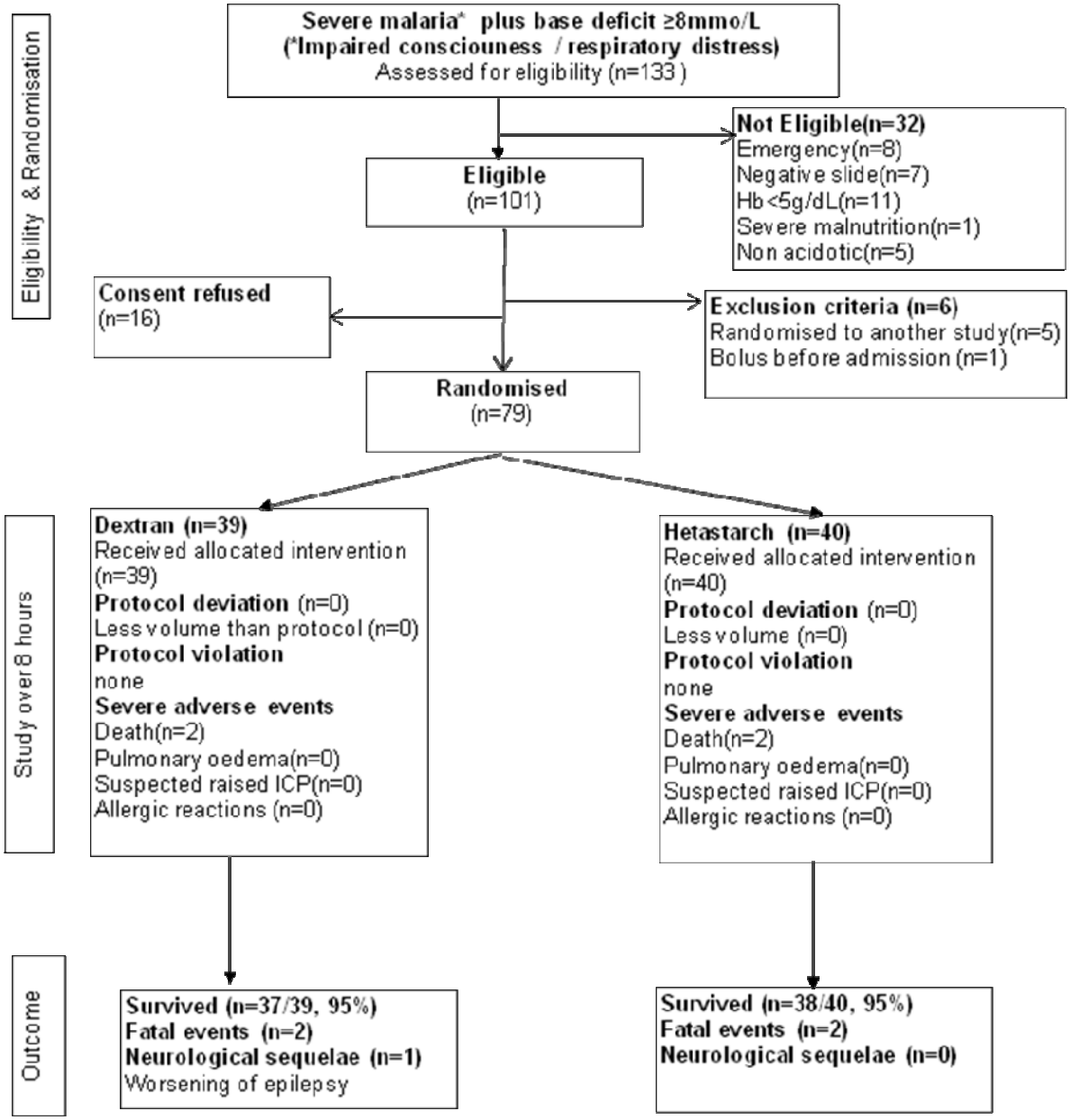


Table 6-5: Baseline characteristics

	6% Dextran (N=39)	HES (N=40)	P-value
Clinical features n (%)			
Coma (Blantyre Coma Score ≤2)	18(46)	21(53)	0.57
Deep breathing	26(67)	26(65)	0.88
Severe tachycardia (>160 beats per minute)	16(41)	19(48)	0.56
Severe tachypnoea (>40 breaths per minute)	25(64)	27(68)	0.75
Delayed capillary refill≥3 seconds	9(23)	5(13)	0.22
Core-toe temperature gradient	14(36)	13(33)	0.75
Weak Pulse volume	4(11)	5(13)	0.68
Hypotension (Systolic blood pressure <80mmHg)	2(5)	1(3)	0.54
Seizures	9(23)	10(25)	0.84
Prostration	19(50)	16(40)	0.52
Posturing	4(10)	9(23)	0.14
Weight for age Z-score<3	2(8)	0	0.22
Hypoglycaemia <3	5(13)	12(30)	0.09
Creatinine>80mmol/l	12(31)	15(38)	0.74
Potassium>5mmol/l	4(10)	5(13)	0.51
Mean laboratory variable [Standard Error]			
Haemoglobin level, mg/dl	8.18[0.3]	8.79[0.3]	0.16
pH	7.27[0.02]	7.3[0.02]	0.25
pCO_2,mmol/L	3.49[0.25]	3.6[0.26]	0.70
Base Deficit, mmol/L	12.32[1]	12.12[0.6]	0.86
Sodium level, mmol/l	132.7[1.2]	133.3[0.9]	0.68
Creatinine level, mmol/l	81.9[8.2]	84.4[5.5]	0.79
Parasitaemia[&](×10^3parasites/µL)	4.4(1.4,12.9)	4.1(1.7,10.2)	0.92

[&] Geometric mean (95% Reference Range)

6.1.2.2. Primary endpoints

Resolution of shock

Analysis was by intention to treat (ITT). There were no protocol violations/deviations therefore per protocol (PP) analysis was not warranted. Similar proportions in the two intervention arms attained resuscitation end-points at 4 and 8 hours (Table 5.5). Thirty-two percent (22/77) still had tachycardia at 4 hours but without any other features of impaired perfusion therefore further boluses were not administered unless they had capillary refill time >2 seconds (18 children) for which they received bolus infusion (Table 6.6).

Volume of bolus

Participants randomised to HES required significant lower mean volume of bolus to attain resuscitation targets compared to those randomised to Dextran, 22m/kg (95% CI: 20-24ml/kg) versus 26m/kg (95% CI: 23-28ml/kg) respectively, p=0.06. There were however no differences in the total volume of fluids (bolus plus maintenance) given over 24 hours (Table 6.6). Children who died received significantly higher volume of bolus fluid (mean 33ml; SD ±7) as compared to survivors (mean 24ml; SD ±1) (p=0.04).

Table 6-6: Primary endpoint

Outcome	Category	Dextran	HES	p-value
Attained resuscitation targets	**Time**	**n/N (%)**	**n/N (%)**	
	1 hr	20/39(51)	20/40(50)	0.91
	4hrs	20/39(51)	23/38(61)	0.48
	8hrs	23/37(62)	25/39(64)	0.99
Bolus Volumes, mean [95% CI]	4hrs	26(23-28)	22(20-24)	0.06
Total volume, mean [95% CI]	24hrs	49(41-57)	50(42-58)	0.85

6.1.2.3. Secondary endpoints

Death and neurological sequelae

There was a total 5/35 (14%) adverse events: 4 deaths (5%) and 1 (0.01%) neurological sequelae. There were 2 deaths in each the study arm and 3 of the 4 fatalities occurred in those with coma while the fourth fatality had agitation at admission. Mortality in this study presented a case fatality in the sub-group with coma plus metabolic acidosis of 8% (3/39. A one month post-discharge review

of all patients who were randomised found no mortality after discharge and only one case of worsening of pre-existing epilepsy in a child who received Dextran. This was recorded as neurological sequelae and reported.

Resolution of acidosis

There was better resolution of acidosis in participants who HES compared to Dextran both at 4 and 8 hours (Table 6.7).

Fluid overload or allergic reactions

We did not record any evidence of fluid overload (pulmonary oedema or raised intracranial pressure) or allergic/febrile reactions to nay of the fluids used.

Other adverse events

Urine output and serial plasma creatinine levels, measurements for renal impairment, measured over 24 hours were similar in two groups. No gross coagulopathy or bleeding problems were seen but we did not do other coagulation tests to investigate any subtle effects of the coagulation by any of the fluids.

Table 6-7: Secondary endpoints

Outcome	Category	Dextran	HES	p-value
Secondary outcomes				
Persistence of acidosis	4hrs	11/39(28)	3/38(8)	0.05
	8 hrs	10/36(28)	3/39(8)	0.05
Fatality	Overall	2/39(5)	2/40(5)	1.00
	8hrs	1/39 (3)	2/40(5)	1.00
Creatinine levels <80, n/N (%)	1 hr	12/39 (31)	10/40 (25)	0.89
	4 hrs	3/39 (8)	1/38 (3)	0.52
	8 hrs	2/36 (6)	1/39 (3)	0.57

6.1.2.4. Serial measurements of haemodynamic parameters

Mean heart rates decreased over time in both study arms and the decline was steeper within the first 8-10 hours of admission but thereafter declined gradually (Figure 6.3). Mean respiratory rates also decreased over tine in both arms but there was greater reduction in those who received HES compared to dextran (Area Under Curve, ranksum, p=0.07; and Maximum Value, ranksum, p=0.06, of the serial respiratory rates) (Table 6.8 and Figure 6.4).

Table 6-8: Summary of serial measurements

Outcome	Category	Dextran	HES	p-value
Summary measure				
AUC for heart rate (SD)		5574 (271)	5384 (250)	0.46
Mean max heart rate [95% CI]		165 [158-172]	168[162-174]	0.47
AUC for SBP (SD)		3945(181)	3885(179)	0.58
Mean max. SBP [95% CI]		116 [108-115]	113 [108-118]	0.61
AUC for respiratory rate (SD)		1749 (101)	1498 (78)	0.07
Mean max respiratory rate [95% CI]		62 [58-67]	56[52-61]	0.06

AUC=area under curve, SD=standard deviation, CI=confidence interval, SBP=systolic blood pressure

Figure 6-3: Mean heart rate and 95% confidence intervals over 48 hours' observation

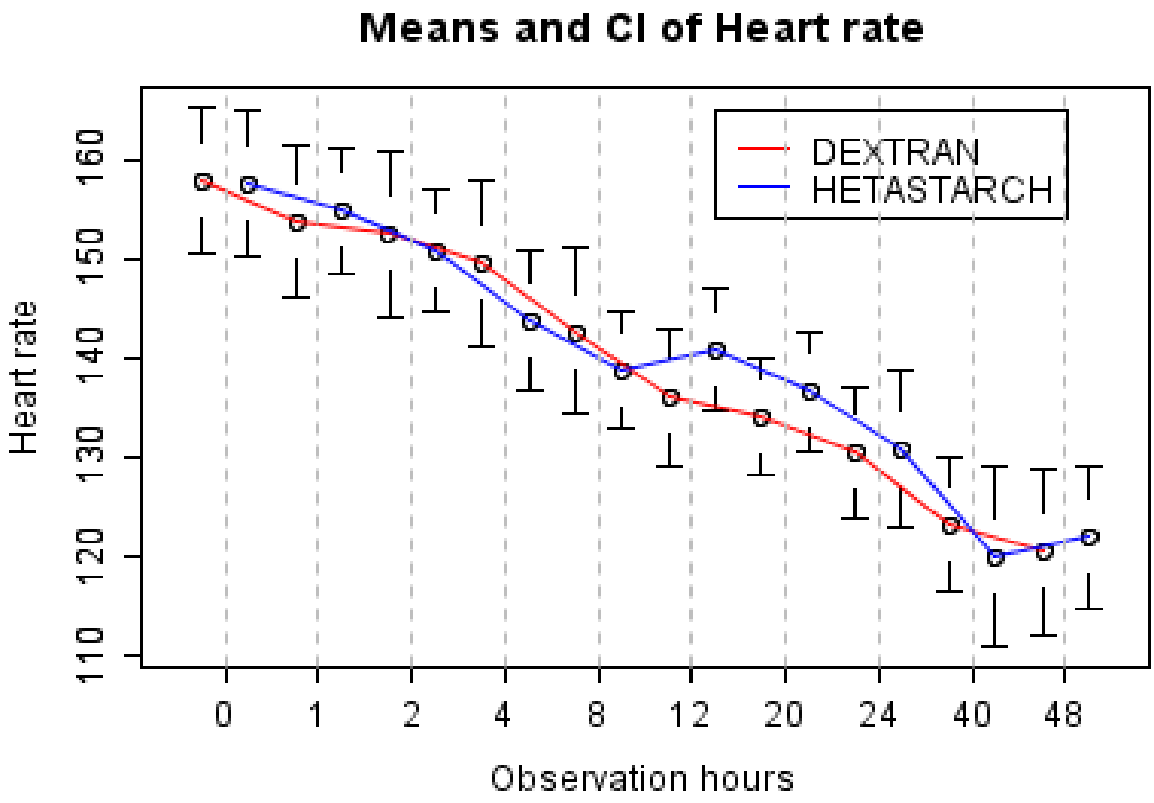
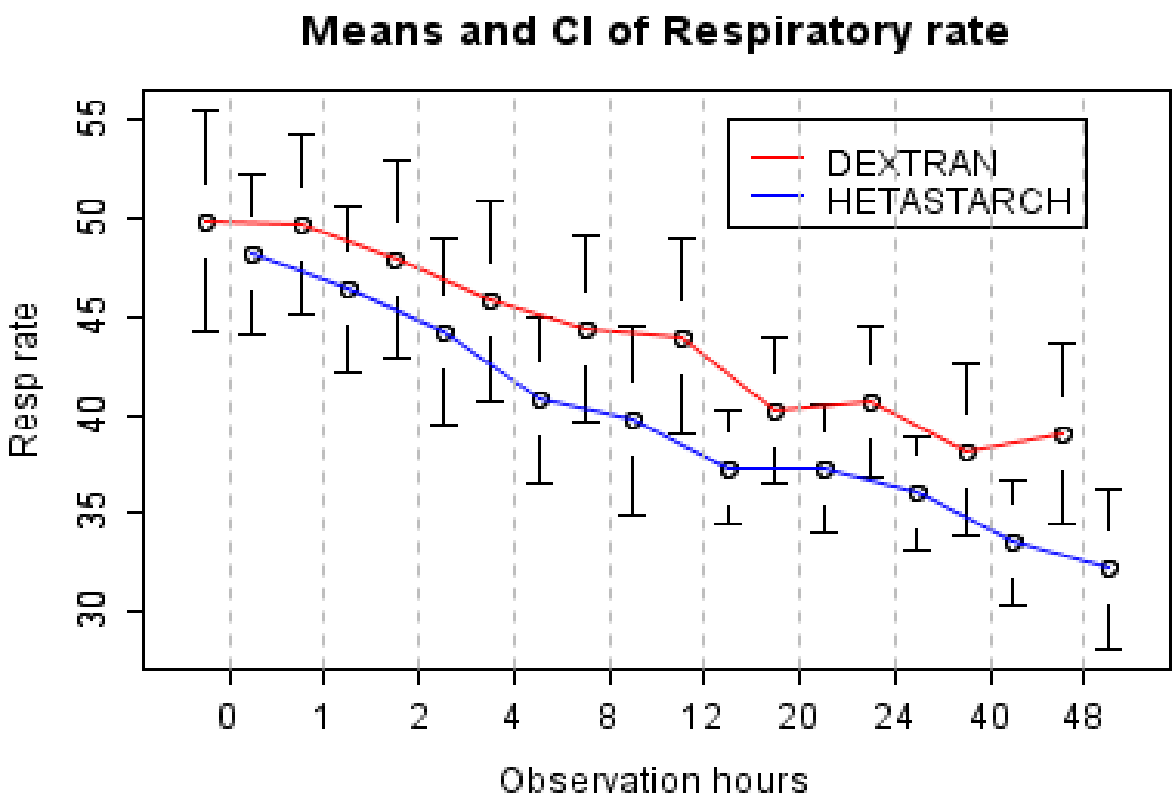


Figure 6-4: Mean respiratory rate and 95% confidence intervals over time



6.1.2.5. Summary of findings

1. There was similar resolution of shock, determined by resolution of clinical features of shock, in participants randomised to Dextran and HES.

2. Fluid resuscitation using HES resulted in significantly better resolution of acidosis and respiratory distress (Kussmaul/deep breathing) compared to using Dextran.

3. No incidences of pulmonary oedema, fluid overload, allergic reactions or gross bleeding seen in children resuscitation using either Dextran or HES.

4. There was low mortality and similar survival in participants who received either Dextran or HES. Low mortality should however be interpreted in the context of less severely ill group of children with severe malaria because children with emergency conditions such a hypotension (decompensated shock) were excluded due to ethical concerns about safety of Dextran. Randomisation was therefore restricted to cases where prior informed consent could be obtained.

5. No renal impairment, measured by urine output and creatinine, over 24 hours of observation in children who received HES. However, this was inadequate follow-up duration to conclusively rule out renal impairment.

6. No serious adverse events, such as neurological, sequelae related to the intervention fluids were seen at one month follow-up.

6.2. PHASE II TRIAL OF ISOTONIC FLUID RESUSCITATION IN CHILDREN WITH SEVERE MALNUTRITION AND HYPOVOLAEMIA

6.2.1. RESULTS OF THE PILOT PHASE

This observational phase was halted after 7 children out of the original desired sample size of 20 were recruited, since all 7 died. All were characterised by advanced decompensated shock that was inadequately corrected by WHO guideline with oliguria as a prominent feature- many developed complications of early oral feeding. Detailed description of the 7 cases is summarised in Table 6.9.

Table 6-9: Characteristics of children recruited to Faze I of the FIM study

Patient number	*Age Sex*	*Clinical features on arrival at HDU*	*Complications*	*Pre terminal events*
FIM 1.1	4years Male	Diarrhoea, vomiting and cough for 7days HIV: on Septrin prophylaxis *Prostration, deep breathing, chest indrawing, weak pulse, CRT>3s, temperature gradient*	• Anuric for 12 hours, urine output 0.7ml/kg over next 12 hours and subsequently was anuric Serum creatinine rose from 84µmol/L(admission) to 141 µmol/L(24 hours) • Increasing acidosis: Admission pH 7.254 fell to 7.121 at 24 hours	Cardio-respiratory arrest ≈36 hours post admission to HDU
FIM 1.2	6½y Male	Bloody diarrhoea Extensive dermatosis *Prostration, deep breathing, chest indrawing, weak pulse, CRT>3s, temperature gradient*	• Transferred Day 5 to HDU • Anuric during whole admission • Potassium fell to 1.1mmol/L • Group G *streptococcus*/ *S. aureus* on blood culture	Cardio-respiratory arrest ≈7½ hours after transfer to HDU
FIM 1.3	15m Male	Dermatosis. *Prostration, deep breathing, chest indrawing, weak pulse, CRT=4s, temperature gradient*	• Oliguria initially 24 hours then anuric subsequently • Creatinine rose from 44µmol/L to 124µmol/L (36 hours)	Cardio-respiratory arrest ≈42 hours after admission to HDU
FIM 1.4	21m Male	Hypoglycaemia *Prostration, deep breathing, CRT=4s,*	• Transferred Day 7 to HDU • Not able catheterise but reported to have had a wet bed. Serum creatinine improved from 129µmol/L (admission) to 97µmol/L (24 hours) • Clinically improved on first day before collapse on day 2.	Cardio-respiratory arrest ≈30 hours after transfer to HDU
FIM 1.5	38m Male	Prolonged convulsions Measles 2 weeks earlier Vomiting & bloody diarrhoea for 2 days *Coma, deep breathing, hypoxia (45% on high flow oxygen), CRT =3s, weak pulse, severe dehydration, temperature gradient*	• Oliguria over initial 24 hours urine output improved to 1.6ml/kg/h (Re-transfused on Day 1-2) but declined D3 to 0.7ml/kg/hr.Sudden deterioration at 86hrs : features of advanced shock and severe diarrhoea recurred • Serum creatinine gradually rose from 73µmol/L (admission) to 176µmol/L (Day 4).	Cardio-respiratory arrest ≈96 hours after admission to HDU
FIM 1.6	29m Female	Diarrhoea, cough & fever for 7 days *Prostration, deep breathing, weak pulse, CRT=3s,*	• Initial response good with urine output 1.7ml/kg/hour; • Osmotic diarrhoea developed – rapidly lead to development of advanced	Cardio-respiratory arrest ≈36 hours after transfer to HDU (1 day in the

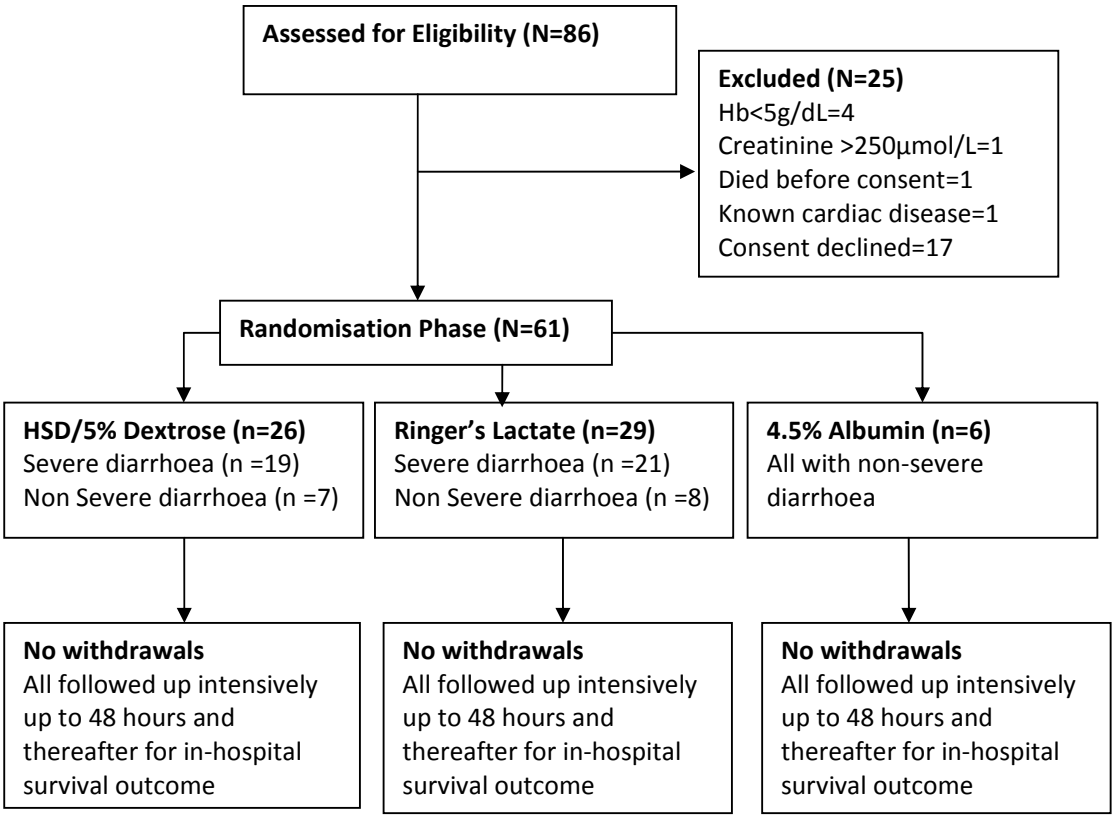
		temperature gradient	shock again • Serum creatinine increased from 66µmol/L at admission to 117µmol/L on day 2 in HDU	general ward)
FIM 1.7	18m Male	Fever & cough for 30 days Diarrhoea for 7 days Vomiting for 3 days Prostration, deep breathing, CRT=2s, • HIV	• Developed high output (osmotic-type) diarrhoea on feeds. Anuria –despite boluses of HSD/5D and transfusion • Serum creatinine increased from 73µmol/L(admission) to 131µmol/L (day 2) • Patient continued to have high volume stool output even on oral rehydration salts.	Cardio-respiratory arrest ≈40 hours after transfer to HDU (2 days in the general ward)

Results below report exclusively on the results of randomised controlled trial (RCT) phase, which compared two isotonic fluids (Ringer's lactate [RL] and 5% human albumin solution [HAS]) to the WHO recommended half-strength Darrow's with 5% dextrose (HSD/5D).

6.2.2. RESULTS OF THE RCT PHASE

Recruitment commenced in November 2006 and ended in May 2008. Eighty six (86) severely malnourished children with shock were assessed for eligibility. Of these, 25 were ineligible for recruitment and 61 were enrolled (Figure 6.6); 40 had hypovolaemic shock secondary to dehydrating diarrhoea (Group A) and 21 had hypovolaemic shock, presumed to have been secondary to sepsis or a sepsis-like syndrome (Group B). Children excluded had neither cardiogenic shock nor pulmonary oedema at admission.

Figure 6-5: Trial flow



6.2.2.1. Baseline characteristics

Sixty one children were recruited in the RCT phase: 40 in Group A (including 21 randomised to RL and 19 to HSD/5D) and 21 in Group B (8 allocated to RL, 6 to HAS, 7 to HSD/5D). Analysis was by ITT and included 26 children who received HSD/5D and 29 who received RL. Owing to the small numbers who received HAS, comparison with other treatment arms was not ideal, therefore, only mortality and safety outcome is presented. Baseline characteristics were similar for children randomised to the three different fluids (Table 6.10). Haemodynamic responses in participants who received HAS was also similar to that seen with other fluids (Table 6.10). Mortality among those who received HAS was 50% (3/6).

Table 6-10: Characteristics of participants who received albumin solution

	Characteristic	HAS (n=6)
Male, n (%)		5(62)
Age, months (IQR)		17(20)
Feature	N (%)	
	MUAC, mean ±SD	11.0(1.4)
	WHZ, mean ±SD	-3.6(0.6)
	Severe wasting	4(67)
	Kwashiorkor	1(17)
	Desquamation	1(17)
	HIV positive*	4/8(50)
Severity	N (%)	
	Deep breathing	2(33)
	Hypoxia (<95%)	1(17)
	Tachycardia[a]	2(33)
	Capillary refill >2s	3(50)
	Weak pulse volume	1(17)
	Temperature gradient[b]	2(33)
	Hypotension[c]	0
	WHO shock criteria	2(33)
Hydration		
	Reduced skin turgor	3(50)
	Sunken eyes	3(50)
Consciousness		
	Coma	2(33)
	Prostration	0
Abnormal biochemistry N (%)		
	Creatinine >80[d]	3(50)
	Hypokalaemia[e]	2(33)
	Hyperkalaemia[f]	1(17)
	Hyponatraemia[g]	1(17)
	Hypernatraemia[h]	0
	Hypoglycaemia[i]	1(13)
Laboratory variable, mean ±SD		
	Haemoglobin	9.6(2.7)
	pH	7.32 (0.23)
	Base deficit, mmol/L	9(11)
	Creatinine, µmol/L	108(56)
	Bicarbonate, mmol/L	15(7.9)

[a]heart rate=160beats/min, [b]temperature gradient, [c]systolic blood pressure <70mmHg, [d]Creatinine >80µmol/L, [e]Potassium<3.0mmol/L, [f]Potassium>3.0mmol/L, [g]Sodium<130mmol/L, [h]Sodium>145mmol/L, Glucose[i]<3.ommol/L, [j]Haemoglobin, mg/dL

The rest of the result presents a comparison between participants who received RL and HSD/5D (Table 6.11). The median age was 15 months (IQR; 12, 23), 64% (35) had severe marasmus and 21% (13) had kwashiorkor. Overall, 75% (41) fulfilled the strict WHO definition of advanced shock. Significantly more children in Group A fulfilled WHO criteria for shock, 32/40 (80%), compared to Group, 10/21 (48%) (p=0.01). Group A patients were also more severely acidaemic compared to Group B (pH 7.22±0.19 versus 7.34±0.17; p=0.03). The mean volume for the bolus infused in children

randomised to HSD/5D was 30ml/kg (standard deviation ±10ml) and 39ml/kg (standard deviation ±22ml) in those receiving RL. Mean sodium concentration at admission were similar between recipients of HSD/5D and RL (133[SD±11] versus 134[10) p=0.81, respectively).

Table 6-11: Baseline characteristics for children in Phase II trial

		HSD/5D (n=26)	RL (n=29)	P
Male, n (%)		15(58)	17(59)	0.94
Age, months (IQR)		15(14)	16(6)	0.41
Feature	**N (%)**			
	MUAC, mean ±SD	10.4(1.4)	10.0(1.9)	0.43
	WHZ, mean ±SD	-3.4(1.3)	-3.9(1.0)	0.18
	Severe wasting	14(54)	21(72)	0.15
	Kwashiorkor	8(31)	4(14)	0.19
	Desquamation	2(8)	1(3)	0.60
	HIV positive*	9(35)	14(48)	0.65
Severity	**N (%)**			
	Deep breathing	18(69)	21(72)	0.88
	Hypoxia (<95% or unrecordable)	3(12)	3(10)	0.57
	Tachypnoea (>60brpm)	16(62)	13(45)	0.22
	Severe tachycardia (>160bpm)	11(42)	8(28)	0.25
	Capillary refill ≥3s	15(58)	16(55)	0.53
	Weak pulse volume	13(50)	19(66)	0.24
	Bradycardia (<60bpm)	0	0	
	Temperature gradient	17(65)	23(79)	0.25
	Hypotension (SBP <70mmHg)	5(19)	5(17)	0.44
	WHO shock criteria	18(69)	23(79)	0.39
	Hypothermia (axillary temp< 35^0C)	0	0	
Hydration				
	Reduced skin turgor	8(31)	16(55)	0.07
	Sunken eyes	11(42)	19(66)	0.08
Consciousness				
	Coma	3(12)	4(14)	1.00
	Prostration	15(58)	13(45)	0.34
Abnormal biochemistry N (%)				
	Acidosis (base deficit >8)	12(46)	20(69)	0.09
	Creatinine (>80 mmol/L)	13(50)	13(49)	0.70
	Hyperkalaemia(<3.0 mmol/L)	16(62)	19(66)	0.76
	Hyperkalaemia(>5.5 mmol/L)	2(7)	0	0.22
	Hyponatraemia(<125 mmol/L)	4(15)	3(10)	0.58
	Hypernatraemia (>145 mmol/L)	3(12)	3(10)	1.00
	Hypoglycaemia(<3.0 mmol/L)	1(4)	4(14)	0.36
	Hyperglycaemia(>10.0 mmol/L)	0	0	
Mean laboratory variable, ±SD				
	Haemoglobin, g/dl	8.7(2.2)	8.9(1.9)	0.67
	pH	7.25(0.25)	7.26(0.13)	0.79
	Base deficit, mmol/L	14(11)	17(6)	0.26
	Creatinine, µmol/L	107(78)	95(58)	0.53
	Bicarbonate, mmol/L	14(13)	10(5)	0.16

*7 children were missing HIV test results: 4(15%) HSD/5D; 3(10%) RL arms

6.2.2.2. Primary outcomes

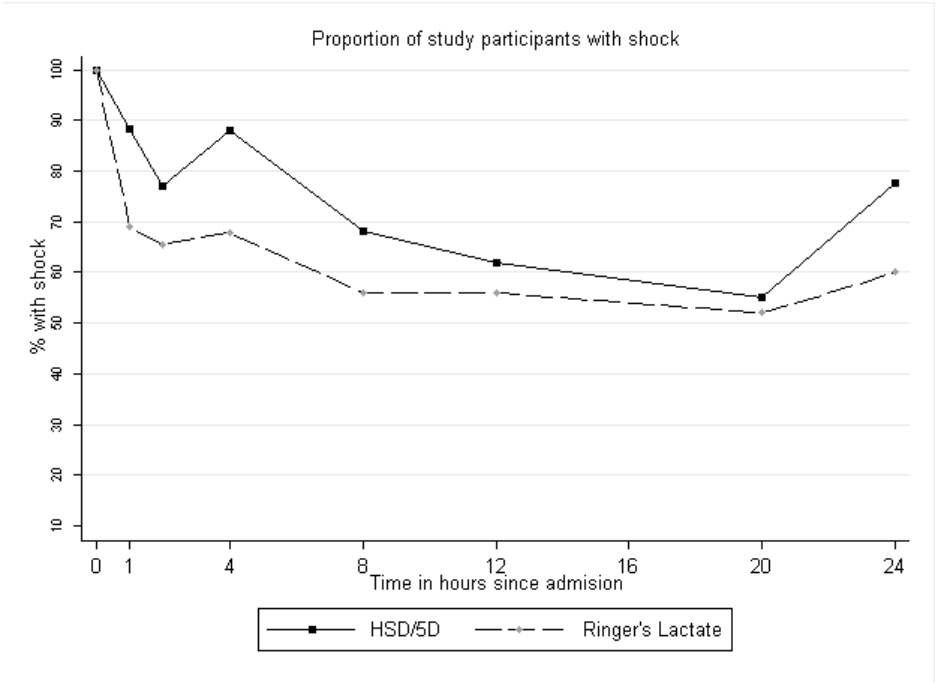
Table 6-12: Primary and Secondary outcomes

	Time	HSD/5D (n=26)	RL (n=29)	p
PRIMARY OUTCOMES				
Number with shock, n/N(%)	8 h	15/22(68)	14/25(56)	0.39
	24h	14/18(78)	14/25(56)	0.14
Oliguria (<1ml/kg/hour), n/N(%)	8 h	9/22(41)	3/25(12)	0.02
	24h	8/18(44)	6/25(24)	0.16
Tachycardia (>160 bpm), n/N(%)	8 h	6/22(27)	4/25(16)	0.34
	24h	8/14(44)	4/25(16)	0.04
Creatinine, mean(±standard deviation)	8 h	112(85)	104(60)	0.73
	24h	89(56)	112(87)	0.39
SECONDARY OUTCOMES				
Tachypnoea (>60 bpm), n/N(%)	8 h	7/22(32)	2/25(8)	0.04
	24h	7/18(39)	3/25(12)	0.04
Base deficit, mean(±standard deviation)	8 h	10(13)	15(7)	0.16
	24h	12(8)	8(9)	0.38
In-hospital mortality, n/N (%)		15/26(58)	13/29(45)	0.34

Resolution of shock

Both treatments did not result in prompt resolution of shock but a higher proportion of children who received HSD/5D still had features of shock at 8 hours compared to RL (15/22(68%) and 14/25(56%), respectively), p=0.39 (Figure 6.6). There was also a larger, though non-significant, decline in the proportion with shock amongst recipients of RL compared to HSD/5D especially in those with severe diarrhoea (Group A) (Table 6.12).

Figure 6-6: Proportion of children in shock over 24 hours of observation



A higher proportion of children randomised to HSD/5D **(**WHO solution) remained in shock compared those receiving RL over 24 hours of observation.

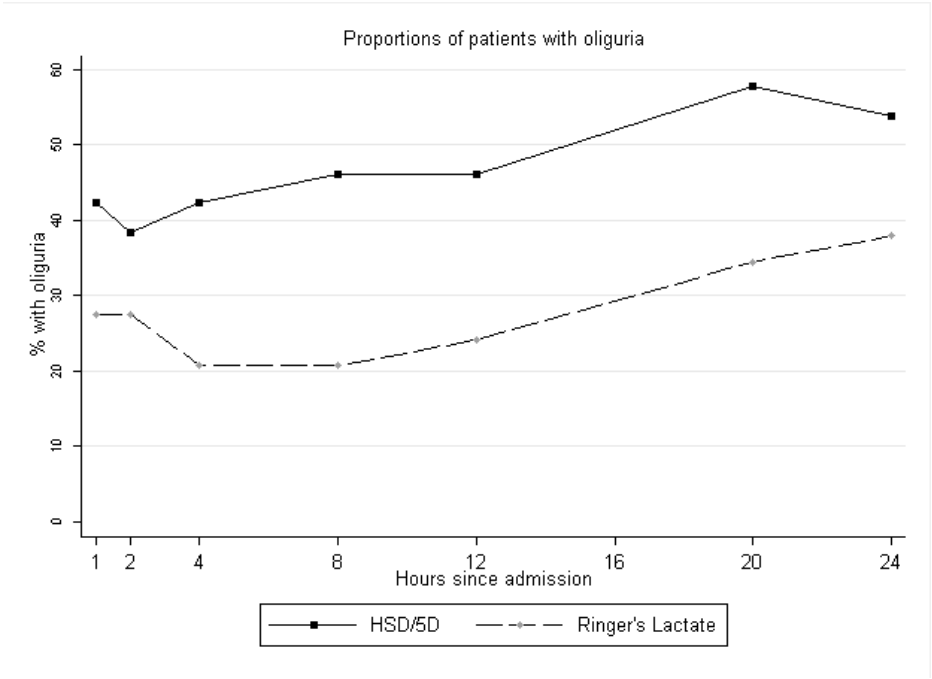
Tachycardia

Persistent tachycardia was common at 8 hours and at 24 hours, indicating ongoing shock but was more prevalent in the HSD/5D arm at 24 hours compared to RL (p=0.04) (Table 6.12). However summary measurement using median area under curve (AUC) of the heart rates did not show a significant difference (Kruskal-Wallis: x^2=0.3; p=0.59) between the two groups.

Oliguria

Oliguria was common in both intervention arms but was more prevalent in the HSD/5D arm at 8 hours (9/22; 41%) than in those receiving RL (3/25; 12%) p=0.02. By 24 hours, oliguria was still common in children receiving HSD/5D regime but was no different from RL group (Table 6.12). This was consistent with the finding of a lower median AUC for the hourly urine output (ml/kg/hr) in HSD/5D recipients (51; IQR, 36, 116) compare to RL recipients (101; IQR, 63, 141) (Kruskal-Wallis x^2=4.6; p=0.03). However, mean serum creatinine levels and proportion with elevated creatinine were similar in both arms during the course of 24 hours observation (Figure 6.7). Creatinine levels in this population may be falsely lower due to small muscle mass therefore it may not be a good indicator.

Figure 6-7: Proportion of children with oliguria over 24 hours of observation



6.2.2.3. Secondary outcomes

Respiratory distress

Respiratory distress, determined by severe tachypnoea, was less common in the children receiving RL than HSD/5D at both 8 and 24 hour. The mean respiratory rates also remained higher in the HSD/5D arm compared to RL arm at 8 (p=0.002).

Summary estimate using median AUC of respiratory rates showed higher values in participants who died (2262; IQR, 1938, 2897) compared to survivors (2015; IQR, 1547, 2391) (Kruskal-Wallis: x^2=3.6; p=0.06).

Resolution of base deficit

Mean reduction in base deficit, comparing admission to and 24 hours level, was greater in participants who received RL (8.5mmol/L; p=0.002) as compared HSD/5D (1.0mmol/L; p<0.87). Children who received HSD/5D also showed lower base deficit at 8 hours compared the RL (p=0.04) but no difference was noted in survivors to 24 hours (p=0.81). Many trial participants however remained severely acidotic (base deficit >15mmol/L) over the first 24 hours (Table 5.8).

Mortality

Combined in-hospital mortality for the various fluid strategies were as follows: HSD/5D (15/26=58%); RL (13/29=45%) and HAS (3/6=50%) P =0.62). The differences were more striking in Group A but were non-significant (p=0.11). Of all the deaths, 80% (25/31) fulfilled the WHO definition of shock at admission. Case fatality rates for WHO definition of shock were 60% (25/42) irrespective of intervention. The presence of WHO defined shock was associated with an increased risk of death (Risk Ratio=1.90, 95% confidence interval 0.92-3.82; P=0.04). Thirteen (42%) of the fatalities were HIV positive, 14(45%) were HIV negative, and 4 (13%) did not have HIV test results. Infection with HIV did not significantly increase the risk of death (odds ratio 1.18; 95% confidence interval 0.38, 3.72; p=0.76). Case fatality for kwashiorkor was 69% (9/13) and there was trend towards increased risk of death in the presence of kwashiorkor (odds ratio 2.2; 95% confidence interval 0.7, 10.1; p=0.14). With the differences in mortality seen between HSD/5D and RL, the study only had 16% power to demonstrate a difference in mortality if 10% type I error was allowed.

Time to death

Thirty nine percent (12/31) of the deaths occurred within 24 hours of recruitment while 52% (16/31) of fatalities occurred within 48 hours of enrolment. On Kaplan Meier survival analysis, we found no significant difference in the time to death when any of the intervention fluids are used for resuscitation (logrank test: combined (p=0.42), Group A (p=0.26), group B (p=0.22).

Severe adverse events

No child developed clinical features of pulmonary oedema or allergic reaction (to HAS) during the course of study observation. Frusemide or other diuretics were not required or prescribed during the trial. There were no differences in the mean sodium concentrations at admission (134±10 versus 134±10mmol/L, p=0.81), 8 hours (134 ±10 versus 139±10mmol/L, p=0.09), and 24 hours (138 ±9 versus 140±9mmol/L, p=0.47) between those who received HSD/5D and RL respectively. Therefore none of the fluids appeared to increase the risk of hyponatraemia or hypernatraemia.

6.2.3. Summary of findings

1. High mortality was seen in children defined as having shock by WHO criteria who were resuscitated using half-strength Darrow's with 5% Dextrose (HSD/5D) at volumes and rates recommended by WHO guidelines

2. There was improved survival in children with shock treated with HSD/5D following WHO fluid resuscitation guidelines after changing shock definition to include less severe ill group

and with changes in feeding regimen-delayed feeding (gut rest) in those with suspected paralytic ileus (abdominal distension or repeated vomiting).

3. Use of volumes currently recommended by WHO results in inadequate treatment of shock with either HSD/5D or Ringer's lactate. This was shown by a high proportion of children with persisting oliguria in either fluid arm.

4. There was better treatment of shock with Ringer's lactate compared to HSD/5D, using similar volumes, shown by significantly less proportion of children with oliguria who received Ringer's lactate.

5. Low dose resuscitation with isotonic crystalloid (Ringer's lactate) or colloid (HAS) is safe. No incidences of pulmonary oedema or heart failure noted

6. There was trend towards reduced mortality in participants receiving Ringer's lactate compared to HSD/5D but this requires confirmation in appropriately definitely designed trial.

CHAPTER 7 : SYSTEMATIC REVIEW

7.1. Introduction

Hypovolaemic shock is recognised as a major cause of death and morbidity among children requiring emergency care. Fluid resuscitation, with either isotonic crystalloid or colloidal solutions, is the primary management to restore intravascular volume [136] [220]. Physiological rationale have been advanced for preferential use of colloids over crystalloids due to their long intravascular half-life but this has not been backed by clinical experience [29-31]. Earlier Cochrane meta-analysis, concluded that fluid resuscitation using human albumin solution (HAS) resulted in increased risk of death[28-33] but subsequent meta-analyses have concluded that fluid resuscitation using saline and albumin result in similar survival outcomes[27] [30]. The latter conclusion has been influenced by results of the large multi-centre (SAFE trial) trial [34], which enrolled about 7000 adult patients in intensive care across Australia and New Zealand, and which found similar survival in patients who received albumin and saline[34]. Subgroup analysis of 492 participants with head injury showed a worse outcome in those treated with HAS (risk ratio=1.62; 95% CI, 1.12 to 2.34; p=0.009). Sub-analysis of 1218 patients with severe sepsis showed a non significant trend towards improved survival participant with sepsis treated with HAS (risk ratio=0.87; 95% CI, 0.74 to 1.02; p=0.09)[34]. These sub-analyses therefore highlighted a particular group of patients (with sepsis) to which albumin appeared beneficial.

Conclusions above may not be simply extrapolated to the paediatric population. This is due to a number of differences in physiology between adults and children. These include compensatory mechanisms (tachycardia in children, increased contractility in adults), different range of illnesses, and children have larger surface area to volume ratio hence suffer more fluid losses during illness compared to adults. Children frequently present with impaired consciousness, so concurrent meningoencephalitis can not be excluded, for whom there is a theoretical benefit that colloids may be the safer option for fluid resuscitation[229] [230] [312]. Therefore, separate paediatric guidelines have been developed for the emergency assessment and treatment of children.

None of the meta-analyses have addressed fluid resuscitation for shock in children due to few trials in this population. Evidence supporting the current guidelines for fluid resuscitation in paediatric shock has been graded as 2C (well-done observational studies with inconsistency of results plus problems with subgroup analyses)[137]. The previous systematic reviews have also combined clinically heterogeneous population of patients without focus on groups for which colloids may have plausible benefit[313-315]. This review focuses on the evidence behind the fluid management guidelines for the management of shock in children with severe infections and shock. It excludes conditions such as

trauma, burns, surgical conditions, and severe dehydration (gastroenteritis/diarrhoea) for which successive meta-analyses have reported superior benefit in using crystalloids[27 28 32 316]. We describe all trials available without limiting to comparisons between colloids only or crystalloids only. A meta-analysis has been done where studies could be combined.

7.2. Methodology

Information sources

The following electronic sources were searched; MEDLINE (1950 to September 2008), EMBASE (1980 to September 2008), PUBMED, and the Cochrane library. Additional studies that may have been missed from the searches were searched from the reference lists of the studies retrieved. Studies reported in previous Cochrane meta-analyses were also reviewed to assess if they met the inclusion criteria.

Search strategy

Searches were limited to children aged between 1 month and 12 years but there was no language restriction. Studies done in children with diarrhoea, trauma or surgery were excluded. Our strategy was developed by breaking the review question into exposure, intervention, population, publication language, and key words as recommended by the National Health Service (NHS)-Centre for Reviews and Dissemination (CRD)[317]. The highly sensitive MEDLINE search filters were also used[318]. Our review only included studies published up to September 2008 and authors of identified papers were not contacted to establish if they had any unpublished work. Search strategy is summarised in table 7.1.

Automated weekly searches of MEDLINE and EMBASE databases to retrieve any new relevant publications were done continually since the original search conducted in September 2008. This was using the original search terms and the results were directly sent to the authors email inbox. Only one study conducted in Kilifi and published in late May 2011 (FEAST trial[41]) was found relevant since the original search.

Study selection and methodological assessment

Two investigators independently reviewed the titles and abstracts of all the studies retrieved and full manuscripts of potentially relevant studies obtained and assessed to ascertain whether they met the inclusion criteria. Disagreements were resolved with the input of a third investigator who was the senior most. Methodological quality of the selected studies was assessed using a pre-developed proforma which collected information on study design, adequacy of randomisation, degree of allocation concealment, blinding/masking, and follow up.

Data extraction

The two unblinded investigations collected information on disease category, the study authors, year of publication, country where the study was conducted, study design (randomisation, allocation, masking), number of participants, fluid interventions given, outcome measures used, side effects of interventions and mortality.

Table 7-1: Summary of search strategies used to retrieve the relevant studies

Search element	MEDLINE	EMBASE	Cochrane Library
Exposure	Thesaurus term exploded Shock Shock, septic Hypovolemia Multi Organ failure Hypotension +Subheading Therapy Prevention & Control	Thesaurus term exploded Shock Shock, septic Hypovolemia Multi Organ failure Hypotension +Subheading Therapy Prevention & Control	Mesh term exploded all trees Shock, septic Hypovolemia Hypotension Key word: Shock
Intervention	Thesaurus term exploded Colloids Fluid Therapy Dextrans Polygeline Hetastarch Plasma Substitutes +Subheading Administration & Dosage, Therapeutic Use, Toxicity Therapy Adverse effects	Thesaurus term exploded Colloids Fluid Therapy Dextrans Polygeline Hetastarch Plasma Substitutes +Subheading Administration & Dosage, Therapeutic Use, Toxicity Therapy Adverse effects	Mesh term exploded all trees Colloids Fluid Therapy Dextrans Polygeline Hetastarch Plasma Substitutes
Keywords (for intervention)	albumin*, ppf, gelatin*, colloid*,gentran*, haemaccel, hemaccel, pentastarch pentaspan, gelofusine, Gelafundin, crystalloid*, ringer*, hartman*, sodium*, fluid therap*, plasma substit*, volume replace*, plasma replace*, fluid replace*, fluid restor*, fluid resusc*, fluid expansion Searched in: mp=title, original title, abstract, name of substance word, subject heading word	albumin*, ppf, gelatin*, colloid*,gentran*, haemaccel, hemaccel, pentastarch pentaspan, gelofusine, Gelafundin, crystalloid*, ringer*, hartman*, sodium*, fluid therap*, plasma substit*, volume replace*, plasma replace*, fluid replace*, fluid restor*, fluid resusc*, fluid expansion Searched in: mp=title, original title, abstract, name of substance word, subject heading word	albumin*, ppf, gelatin*, colloid*,gentran*, haemaccel, hemaccel, pentastarch pentaspan, gelofusine, Gelafundin, crystalloid*, ringer*, hartman*, sodium*, fluid therap*, plasma substit*, volume replace*, plasma replace*, fluid replace*, fluid restor*, fluid resusc*, fluid expansion
Population	Humans Infant (1 to 23 months) Preschool child (2 to 5 years) Child (6 to 12 years)	Human Infant (up to one year) Child Preschool child (1 to 6 years) School child (7 to 12 years)	No limits
Publication language	No restrictions	No restrictions	No restrictions

Study design	controlled.mp controlled clinical trial*.mp clinical.mp, trial*, randomi* controlled trial*.mp, double.mp, blind.mp double blind.mp placebo*.mp random*.mp single.mp single blind.mp triple.mp triple blind.mp mask*.mp controlled trial*.mp meta analysis.mp or Meta-Analysis/ clinical trial*.mp metanalysis.mp exp Research Design/ prospective*.mp, Prospective Studies/ Evaluation Studies/ Cross-Over Studies/ Follow-up Studies/ Comparative Studies/	controlled.mp controlled clinical trial*.mp clinical.mp, trial*, randomi* controlled trial*.mp, double.mp, blind.mp double blind.mp placebo*.mp random*.mp single.mp single blind.mp triple.mp triple blind.mp mask*.mp controlled trial*.mp meta analysis.mp or Meta-Analysis/ clinical trial*.mp metanalysis.mp exp Research Design/ prospective*.mp, Prospective Studies/ Evaluation Studies/ Cross-Over Studies/ Follow-up Studies/ Comparative Studies/	controlled.mp controlled clinical trial*.mp clinical.mp, trial*, randomi* controlled trial*.mp, double.mp, blind.mp double blind.mp placebo*.mp random*.mp single.mp single blind.mp triple.mp triple blind.mp mask*.mp controlled trial*.mp meta analysis.mp or Meta-Analysis/ clinical trial*.mp metanalysis.mp exp Research Design/ prospective*.mp, Prospective Studies/ Evaluation Studies/ Cross-Over Studies/ Follow-up Studies/ Comparative Studies/
Limits	Studies with the following keywords in the title excluded; diarrh*,gastr*,burn*,surg*oral*,traum* ORS*, choler*, shigel*, women, caesarean, maternal, enter*, injur*, dysent*	Studies with the following keywords in the title excluded; diarrh*,gastr*,burn*,surg*oral*,traum* ORS*, choler*, shigel*, women, caesarean, maternal, enter*, injur*, dysent*	Studies with the following keywords in the title excluded; diarrh*,gastr*,burn*,surg*oral*,traum* ORS*, choler*, shigel*, women, caesarean, maternal, enter*, injur*, dysent*

Eligibility and exclusion criteria

We included controlled trials, quasi randomised trials, cohort studies, and randomised controlled trials comparing different intravenous fluids for the treatment of shock; trials where the fluids were given as boluses; enrolled children aged between 1 month and 12 years; trials with above whether comparing crystalloids versus colloids, crystalloids versus crystalloids, or colloids versus colloids; trials investigating fluid resuscitation conducted in any infectious disease condition (sepsis, malaria, dengue and any other infectious). Studies that reported fluid resuscitation in diarrhoeal disease, burns, trauma/injury cases, and where fluid was given for a surgical procedure or anaesthesia purposes were excluded.

Synthesis of results

Qualitative description of studies is given where statistical pooling was not possible but a quantitative summary (meta-analysis) where possible. Both clinical and methodological heterogeneities were assessed by reviewing and comparing the patient populations, interventions, outcomes, disease spectrum covered, study design, and risk of bias. REVMAN software was used to assess the risk of bias by assessing adequacy of sequence generation, allocation concealment, blinding, completeness of the data, and selective reporting [319 320].

Summary measures

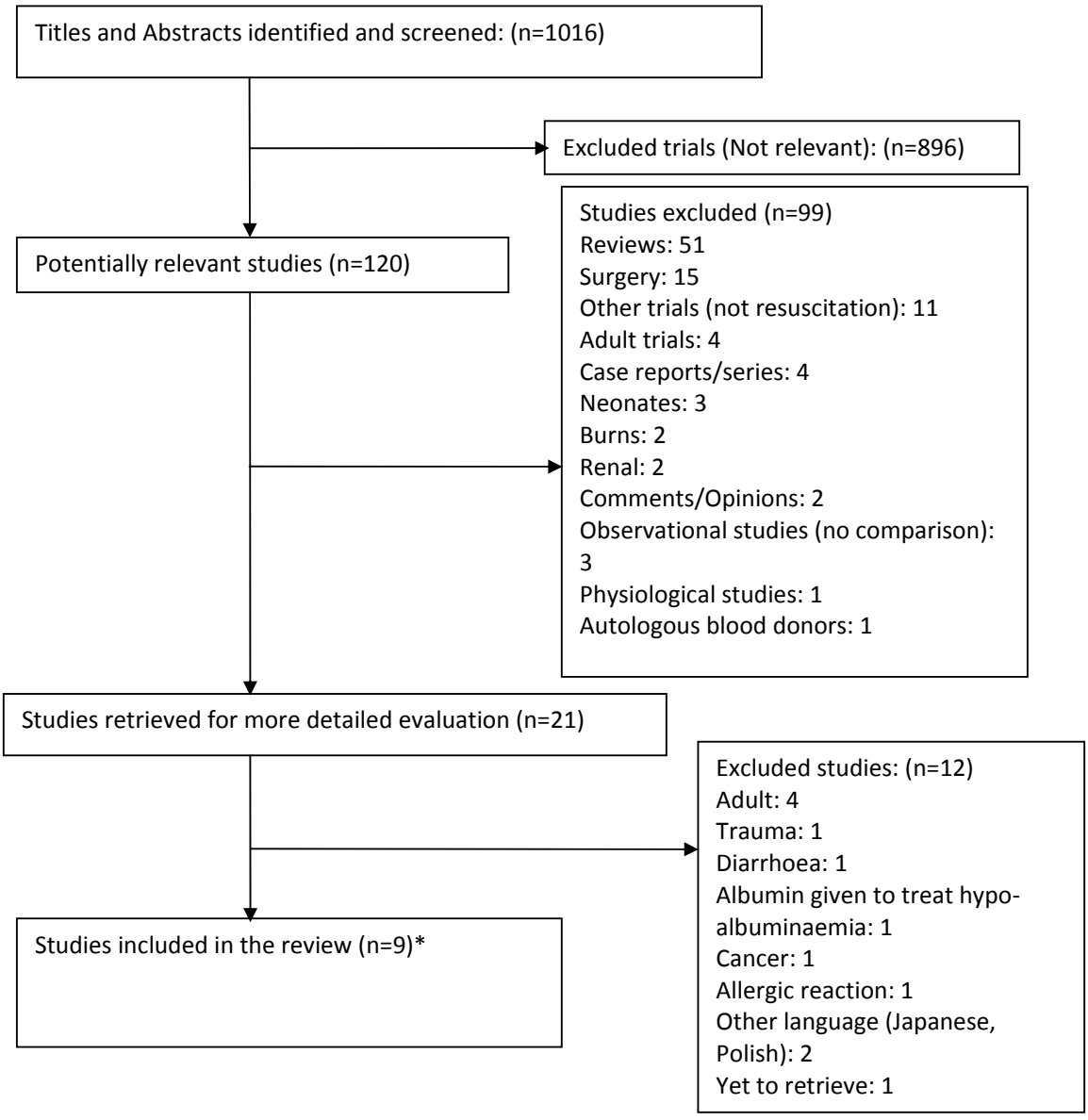
For studies that compared crystalloids against colloids (any colloid or HAS alone) reporting at least one death (in either arm), Peto odds ratio was calculated using the fixed-effects model for each study, a forest plot derived and a chi-square test for statistical heterogeneity calculated. Peto odds ratio was used because of rare events (mortality) in children with dengue septic shock. Studies which were judged to have clinical or methodological heterogeneity were not combined.

7.3. Results

Study selection

A total of 1016 studies were identified from our original search covering period until September 2008, out of which 120 studies were found to fulfil inclusion criteria. Twenty one studies were selected from the relevant studies, full copies retrieved and more detailed methodological evaluation done. Only 9 studies were finally identified as meeting the inclusion criteria (Figure 7.1)[34 321-331]. The initial section of the results presents the findings of the systematic review until September 2008 and later sections incorporates the findings of the only trial retrieved later (FEAST trial[41]) and presents both narrative review and meta-analysis with FEAST results included.

Figure 7-1: Summary of paediatric fluid trials up to September 2008



**1 further relevant study-FEAST trial-published in May 2011 and included in later sections*

Study characteristics

The total number of patients reported in the studies was 1198 (until September 2008), with the largest study reporting 512 patients and the smallest with 27 patients. The characteristics of the nine studies that we included are reported in table 7.2 while table 7.3 describes excluded studies**.** All

these studies were conducted in low income settings; four studies in Kenya[19-21 141], and five studies in Asia[37 38 40 271 332]. Four studies were in children with malaria, four in those with dengue shock syndrome, and one study was in children with sepsis.

Summary of risk of bias within studies

Two studies conducted in Kilifi in children with severe malaria[21 141] did not have adequate sequence generation, no allocation concealment, were open labelled, and with quasi randomisation. The other two Kilifi studies[19 20] had adequate sequence generation and allocation concealment, but were also unblinded but with a similar follow-up, up to hospital discharge. The studies in dengue shock syndrome in Vietnam were all randomised, double blind, with adequate allocation concealment and adequate sequence generation[37 38 40] but the one conducted in the Philippines[271] only reported that there was 'systematic allocation' without details but follow-up was described and protocol violation was blamed for all the deaths. The trial in septic shock was done India[332] and was open labelled, with adequate randomisation and sequence generation, and follow up was also described. Patients in the sepsis trial either had a focus of infection or a systemic infection.

Risk of bias across studies

Studies in dengue shock that were done in Vietnam had a low risk of bias but limited information about mortality. Most information on the effect of colloids on mortality are derived from studies conducted in severe malaria which were unblinded, small in size, and two studies had quasi-randomisation- all factors that increase risk of bias. The study in sepsis also had high risk of bias because it was small in size and had no sample size calculation. The study in dengue conducted in the Philippines had a high risk of bias due to the study design.

Table 7-2: Characteristics of the studies retrieved on paediatric fluid resuscitation

Methods	Participants	Interventions	Outcomes	Comments
Akech 2006				
Controlled trial (quasi randomisation) −Sequential blocks of 10 −No blinding −No allocation concealment −Follow up to discharge from hospital for adverse events	88 children with malaria −Aged >3 months with metabolic acidosis (base deficit >8mmo/L); −Hb >5g/dL; Plus a clinical feature of shock	−Gelofusine (n=44), −4.5% human albumin solution (HAS) (n-44) Bolus 20 or 40ml/kg over 1 hour in decompensated shock. Further 20ml/kg if still in shock at 1 hour.	−Resolution of shock −Resolution of acidosis at 1 and 8 hours −In-hospital death −Adverse events −Neurological sequelae −Allergic reactions	−Quasi randomisation. −Inadequate allocation concealment −inadequate sequence generation −Colloid versus colloid comparison
Cifra 2003				
Quasi randomised trial Patients were allocated 'systematically' −Alternate allocation −No information on blinding −All outcomes in-hospital −No loss to follow-up	Dengue shock syndrome; 27 children	−6% Hydroxyethyl starch (Haes-Steril) (n=11) −Ringer's lactate (n=16)	−Duration of control of shock, −frequency of recurrence of shock, − length of ICU stay −Mortality	−Inadequate allocation concealment −Inadequate sequence generation
Dung 1999				
Randomised controlled trial (RCT) −Allocation concealment using numbered opaque envelopes −Double blind using opaque envelopes in blocks of 10 −Fluid masked using black opaque	Dengue shock syndrome; 50 children aged 5-15 years, who had not received IV fluid therapy during current illness	−Dextran 70 (n=12), −3% gelafundin(n=13), −Ringer's lactate(n=13), and −Normal saline(n=12). Bolus 20ml/kg over 1 hour, 10ml/kg over second hour	−Recovery from shock (pulse pressure ≤ 20mmHg), −Duration & number of episodes of shock, −Improvements in cardiac output and haematocrit values and, − Requirements for further fluid resuscitation	−Adequate allocation concealment and adequate sequence generation −No deaths

containers. –Follow-up to hospital discharge				
Maitland 2003				
Controlled trial (quasi randomisation) –Alternate systematic allocation –Allocation also based availability of study fluid –No blinding –No allocation concealment –Follow-up to 48 hours post-admission for haemodynamic variables & blood gases (acidosis)	53 children with severe malaria: –Aged 6months-12years –Metabolic acidosis (base deficit >8mmol/L) –Divided into severe anaemia (Hb<5) & those without severe anaemia	–0.9% saline (n=20) or –4.5% HAS(n=32), –mixture of saline and HAS (n=1) Aliquots of 10ml/kg given to achieve central venous pressure (CVP) between 5-8cm H2O. Bolus of 10-40ml /kg given over first hour after admission	–Resolution of acidosis/base deficit reduction at 8 hours, –CVP between 5-8cmH_2O and, –improvement of haemodynamic indices	–Inadequate allocation concealment and, – Inadequate sequence generation
Maitland 2005a				
Randomised controlled trial –No blinding –Allocation concealment using opaque envelopes –Follow-up to discharge from hospital for adverse events	150 children with severe malaria: –Aged 6months-12years, –Metabolic acidosis (base deficit >8mmol/L) –Hb >5g/dL	–0.9% saline (n=61), –4.5% HAS(n=56), or –No bolus(n=33) –Moderate acidosis (base deficit 8-15mmol/L) given 20ml/kg or No bolus (control). –Severe acidosis (base deficit >15mmol/L) given 40ml/kg, no control group. –Rescue if hypotensive or oliguria	–Resolution of acidosis/base deficit reduction at 8 hours, –In-hospital death, –Neurological sequelae, –Need for rescue therapies	–Adequate allocation concealment –Computer generated randomisation sequence produced by an independent statistician -information provided by authors of the review who conducted the studies
Maitland 2005b				
Randomised Controlled trial –Allocation concealment using	61 children with symptomatic severe malaria anaemia: –Aged >2months PLUS – Metabolic acidosis (base deficit	–0.9% saline (n=20), –4.5% HAS (n=23), or –Control (No bolus) (n=18)	–Resolution of acidosis/base deficit reduction at 8 hours, – In-hospital death,	–Adequate allocation concealment –Computer generated randomisation sequence

a sealed card system –No blinding –Follow-up to discharge from hospital for adverse events	>8 mmol/L)	Bolus 20ml/kg of normal saline or albumin over 1 hour whilst awaiting blood transfusion	–Neurological sequelae	produced by an independent statistician -information provided by authors of the review who conducted the studies
Maitland 2011		–	–	–
Randomised Controlled trial –Allocation concealment using a sealed card system –Random sequence generation –No blinding, no masking –follow-up to one month	3170 children with severe febrile illness enrolled at admission: –Aged 2months-12years, –fever (≥37°C or <36°C) or history of fever, –impaired consciousness and/or respiratory distress, –plus a feature of impaired perfusion –Excluded severe dehydration (gastroenteritis), burns, trauma, sickle cell disease, severe malnutrition, chronic renal disease, pre-existing heart disease, or if has features of fluid overload at admission	–0.9% saline(n=1047) –5% HAS (n=1050) –control (n=1044) –Hypotensive shock; 0.9% saline (n=16), 5% HAS (n=13) Intervention: Bolus arms-20ml/kg (later 40ml/kg) over first hour of admission OR 40ml/kg (later 60ml/kg) if has hypotensive shock over first hour of admission. Further 20 ml/kg if has sign of shock at 1 hour. Beyond 2 hours-40ml/kg if has hypotensive shock otherwise no bolus. Control arm-4ml/kg/hour of low-sodium salt solution if deemed necessary. Stopped as per clinical judgement	–48-hour survival –1 month survival –disability free survival at 1 month –adverse events-pulmonary oedema, raised intracranial pressure, allergic reactions	–Adequate allocation concealment and adequate sequence generation –Complete follow-up-good retention
Ngo 2001				
Randomised controlled trial (RCT) –Double blind with fluid masked using black opaque containers. –Allocation concealment using opaque envelopes	230 children with Dengue shock syndrome, –Aged 5-15 years and not received IV fluid therapy during current illness	–Dextran 70(n=55), –3% gelatin (gelafundin) (n=56), –Ringer's lactate(n=55), or –Normal saline(n=56), –Bolus 20ml/kg over 1 hour, 10ml/kg over second hour –8 children had dengue haemorrhagic fever (DHF) grade IV and not randomised	–Recovery from shock (pulse pressure ≤ 20mmHg), –Duration & number of episodes of shock, –Improvements in cardiac output and haematocrit values and, – Requirements for further	–Adequate sequence generation and adequate allocation concealment. –No deaths

in blocks of 10 –Follow up to hospital discharge			fluid resuscitation	
Upadhyay 2005				
Randomised controlled trial (RCT) –Open label, randomised –Random tables used to generate numbers, –Allocation concealment using sealed envelopes and kept with one investigator –Monitoring till 6 hours post stability then till recovery	60 children with sepsis; –Aged 1 month -12 years. –Septic shock, without clinical evidence of organ failure at admission or hypotension	–Normal saline (n=31) or, –Haemaccel (n=29). Bolus 20ml/kg of 0.9% saline or Haemaccel till haemodynamically stable or if CVP >10mmHg	–Haemodynamic stabilization (heart rate, capillary refill time, pulse volume & blood pressure in normal range), – Plasma volume at the end of fluid resuscitation and, –Incidence of organ dysfunction	Adequate allocation concealment and adequate sequence generation
Wills 2005				
Randomised controlled trial (RCT). –Computer-generated random numbers –Double blind-treatment packs in sealed special cardboard containers, identified only by study number –Independent staff not involved in care prepared packs and randomisation	512 children with Dengue shock syndrome; –Children aged 2-15 years with clinical DSS	–Ringer's lactate (n=128), –6% Detran70 (n=193), or –6% hydroxyethyl starch (n=191) –Group1=moderate shock (pulse pressure, >10 and ≤20mmHg)-Dextran, Starch, or Ringers Lactate –Group2=severe shock (pulse pressure,<10mmHg) allocated to Dextran or starch and given 15ml/kg over 1 hour, 10ml/kg over second hour	–Requirement for rescue colloid at any time after infusion of study fluid, –Time taken to achieve initial cardiovascular stability (pulse pressure ≥25 & systolic blood pressure ≥ 80mmHG for minimum of 2 hours), –Volumes of rescue colloid and total parenteral fluid required, –Number of days in hospital, –Change of haematocrit,	Adequate sequence generation and adequate allocation concealment

–Pre-sealed and pre-labelled envelops used in emergency –Allocation concealment –Follow-up to discharge from hospital	–Allergic reactions

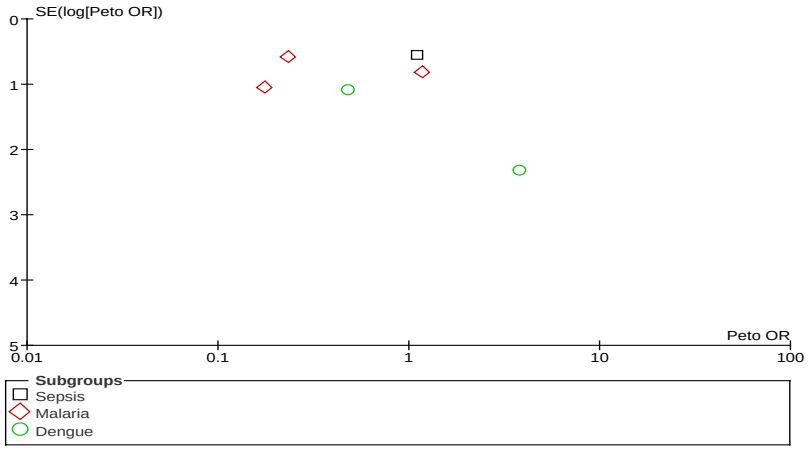
Table 7-3: Characteristics of excluded studies

Study	Reason for exclusion
Alpar 2004	Trauma
Beards 1994	Adults
Finfer 2004	Adults
Haibach 1976	Not retrieved
Ochocka 1984	Article in Polish, not retrieved
Pockaj 1994	Conducted in patients with cancer
Rackow 1983	Adults
Rahman 1988	Diarrhoea
Schortgen 2000	Adults
Tanaka 1975	Article in Japanese, not retrieved
Veneman 2004	Albumin given to treat hypo-albuminaemia
Weis 1983	Interventions given to test for allergic reaction

Publication bias

The funnel plot of studies included in the meta-analysis was symmetrical on visual inspection, with studies with odds ratios <1 and >1 equally represented. Therefore, there was no evidence of evidence of publication bias from the funnel plot-Figure 7.2.

Figure 7-2: Funnel plot to assess the risk of publication bias



Qualitative description of study findings

Patient-important outcomes considered in the review were efficacy in the treatment of shock, mortality, and adverse events.

Treatment of shock

Different parameters were used to define resolution of shock in the studies including: the volume of fluids needed for resuscitation, the time taken for haemodynamic stabilisation, the need for "rescue" fluids, acid-base normalisation and recovery, duration of shock, and any subsequent episodes of shock. No differences were seen in the recovery from shock patients with sepsis or malaria resuscitated using various fluids compared in the trials. In severe malaria, patients who received equivalent volumes of either 0.9% saline or 4.5% HAS had similar improvements in the central venous pressure (CVP)[21], reduction in acidosis and other features of shock[19 20]. Similar results were seen in the trial HAS to Gelofusine[141]. In the sepsis trial, which enrolled 60 patients, there was similar haemodynamic stability (heart rate, capillary refill time, pulse volume, and blood pressure) at 6 and 12 hours among those resuscitated using saline compared to gelatin polymer (Haemaccel®)[333] but resuscitation with saline required 20ml/kg more than the volume of gelatin polymer to achieve haemodynamic stability (measured by capillary wedge pressure). However, in dengue shock colloids had consistent better efficacy compared to crystalloids for treatment severe shock as determined by

faster restoration of cardiac index, normalisation of haematocrit, and/or blood pressure[37 38 40 271]. In moderate DSS shock, defined by pulse pressure >10mmHg and ≤20mmHg, shock correction using Ringer's lactate had similar results to colloids (starch or dextran)[272].

Mortality

None of the studies was designed definitively with mortality as a primary outcome. Only five deaths occurred in the four dengue trials dengue which enrolled 819 children. A total of 352 children were enrolled fluid expansion trials in children with severe malaria. Two studies involved a 'no bolus' control, which included a total of 51 children [334 335] and 301 enrolled to fluid bolus arms. One study comparing 0.9% saline to HAS demonstrated a significant overall reduction in mortality in the group randomised to albumin (HAS-2/56 versus saline-11/61; p=0.013) and in the high risk subgroup, where acidosis and shock was complicated by coma (HAS-1/21 versus saline-11/24; p=0.002). However there were no differences between the fluid intervention arms in cases without coma (P=0.7)[335]. Reduced risk of mortality with HAS was also seen in the trial comparing HAS to Gelofusine where children randomised to the HAS arm had a lower mortality compared to Gelofusine arm (HAS-1/44 versus Gelofusine-7/44; p=0.06), and particularly in the sub group with coma (HAS-1/25 versus Gelofusine-6/23; p=0.04) [336]. In sepsis, there was no difference in mortality in fluids used; 9/31 (29%) of saline recipients died compared to 9/29(31%) in the Haemaccel group[332].

Adverse events

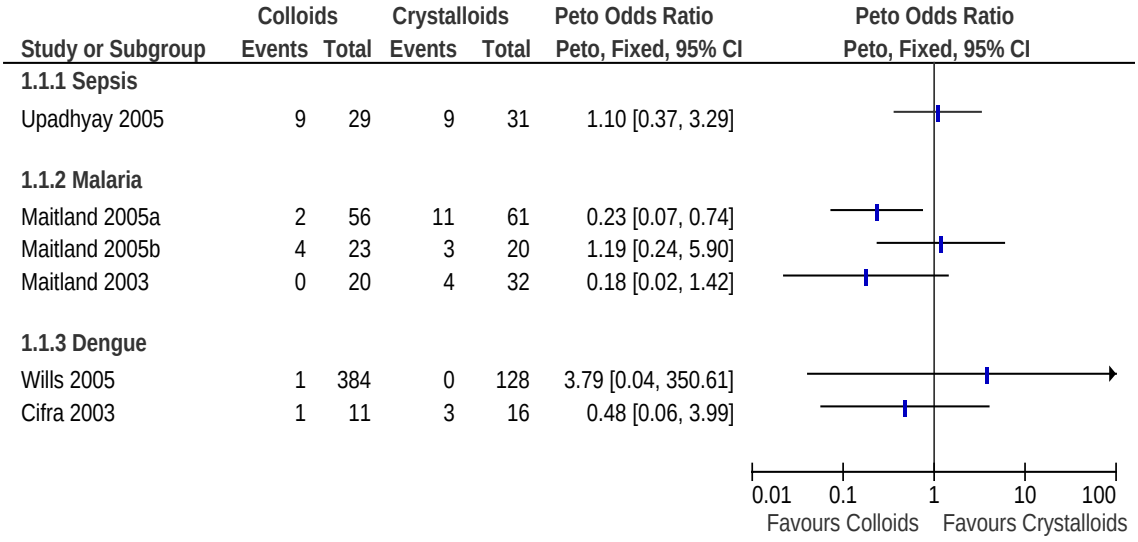
Children with severe malaria who received HAS showed a non-significant increase in neurological sequelae in survivors compared to those receiving other fluids; 9/97 (9%) in albumin, 6/54(6%) in saline and 1/37 (3%) in Gelofusine. A single episode of allergic reaction was reported in a child who received Gelofusine. Pulmonary oedema was reported in 2/61 (3%) children who received saline. Children with DSS treated with dextran (15/193, 8%) developed signs of severe reactions which included fever and rigors without systemic disturbance whilst one (1/191) child receiving starch (6% hydroxyethyl starch) developed an afebrile event with an urticarial rash in the same trial[40]. In another dengue trial 5/56 (9.0%) children receiving gelatin polymer (Gelafundin) and one (1/70) receiving dextran developed allergic reactions. Single episodes of severe epistaxis and haematoma have been reported in two children who received dextran. No adverse reactions were reported in the sepsis trial.

7.3.1. Meta-analysis

Colloids versus crystalloids

Six trials (3 malaria trials[19-21], 2 dengue trials[40 271] and one sepsis trial[332]) with at least one death were chosen for comparison between colloids and isotonic crystalloids (normal saline or Ringers Lactate) [19-21 333 272 271]. A total of 811 subjects were included; 523 randomised to colloids, 288 to crystalloids and a total of 48 deaths (17(35%) received colloids and 31(65%) received crystalloids). A composite estimate was not provided because of clinical heterogeneity in the risks of mortality between the different conditions- dengue, malaria and sepsis although forest plots did not indicate statistical heterogeneity (chi^2 =2.66, p=0.26). Four out of six studies showed better survival in children resuscitated with colloids compared to crystalloids but imprecision was common since the confidence intervals crossed the null value. The results are summarised in a forest plot in Figure 7.3.

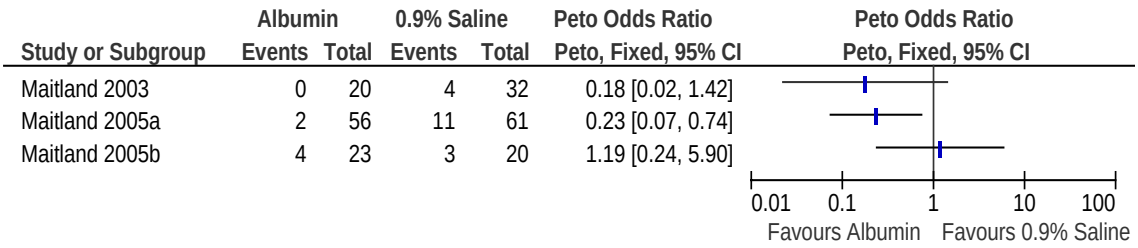
Figure 7-3: Mortality in children resuscitated using colloids versus crystalloids



Albumin versus crystalloids

Only studies in severe malaria compared albumin to crystalloids. Even in this sub-group, there was still clinical heterogeneity because one study enrolled children with severe anaemia, where fluid resuscitation was given as pre-transfusion management[19], whilst the other two studies excluded children with severe malaria anaemia[20 21]. Therefore a summary estimate was not calculated-Figure 7.4. The largest of these trials showed a significant reduction in mortality for those resuscitated using HAS compared to saline[335], another trial showed non-significant reduced mortality[337], whilst the third trial (in those with severe malaria anaemia) showed a non-significant reduced survival[334] in those treated with HAS. The study comparing HAS to Gelofusine showed a non-significant reduction in mortality in those resuscitated using HAS; mortality in HAS arm was 1/44 (2%) compared to 7/44 (16%) in gelofusine arm, Peto odds ratio= 0.20, 95% confidence interval 0.05-0.83 (p=0.03).

Figure 7-4: Mortality in children resuscitated using albumin versus crystalloids



Septic shock

There was no difference in the risk of mortality between saline and gelatin polymer in the single trial in septic shock; Peto odds ratio 1.10; 95% confidence interval, 0.37, 3.29; p=0.87).

7.3.2. Meta-analysis including the FEAST trial results

The FEAST trial was a large multi-centre definitive randomised trial that enrolled 3170 children aged between >60 days and <12 years with severe febrile illness and impaired perfusion admitted to six hospitals in East Africa[41]. Severe febrile illness was defined as fever (axillary temperature ≥37.5°C or <36°C) or history of fever in current illness plus impaired consciousness (coma or prostration) or respiratory distress (deep breathing, chest indrawing, increased work of breathing). Coma was defined as inability to localise painful stimulus and prostration as inability to sit unsupported, or to breast feed if < 8 months. Impaired perfusion was defined as one or more of; capillary refill > 2s, lower limb temperature gradient, weak radial pulse volume, or severe tachycardia. Decompensated shock was defined as hypotension or unrecordable blood pressure in the presence of any of the above signs of impaired perfusion. Children with the following were excluded: severe dehydration (gastroenteritis), burns, trauma, sickle cell disease, severe malnutrition, chronic renal disease, pre-existing heart disease, or if they had features of fluid overload at admission.

Eligible children without decompensated shock were enrolled to 5% human albumin bolus (1050 children), 0.9% saline bolus (1047 children), or control/no bolus/maintenance fluid (1044 children) in the ratio of 1:1:1. Those with decompensated shock were enrolled in 1:1 ratio to either saline bolus (16 children) or albumin bolus (13 children). Children with impaired perfusion received 20ml/kg (40ml/kg after protocol change) of bolus over one hour at admission and further 20ml/kg bolus within the next hour if there were signs of impaired. Further boluses beyond 2 hours were only given if there was decompensated shock-40ml/kg (60ml/kg after protocol change) over 1 hour of bolus. Children with decompensated shock received 40ml/kg (60ml/kg after protocol change) over 1 hour bolus at admission otherwise the rest of criteria for administering fluid were similar to the group with impaired perfusion only. Children randomised to control received 4ml/kg/hour of low-sodium

salt solution if deemed necessary by the attending clinician. Maximum fluid boluses infused were 80ml/kg (100ml/kg after protocol change) within 24 hours. Children randomised to boluses also received maintenance fluid at similar rates after the boluses. Other management apart from the boluses were similar in the boluses and control arms.

This was a pragmatic trial and enrolled children with both positive and negative malaria slide. Randomisation was done by sealed enveloped that had been independently prepared away from the trial sites through randomly generated sequences. There was no masking of the interventions or blinding but there was adequate concealment of allocation. The primary outcome for the study was mortality within the first 48 hours of admission. Secondary outcome was mortality and neurological outcome at one month after enrolment-all enrolled children reviewed at one month. The study was adequately powered to answer several questions such as; overall effect of fluid bolus on mortality (bolus versus control), saline versus albumin, and compare bolus efficacy in subgroup with malaria and in the non-malaria group. The non-malaria group is classified here as having sepsis. There was complete reporting of both primary and secondary outcomes. Children with neurological sequelae at one month were booked for review at 6 months post-enrolment, an adequate duration to detect ongoing impairment or resolution.

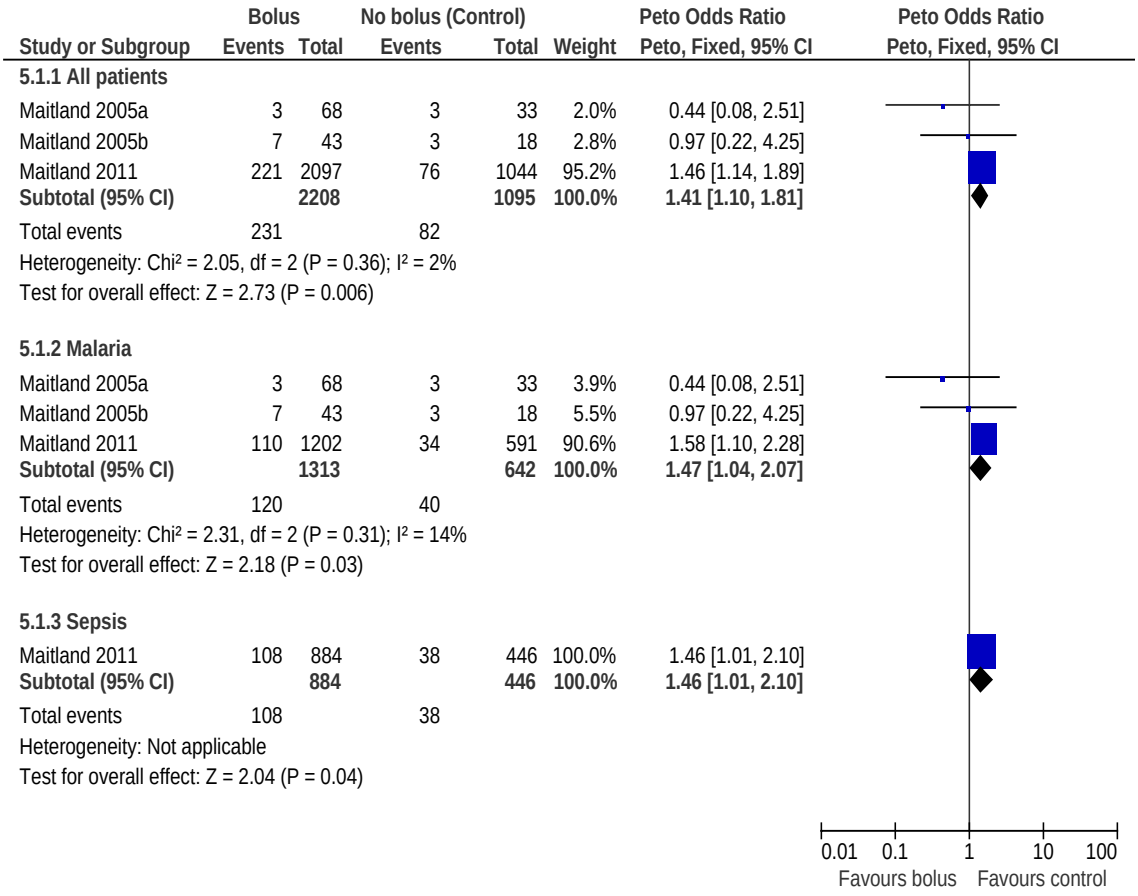
Two cases, unlikely rated, of suspected allergic reaction were reported in the saline arm; suspected pulmonary oedema was reported in 24 children (13 in the albumin-bolus group, 6 in the saline-bolus group, and 5 in the control group); and increased intracranial pressure in 42 children (14 in the albumin-bolus group, 18 in the saline bolus group, and 10 in the control group). However additional information provided by the study team in the web appendix show[41] that few of the suspected cases of pulmonary oedema (only 1 in HAS arm) or raised intracranial pressure were (3 events; 2 in HAS and 1 in no bolus) related to the intervention given after adjudication by and an independent end-point review committee.

7.3.3. Bolus versus control (no bolus)

The FEAST trial[41] and two other trials[19] [20] conducted in Kilifi have involved patients enrolled to a control arm. In one trial, control/no bolus was only used in the arm with moderate acidosis but only boluses (saline or albumin) in severe acidosis[20]. Therefore comparison between bolus and control in that study[20] has been limited to the sub-group with moderate acidosis. Another study was in children with severe anaemia investigating the safety of pre-transfusion fluid bolus resuscitation[19].

A total 3303 children are therefore included in this comparison; 2208 who received bolus, and 1095 who received no bolus (control) and shows increased risk of death with bolus infusion compared to maintenance (Peto odds ratio 1.41; 95% confidence interval, 1.10, 1.81; p=0.006). The risk of bolus versus no bolus treatment in subgroups with malaria and suspected sepsis is also summarised in Figure 7.5. Combined estimate is provided for various subgroups after inclusion of the FEAST trial results because most of the data on mortality was provided by the FEAST trial (RCT with optimal design) therefore the effect of heterogeneity is reduced.

Figure 7-5: Mortality in children resuscitated using bolus versus no bolus (control)

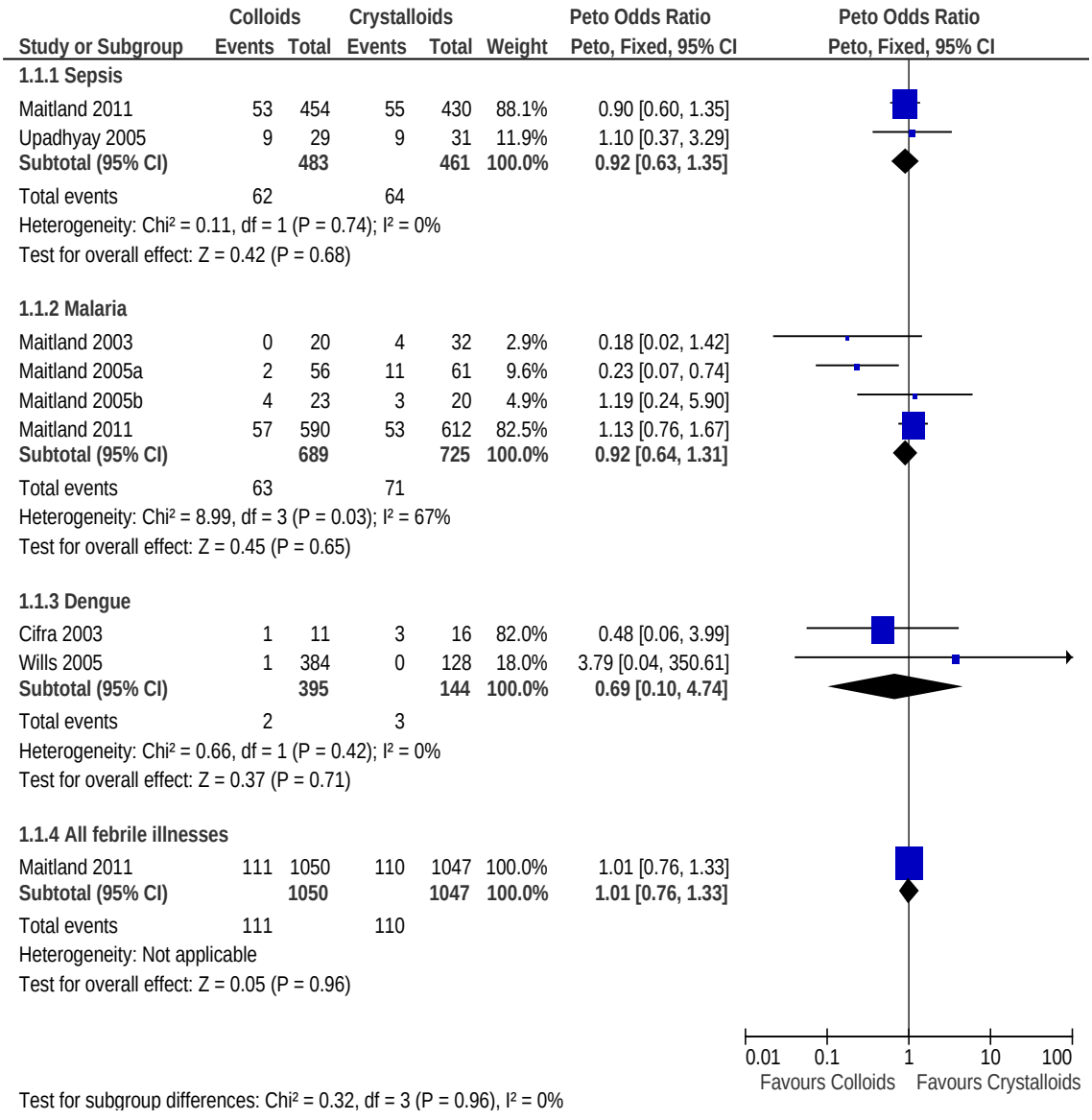


7.3.4. Colloids versus crystalloids after FEAST trial

There was similar survival in children with febrile illnesses and shock treated with colloids or crystalloids (Peto odds ratio 1.01; 95% confidence interval, 0.76, 1.33; p=0.96)-Figure 7.6. Similar results were seen in subgroups with bacterial sepsis, malaria, or dengue. Despite the finding of the meta-analysis, colloids should still be used in severe DSS because definitive trials show that colloids

are better than crystalloids in severe DSS. DSS has low overall mortality and trials in dengue were not designed to with mortality as an end-point.

Figure 7-6: Mortality in children resuscitated using crystalloids versus colloids after FEAST trial



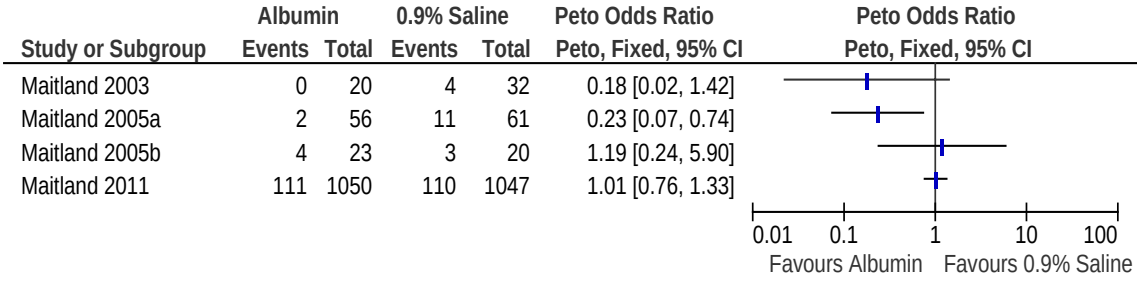
**Sepsis in the FEAST trial[41] reported above (Maitland 2011) defined as children with negative malaria blood slide.*

7.3.5. Albumin versus crystalloids after FEAST trial

There was no difference in survival in patients resuscitated using albumin compared to crystalloids in children with severe febrile illnesses and shock (Peto odds ratio 0.91; 95% confidence interval, 0.70, 1.19; p=0.49). These trials however had statistical heterogeneity (*Chi^2=8.34, p-0.04)* therefore should

not be combined (Figure 7.7). The trials in malaria had statistical heterogeneity since the initial studies demonstrated survival benefit with HAS compared to saline while the main trial shown similar survival in participants treated with either fluid. This may have been due to the small size of initial trials and methodological shortcomings (non randomisation, lack of concealment of allocation) among other explanations.

Figure 7-7: Mortality in children resuscitated using albumin versus crystalloids after FEAST trial



7.4. Summary of findings

1. Only ten trials conducted worldwide on fluid resuscitation for shock in children with infectious illnesses (non-traumatic and non-diarrhoeal) conditions.

2. Existing trials on fluid resuscitation for shock in children with infectious conditions all done resource poor countries.

3. Definitive trials in dengue septic shock (DSS) show that crystalloids and colloids have equal efficacy in treating moderate shock. Crystalloids are therefore preferred in moderate shock due to their low cost and wide availability. However colloids are superior to colloids in treating severe shock and are therefore the fluids of choice in severe cases. The trials in DSS have not addressed the mortality question because of low case fatality of dengue in the centres conducting the trials.

4. Non-definitive small-size phase II trials showed that fluid resuscitation for shock in severe malaria using HAS could result in better survival compared to saline or Gelofusine (a colloid). The trials also suggested that mortality in those resuscitated using saline and Gelofusine would be similar. But these results were not confirmed in the large multi-centre definitive trial (FEAST trial) which showed similar survival in children receiving saline or albumin.

5. Meta-analysis of existing paediatric fluid trials in sepsis, largely influenced by the FEAST trial, demonstrates similar survival in children with shock in severe febrile illnesses or bacterial sepsis resuscitated with either colloids or crystalloids in children.

6. New evidence show that treatment of shock in children with severe febrile illnesses with fluid bolus (saline or albumin) is harmful when compared to no bolus (control) in resource poor settings. There are currently no studies in resource-rich settings comparing the safety and efficacy of bolus versus maintenance for treatment of shock.

7. Findings do not apply to conditions excluded such as severe dehydration (gastroenteritis), burns, trauma, sickle cell disease, and severe malnutrition.

CHAPTER 8 : DISCUSSION

This chapter interprets the findings of the studies on development of clinical criteria for diagnosis of shock, haemodynamic status and myocardial function of children with severe illness, safety and efficacy of synthetic colloidal fluid resuscitation in children with severe malaria with shock, safety and efficacy of isotonic fluid resuscitation for shock in severe malnutrition, and summary of the evidence basis for current paediatric fluid resuscitation guidelines. The discussion synthesises these subjects and includes the following topics:

1. Validity of clinical signs for diagnosis of shock in children
2. Validity of international shock diagnostic criteria
3. Haemodynamic status of children with severe illness and/or impaired perfusion
4. Myocardial performance of children with severe illness and/or impaired perfusion
5. Safety of colloids for fluid resuscitation for treatment of shock in children with severe malaria
6. Safety of isotonic fluid for treatment of shock in children with severe malnutrition
7. Evidence base of current paediatric fluid resuscitation guidelines in children with shock in severe febrile illnesses.

8.1. Validity of clinical signs for diagnosis of shock in children

8.1.1. Performance of various clinical signs on the Kilifi dataset

Lactic acidosis (defined by a raised lactate in the presence of acid-base changes) in severe acute infectious illness is held as the 'sine qua non' resulting from poor tissue perfusion. Based upon this assumption I investigated the relationship of these biochemical changes with other clinical markers of impaired perfusion. The primary investigation utilised a prospective admission dataset on unselected children aged >60 days to ≤12 years admitted to Kilifi district hospital, Kenya, over a 3-year period between 2002 and 2004. Selected for this investigation were parameters that are incorporated in international shock definitions and the dataset was further refined to children with abnormal temperature (pyrexia, >38.5°C and hypothermia, <36.0°C). On multivariable analysis, one of capillary refill time >2 seconds, weak pulse, or bradycardia were found to be both associated and predictive of tissue hypoperfusion (defined as base deficit >10mmol/L **plus** serum lactate >3.5mmol/L). The terms tissue hypoperfusion and impaired perfusion are used interchangeably in

this thesis. These clinical criteria were hence referred to as 'derived shock' for the purpose of this thesis. Derived shock criteria had a low sensitivity but a high specificity therefore biochemical markers of impaired perfusion (lactic acidosis) were unlikely in its absence. Each individual sign had lower sensitivities and specificities for predicting lactic acidosis when compared to the derived shock criteria.

When investigated further, the individual clinical markers of shock were not useful in non-severe disease for identifying children with biochemical markers of impaired perfusion and poor outcome. The practical utility is limited to the children with other signs of severe disease, defined as respiratory distress (deep breath or chest indrawing) and/or impaired conscious (prostration or coma). Even within those with severe disease, some of the clinical signs commonly used to define shock in international definitions such as tachycardia[229 230] and temperature gradient[7 8 11 12 136 220] were neither associated with death nor predictive of biochemical markers of impaired perfusion. Clinical signs selected (capillary refill time >2 seconds, weak pulse, or bradycardia) had significant positive likelihood ratios to biochemical measures of impaired perfusion and fatal outcome indicating that they are good predictors for these outcomes. Applying other shock criteria used in other definitions to investigate whether these predicted biochemical measures of impaired perfusion and compare these to the derived shock definition demonstrated that derived shock LR+ was 3.7, compared to WHO shock definition [LR+=13.8] and FEAST shock criteria [LR+=2.3] were good predictors whereas ACCM definition [LR+=1.7] was poorly predictive. One of the reasons for its poor performance is that ACCM criteria[220] and similarly PALS definitions[11] allow a single clinical sign (of shock or disease severity) whereas these other three required either two or more features or in the case of FEAST trial definition, a sign of clinical severity plus one of clinical feature of impaired perfusion. All four shock definitions (derived shock, WHO, FEAST, and ACCM) were able to identify children at a signficicantly increased risk of death. The WHO definition had the highest odds ratios (OR=13.8[6.0, 13.4]), followed by derived shock (OR=6.1[5.0, 7.4]), then FEAST (OR=3.2[2.7, 3.8]), and lastly ACCM definition (OR=2.5[2.1, 2.9]). The definition called 'derived shock' also performed well in the validation set, ROC=0.66[0.62, 0.70]; severe disease sub-group ROC=0.70[0.65, 0.75], non-severe disease, ROC=0.53[0.48, 0.58].

Appropriate statistical approaches were applied in this study. The initial step in determining lactate and base deficit cut-off values was through determination of the optimum cross-over point for sensitivity and specificity curves for each of the two in predicting death. The second step was by establishing cut-off values for the two variables with significant likelihood ratios for predicting mortality. Likelihood ratios were preferred to sensitivity and specificity although sensitivity

represents the proportion of true positives that are correctly identified by a given test (i.e. the numbers with actual condition) while specificity is the proportion of true negatives that are correctly identified by a test (i.e. how good the sign is at predicting the measure of interest)[282]. Sensitivity and specificity do not show how particular test results predict risk of abnormality and only describe how normality or abnormality predicts a particular test result. Sensitivity, specificity, and predictive values (NPV and PPV) are dependent on prevalence of the target disease in the study population and therefore differ in populations with different disease prevalence. Likelihood ratio (LR) overcomes the shortcomings encountered when using sensitivities, specificities, and predictive values for diagnostic tests[280]. It summarises how many times more (or less) likely patients with the disease are to have that particular result than patients without the disease. Likelihood ratios (LR+ and LR-) shows how useful a test is and provide the probability of abnormality even in the context of varying prevalence (prior probabilities). Use of likelihood ratios in this study therefore enables generalisation of the results to population with different prevalences of shock.

8.1.2. Validity of clinical signs for diagnosis of shock in children

Septic shock comprises of sepsis, SIRS plus suspected or proven infection, plus impaired perfusion. Various international criteria for shock use various clinical signs to define impaired perfusion which include the following; tachycardia[7 8 12 41 137], delayed capillary refill time[7 8 11 12 41 136 137 220], cool and pale peripheries (alternative a core-toe temperature gradient)[7 8 11 12 41 220], weak pulse[7 8 11 12 41 220], widened pulse pressure[11], oliguria[11 220], and hypotension[11 41 220]. Biochemical markers such as elevated lactate[137 178] and elevated base deficit[137 178] are widely held as robust measures of impaired tissue perfusion (consequent upon poor oxygenation and cellular hypoxia) in severe illness. Each sign may have varied relationship to the biochemical measures of impaired perfusion.

Heart rate

Heart rate is regarded as a sensitive indicator of cardiac output in children since tachycardia is the main compensatory mechanism in cases of reduced stroke volume (cardiac output=stroke volume × heart rate)[159 338]. While adults can maintain their cardiac output during reduced stroke volume by increasing their contractility, children's myocardial fibres are shorter and less elastic and therefore unable to significantly increase stroke volume[159 338]. During shock (reduced stroke volume) there is a compensatory increase in heart rate, tachycardia, which may be used to diagnose early shock. However tachycardia is a non-specific sign and may be secondary to other causes such as fear, fever, anxiety, pain, exercise, hypoxia, parasympathetic and sympathetic tone, endogenous enkephalins, drugs, and hormones[338 339]. Duke and colleagues in a study investigating at markers of tissue

perfusion did not find any relationship between heart rate and survival[340]. A number of studies in haemorrhagic shock in adults have shown poor association between tachycardia and hypotension hence questioning its validity for predicting hypotension (a sign of shock in adults) in that population [341-347]. An early experimental haemorrhage in dogs by Gregersen and Root showed tachycardia in animals with haemorrhagic shock showing other features of shock but the outcome was not associated with the degree of tachycardia[348]. However, a number of animal studies have demonstrated that tachycardia is not always present following major blood loss[349-352]. Brasel *et al*[339] reviewed trauma registry in USA and revealed that heart rate was neither sensitive nor specific in determining need for emergency surgical intervention to control bleeding. Since heart rate increases with increments in body temperature a multicentre study by Leibovici et al[353] that controlled for this factor, found increased risk of death in adult patients with excessive tachycardia, defined as pulse/temperature ratio >2.71bmp/°C. The study included conditions such as SIRS, febrile neutropenia, on antibiotic prescriptions, and those having blood culture investigations. Of interest, there was no association between presence of excessive tachycardia and death in patients in subgroup with septic shock. There are no similar published data in children. From the foregoing description (mostly in haemorrhagic shock) it can be seen that previous studies have not firmly established any clear association between heart rate and shock or outcome. These findings concur with the data presented in this thesis.

Bradycardia

Tachycardia is a compensatory mechanism to that serves to maintain cardiac output and blood pressure (mean BP=cardiac output × SVR). Where shock has been present over a prolonged period including the development of low blood pressure, usual homeostatic or compensatory mechanisms are said to fail or be overwhelmed. As a result heart rate, cardiac output and blood pressure fall[159 169 344]. Like in the study presented in this thesis, bradycardia has been shown to be associated with haemorrhagic shock in adults. Secher *et al* in 1984 demonstrated the association between bradycardia and hypotension in adults with haemorrhage and also showed poor outcome in participants with bradycardia[344 354]. Demetriades and colleagues in a retrospective analysis however showed similar overall survival in 750 adults with haemorrhagic shock and relative bradycardia (defined as defined as a systolic pressure less than or equal to 90 mm Hg (shock) plus a pulse rate less than or equal to 90 beats per minute (bradycardia)) compared outcome to those with tachycardia[346]. They however reported poorer survival in tachycardic patients with more severe injury[346]. Barriot and Riou, who defined relative bradycardia as pulse rate less than or equal to 60 beats per minute in shocked patients (defined as blood pressure less than or equal to 70 mm Hg),

reported that those with bradycardia had more rapid and severe haemorrhage compared to those with tachycardia[342]. They also reported better outcome with volume resuscitation than when treatments aimed at for alleviating bradycardia (atropine). Similar data are not available for children with sepsis except for a prospective study in Kenyan children with severe malnutrition. In 920 cases of severe malnutrition it found that bradycardia (present in 15, 1.6%) was a risk factor for early mortality (OR=8.8[2.6, 30.0]) but not tachycardia[4]. The study did not find bradycardia as terminal event and its presence was accompanied by features of shock such as weak pulse, severe acidosis, and elevated creatinine. There were no studies available describing relationships between bradycardia and objective measurements of cardiac output.

Clinical signs of peripheral perfusion

During shock blood there is reduced perfusion of organs and blood flow is diverted form non-vital organs such as skin, gut, muscles, and subcutaneous tissues and flow is prioritised to vital organs such as brain, heart and kidneys[159]. These vital organs have vasomotor autoregulation which helps to maintain flow during low perfusion pressures. Examination for signs of impaired circulation to non-vital organs, especially skin which is easy to examine, is thought to provide an early indication of shock. Determination of skin temperature of extremities (hands and feet), temperature gradient, and capillary refill time are the methods advocated to determination of peripheral perfusion[159 169].

Cool peripheries

Normally heat is transferred from the body core to the skin by circulating blood. This is however reduced during impaired perfusion as consequence of compensatory vasoconstriction to non-vital centres (e.g. skin) and the skin becomes cool (cold), pale, clammy or mottled. Patients are regarded to have cool extremities if both upper and lower limbs are found cool on examination or if the legs are cool in the absence of peripheral vascular disease[355 356]. Kaplan et al reported a retrospective study of 264 adults in which they investigated the ability of a finding of cool peripheries to predict hypoperfusion, which was defined in the study as arterial lactate >2.2 mmol/L or pH≤7.25 (without acute or chronic renal failure) or cardiac index ≤2.5 L/min/m^2 body surface area, or hypotension (systolic blood pressure ≤90 mm Hg). The cohort included 264 patients admitted to surgical intensive units with trauma (n=80), sepsis (n=111), vascular disease (n=46), and other surgical conditions (n=25). They reported that compared to adult patients with warm peripheries, patients with cool peripheries had significant lower mean cardiac output, cardiac index, pH, total serum bicarbonate, and mixed venous oxygen saturation but a higher mean serum lactate concentration[356]. The subgroup with sepsis in this study was small and there were a number of concurrent medications being administered (included vasoactive medications which have direct effects upon clinical markers

of perfusion and acid-base balance, especially adrenaline). The adults were in intensive care and therefore are not directly comparable to the cohort presented in this thesis (children at admission to hospital and managed without access to PICU). Hasdai et al reported cold and clammy skin as an important predictor of 30 day mortality in adults (OR=1.68[95% CI; 1.15, 2.46] with cardiogenic shock following myocardial infarction[357]. In this thesis we sued temperature gradient rather than cool peripheries. A systematic review of clinical signs predictive of serious infection in children presenting to hospitals in resource rich countries reported that pallor or mottled peripheries were unhelpful as predictors[358]. In general there is insufficient published data in children describing the relevance and predictive value of cool peripheries for diagnosis of septic shock.

Temperature gradient

Measurement of temperature gradient as an indicator of peripheral perfusion was initially described by Ibsen[359] in 1967 and Joly and Weil in 1969[360]. Ibsen reviewed 10 years data on rectal and toe temperatures gathered in 150 patients with shock who required vasodilatory treatment following failure to respond to fluids[359]. Ibsen reported that the difference in the rectal and skin temperature could be used a guide for fluid administration. Joly and Weil used thermistor probes to measure temperature of various distal sites in a study population of 100 adult patients and found significant correlation between cardiac output and temperature of great toe (r=0.71) and also reported that early measurement of toe temperature predicted outcome in 67% of the cases. Later studies investigating the value of core-peripheral temperature gradient in predicting cardiac output have found conflicting results. Core-peripheral temperature gradient has been found to be a poor predictor of cardiac index, SVR and SVRI post-cardiac surgery both in children [221 361-363] and adults[364]. Murdoch[363] however found correlation between CVP and core-peripheral temperature gradient following cardiac surgery in 10 children and suggested that this could be explained by hypovolaemia. Tibby et al[221] also reported a weak correlation between core-peripheral temperature gradient and SVRI (r=0.29[-0.04, 0.55], p=0.08), SVI (r=-0.29[-0.05, 0.03], p=0.07), and lactate (r=-0.02[-0.02, 0.57], p=0.06), in a sub-group of non-surgical paediatric (general) admissions. However, temperature gradient is affected by other factors such as ambient temperature and use of vasodilatory drugs during anaesthesia and any of these may have affected results. We found that temperature was not predictive of markers of tissue hypoperfusion and thus this study do not contradict existing findings on poor predictive value of temperature gradient in shock despite being a parameter that is reproducible amongst observers. Otieno *et al* reported substantial agreement between clinicians in the assessment of temperature gradient in 100 sick children in Kenya[365].

Capillary refill time

Capillary refill time (CRT) is defined as the time taken for full return of colour of an extremity following application of pressure that causes blanching. CRT was first introduced by Beecher *et al*[366] in 1947 who proposed it as a measure for grading shock. They classified CRT as normal, definite slowing, and very sluggish. It was used much later by Champion (1981)[223] in the assessment of severity of trauma and recommended an upper limit of normal as 2 seconds following suggestion from a medical student[367]. However, Champion omitted CRT from the subsequent publication on trauma score in 1989 with an explanation that it was difficult to difficult to assess at night due to poor ambient light[368]. The use of CRT as clinical sign of shock and the suggested upper limit of 2 seconds were adopted by the American College of Surgeons[369], and American Heart Association and American Academy of Pediatrics in its PALS publication[370] and is presently used by various resuscitation/critical care guidelines[7 8 11 220].

Abnormal CRT values

Various cut-values have been used to define the upper limit of normal CRT (2 , 3 , or 5 seconds) [7 8 12 136 178 220]. However as stated above, the initial choice of 2 seconds as an upper limit was anecdotal[223 367]. A study by Schriger *et al* in healthy population found 2 second limit to be appropriate for children and young adults but 2.9 seconds was the appropriate value for healthy women and 4.5 seconds for the elderly[371]. Tibby, Hatherill, and Murdoch performed 99 measurements in children admitted to PICU after cardiac-surgery or for general conditions and found that children with a CRT>2 seconds had lower median stroke volume index (SVI) and higher mean lactate in non-surgical cases but not in surgical cases[221]. No correlation was found with SVRI[221] but they reported CRT of 6 seconds or more to be the best predictive value for reduced SVI. Once again, the study was in children in a PICU with an unrepresentative population to the population presenting as emergencies- and the cohort were also receiving vasoactive therapies. This raises doubts about the generalisability of their findings to children at admission to hospital, where most decisions about diagnosis of shock and management are made.

Reliability of CRT measurement

The assessment of CRT is affected by various factors including age of the patient[371-374], ambient temperature[371 372 374 375 376], room lighting[377], duration of pressure application[10 371 372 376 377], site of CRT measurement[372-374 378], choice of limb[372 373 379], and position of the limb in relation to the heart (should be raised above the heart to avoid reverse venous refilling)[380] . There are also conflicting findings on the effect of fever on CRT[381 382]. A study by Gorelick *et al* in 32 healthy well hydrated children in a paediatric emergency department concluded that ambient temperature affected CRT. The clinicians were not blinded to intervention (waiting in a room with or without air conditioning)

and therefore susceptible to biased interpretation[372]. In a separate prospective study in 234 children, Gorelick *et al* found that fever does not have clinically important effect on CRT refuting the widely held belief[381].

One of the conclusions of my studies was that abnormal CRT was predictive of biochemical marker of impaired perfusion and outcome in children with abnormal temperature and severe illness. The reliability of CRT has however been questioned since a number of studies have found only fair as opposed to good inter-observer agreement[221 383]. Hannington and colleagues found poor interrater agreement for capillary refill time and weak pulse volume, whereas moderate agreement for temperature agreement[365]. Interrater agreement improved (to moderate) when the capillary refill time was either absolutely normal (CRT=1 second) or abnormal (CRT=4 seconds). Anderson also found poor inter-observer agreement in adult population[375].

Validity of CRT as measurement of impaired perfusion

A number of studies have investigated for association between capillary refill time and laboratory and haemodynamic features of shock. Tibby found that CRT≥2 seconds was related to blood lactate and stroke volume index (SVI) in non-surgical cases admitted to PICU[384]. This study failed to investigate the relationship between abnormal values of haemodynamic function and CRT since only mean values was compared. They also used sensitivity, specificity, negative and positive predictive values to compare the relationship, which are all dependent on prevalence, rather than likelihood ratios which may have been more appropriate[280-282 385]. Prolonged CRT has been reported to have good correlation with severe (>5%) dehydration, determined by weight measurement[386]. In a study in Kilifi, Kenya, CRT >2 seconds identified 50% of children with hypotension and 40% of children with metabolic acidosis who required fluid resuscitation[225]. A systemic review of published literature, which included 1276 children, has established that abnormal capillary refill is a useful predictive sign (likelihood ratio=4.1 [95%CI; 1.7-9.8]) 5% dehydration[387].Capillary refill time has also been found to be associated with signs of impaired perfusion in neonates[388]. LeFlore *et al* reported no association between CRT and heart rate but found that prolonged CRT was associated with elevated blood pressure in term neonates[388]. They suggested that the relationship with elevated blood pressure was a consequence of release of adrenaline leading to peripheral vasoconstriction[388]. Wodey also found a relationship between CRT and cardiac index in neonates, supporting its use to monitor circulation[389].In adults, CRT >2 seconds was found to be a poor predictor of mild-moderate blood loss and in well adult donors did not predict a blood donation of 450 ml but had a sensitivity of 77% in cases of blood loss with hypotension[222]. Lima *et al* reported that CRT >4.5 seconds or finding of

cool extremities was able to identify adults in intensive care with more severe organ damage or higher lactate levels[390].

CRT as a prognostic marker

Evans *et al* reported that CRT> 2 seconds was an independent prognostic indicator of acidosis, coma, respiratory distress, and also increased the risk of death in children with severe and complicated malaria in Ghana[142]. In the study by Evans, the risk of death in children with severe anaemia was 2-fold higher in those with delayed CRT compared to those without[138]. Pamba *et al* reported CRT >2 seconds as a risk factor for mortality in children, particularly malaria, admitted to rural Kenyan hospital[225]; the sign was however useful only in severe disease (impaired consciousness and/or respiratory distress)-which concurs with the findings of my investigation. A prognostic score for African meningococcal epidemics has prolonged CRT (of mare than 3 seconds) as part of the scale[391] but this had not been evaluated.

Pulse character

Inter-observer agreement was only moderate for identification of weak pulse volume in study done in Kenya but it was found to be a marker of poor outcome[4 365]. Inter-observer agreement for weak pulse volume was better (fair agreement) when the values were abnormal. Most criteria for shock list weak or absent pulse as one of the features and bounding pulse for 'warm shock'[220]. Few studies have prospectively evaluated this sign. In this current study I found that weak pulse character was independently associated with mortality and was a good predictor of lactic acidosis.

8.1.3. Validity of international shock criteria

Most criteria to diagnosis paediatric shock employ multiple clinical features for diagnosis except ACCM (see below). A review of the literature has identified all the available shock definitions-some but not all being relevant to initial assessment of a child presenting as an emergency. These include WHO (also used in ETAT)[7 8 10], PALS[11], ACCM[179], IPSCC[178] and Surviving Sepsis Campaign[137]. The exception to initial assessment is IPSCC which is more relevant for fluid refractory shock, since it should only be used in cases which have already received 40ml/kg. The bases for most definitions are consensus or expert opinion as few have been prospectively evaluated. Furthermore, none of the definitions have been evaluated against measures of cardiac output or other proxy measures for shock. The study undertaken for this thesis is therefore the first study to attempt to validate these shock criteria against a biochemical defined impaired perfusion (lactic acidosis).

8.1.4. Validity of acidosis as a proxy measure of tissue hypoperfusion

Lactic acidosis has a complex aetiology and the decision to use it as proxy measurement of tissue hypoperfusion may be disputed[202]. However, choice for using lactic acidosis as the gold standard measurement of tissue hypoperfusion is supported by its adoption within both adult and paediatric guidelines, Surviving Sepsis Campaign and the International Paediatric Sepsis Consensus Conference, as their definitions of septic shock[137 178]. A number of other groups have also used lactate acidosis as a definition of hypoperfusion[197 198]. Two studies in malaria children with malaria have shown association between markers of cardiac dysfunction, cardiac damage, and echocardiogram evidence of hypovolaemia (high IVCCI) with lactic acidosis[392 393]. In an adult study in severe malaria, Day et al reported increased pyruvate/lactate ratio in patients with lactic acidosis, supporting hypoxic aetiology[305]. However others have suggested the accumulation of lactic acidosis in malaria is due to cellular dysfunction[394].

In septic shock and malaria, lactate accumulation is multifactorial and secondary to either tissue hypoxia with consequent ATP generation without oxygen (type A lactic acidosis) or another primary cause which is unrelated to tissue oxygen debt (type B lactic acidosis)[162 202 204]. Causes for tissue hypoxia include circulatory shock (poor oxygen delivery), severe anaemia (low oxygen carrying capacity) and pulmonary problem (low PO_2)[395]. Type A lactic acidosis is thought to play predominant role in septic shock[395].

One proposed mechanism of non-hypoxia dependent cause of lactate accumulation is increased epinephrine production (via β_2- adrenoceptor stimulation) causing increased sodium-potassium ATPase (ATP dependent) pump activity in skeletal musculature[396]. Glycogenolysis and glycolysis are increased in order to support increased ATP production resulting in increased production of pyruvate and lactate once mitochondrial oxidative capacity is overwhelmed. Elevated lactate in this case is often accompanied by hypokalaemia[397]. Other causes of type B lactic acidosis include cytokine-induced mitochondrial dysfunction, reduced lactate clearance, pyruvate dehydrogenase dysfunction, and protein degradation (with production of amino acids which are converted to pyruvate then to lactate)[206 397 398]. Some authors, using experimental studies involving localised inhibition of sodium-potassium pump, have proposed that type B acidosis is the predominant mechanism responsible for elevated lactate levels is sepsis[399] and this would imply that the choice acidosis as proxy measure for impaired tissue perfusion or cellular hypoxia was inappropriate. Interventions such as dichloroacetate aimed at pharmacological reduction of lactate levels while being successful in clearing lactate, have not been successful in reducing mortality in sepsis and

septic shock despite successful reduction of lactate[207 400-402]. Whereas secondary reduction of lactate has been observed consequent to treatment of shock and associated improved outcome based upon reduction in mortality and organ dysfunction[209]. The 'lactate shuttle' theory[396] has been used as one explanation for the disappointing results aimed at non-hypoxic causes. In the theory, hyperlactataemia is explained as an adaptive process where lactate is oxidised to produce energy in tissues where oxygen is available or for neoglucogenesis (in Cori cycle) while preserving glucose in oxygen-deficient tissues[162 396]. It is proposed that reduction of lactate removes this adaptive process and leads to worse prognosis.

Clinical experience in human clinical practice, observation studies and clinical trials support the predominance of type A lactic acidosis due to a number of reasons. Firstly, reduction in lactate level following treatment to for impaired perfusion/shock results in reduced mortality[163 164 209 403]. Secondly, lactic acidosis predicts multi-organ dysfunction in septic shock[404], is a widely interpreted as a marker of tissue perfusion, and its clearance is thought to indicate resolution of tissue hypoxia. Therefore, interpretation of the lactic acidosis in the current investigation suggests that lactic acidosis is associated with a poor outcome and correlates with some but not all clinical markers of impaired perfusion or shock.

The previous studies showing poor correlation between clinical features of shock and lactic acidosis tend to be small in size, unblinded, in heterogeneous study populations, with few data from children, include cohorts exposed to vasoactive agents and solutions which alter acid-base status and therefore difficult to generalise so should be interpreted with caution. The current study has tried to overcome some of the weaknesses of the published data; The study sample of the derivation set was large (N=7673) and an unselected admission population in whom the admitting clinicians were not influenced by the study question. Clinical signs were systematically collected as well as biochemical data to identify lactic acidosis. The admitting clinicians had received adequate training on performing standardised clinical examination, and blood chemistry results were only available to the examining clinician after clinical findings were reported. This study therefore database and analysis to definitively assess the diagnostic utility of the clinical and biochemical signs of shock were conducted retrospectively. Newton *et al*[405] in multicentre study of selected children with suspected severe malaria reported different lactate cut-offs (4.1 and 5mmol/L) to be predictive of adverse outcome. The study also reported that lactic acidosis was unlikely in the absence of deep breathing confirming the earlier findings[286]. The study did not investigate predictive value of various signs of shock. Differences in their statistical methodology, they use sensitivity-specificity and correlation, and non-inclusion of non-malaria subjects could be reasons for their different cut-off. The study

however reported that acidosis and lactate alone were not good predictors of just like it was found in this study.

Base deficit was not chosen to be used in isolation as a measure of acidosis since this may have multiple biochemical contributors including non-hypoxic causes such as renal disease, hepatic dysfunction, and ketonaemia. Furthermore, studies in both adults[215] and children[212 214] with severe malaria have shown the presence of unmeasured acids (other than lactate, phosphate, albumin) in >50% of patients with acidosis.

Evaluation of microcirculation

Lactate measurement is also superior to measurement of microcirculation for evaluation of global perfusion. Near-infrared spectroscopy (NIRS) has been suggested as suitable technique for measuring microcirculation[159]. NIRS is an optical technique that uses light in the near-infrared range (700–1000 nm). Light in that range can pass through skin, bone and other tissue relatively easily but is absorbed in proportion to the concentration of chromophores such as oxy-haemoglobin and deoxy-haemoglobin. These two chromophores have different absorption spectra and their respective concentrations depend upon the tissue oxygenation status. Measurement of NIRS absorption therefore provides an estimate of their concentrations and this can be used to estimate average tissue oxygenation. It has the advantage of proving continuous, direct and non-invasive measurement of tissue oxygen. However, NIRS can only measure microcirculation to certain regions of the body and therefore does not give and indication of the global perfusion or to the rest of the regions/organs.

Orthogonal polarization spectral (OPS) technique has also been used to measure microcirculation[159]. OPS apply a technique referred to as orthogonal polarization of light for transcutaneous evaluation of microcirculation up to 3mm depth in the skin. It produces images that can be visualised and has the advantage of giving real-time images and being non-invasive. However studies have shown that like NIRS, it only gives indication of regional microcirculation which may not directly correlate with global perfusion. Even within a regional microcirculation there may still be differences in perfusion that may be missed with inadequate scanning[306].

Therefore lactate measurement, though imperfect, is the best currently available measurement of tissue hypoperfusion.

8.1.5. Implications of the findings on approaches to diagnosis of tissue hypoperfusion

The international shock criteria were found to have low sensitivity in predicting lactic acidosis bringing into question whether they are appropriate for use in making treatment decisions. Early detection and treatment of shock has been reported to have favourable outcome compared to late intervention[196 406 407], nevertheless the studies reporting these have some methodological biases. Intervention based on early detection of acidosis, when it is used as a proxy measure of hypoperfusion, has been advocated. Direct measurement of acidosis would therefore seem more ideal to detect the group with poor outcome where there are low sensitivities of clinical definitions of shock. Studies in PICU have shown lactate acidosis and persistence of lactate as a risk factor for mortality and MODS[163 199 200 395]. Observational studies also reported reduced mortality following early fluid resuscitation for shock[259 260] and a randomised trial showed reduced mortality following early normalisation of haemodynamic parameters[196]. Lactic acidosis was a risk factor for mortality even in the dataset presented in this thesis. However, the recent findings from the FEAST trial[41] challenge some of the past findings on interventions to treat shock and acidosis. The FEAST trial found increased mortality in children with shock including the subgroup with lactic acidosis, treated with bolus normal saline or HAS compared to no bolus (control). The trial enrolled children with severe febrile illness but excluded those with severe gastroenteritis, severe malnutrition, traumatic cases, and known cases of renal or heart disease. Early diagnosis of lactic acidosis, while an indicator of disease severity, tissue hypoperfusion, and a good prognostic marker[164 399 408], following the findings of the FEAST trial now presents a management dilemma. Fears about harm secondary to inappropriate administration of fluid bolus in absence of shock support the use of clinical signs and shock criteria, which are insensitive, instead of laboratory markers[22-24]. FEAST trial findings support the cautious approach to fluid resuscitation instead of increasing test sensitivity (number diagnosed) that would result if lactate measurement were used.

8.1.6. Limitations of the study

This study was limited by choice of a proxy, lactic acidosis, which as stated above has a complex aetiology that is not always secondary to tissue hypoxia. However, as variously reasoned above, the choice of acidosis is supported by prognostic value of lactate, reduced risk of mortality following lactate clearance with treatment of shock, lack of survival benefit following treatment aimed at non-hypoxic causes of hyperlactataemia and some studies reporting association between serum lactate and central haemodynamic[163].

8.1.7. Implications for diagnosis and management of shock

This study and previous studies have shown conclusive evidence of the prognostic value of lactic acidosis. Acidosis has been used as a proxy for tissue hypoperfusion (shock) as in this study to identify children with poor outcome. The question of whether it would be most appropriate to introduce to laboratory tests that measure biochemical markers at admission to help define cases with impaired perfusion and shock arises. The future use of fluid boluses, where the intervention carries a potential risk, targeting only patients with more severe disease (where benefits outweigh risks) then a clinical definition with low sensitivity and a high specificity may be acceptable. Alternatively, when early intervention may prevent death or morbidity but with at low risk to the patient, a test with high sensitivity (lactate measurement) may be justified. Results from the FEAST trial and subsequent meta-analysis presented in this thesis have shown that treatment of shock with fluid bolus, a widely accepted practice, is harmful when compared to no bolus (control). Guidelines on appropriate approach to diagnosis of shock will need to take into account the management of shock that may be proposed following these results. Identifying children with shock, to avoid fluid boluses and unfavourable outcomes, suggests a need for a highly specific (even if less sensitive) test whereas a more sensitive test may be acceptable for other beneficial interventions with less potential for complications.

8.2. Validity of USCOM device for haemodynamic monitoring

Echocardiography was used as the 'gold standard' to test the reliability for USCOM device for the measurement of haemodynamic and cardiac function. There was a good agreement in the measurement of cardiac output (CO) and cardiac index (CI) using echocardiography and USCOM devices. For the measurement of stroke volume index (SVI), there was moderate agreement. At lower values SVI, USCOM measurements tended to be higher than echocardiography measurements but the reverse pattern was seen at high SVI values. Participants with severe disease and gastroenteritis (dehydration) had lower mean SVI and 60% had abnormally low SVI at admission. USCOM device can therefore replace echocardiography for the measurement of cardiac output and cardiac but caution should be exercised in interpretation of absolute SVI values obtained using USCOM. Agreement was tested using Bland-Altman plot[287 288] and Pitman's test for difference in variance[289], which are the appropriate tests. The different investigators performing USCOM and echocardiography measurements were blinded to each others' readings reducing the likelihood of bias. This study did not study interrater agreement for USCOM measurement by different investigators but previous studies by Meyer and Stewart both found good interrater reliability[195 409].

USCOM device has been compared to other device for measurement of haemodynamic and cardiac function. While pulmonary artery catheter (Swan Ganz) thermodilution (PATD) introduced in 1970s has been regarded as the gold standard for measuring CO, a number of shortcomings has necessitated search for valid alternative methods. PATD is time consuming, invasive, requires high degree of expertise, its use is restricted to intensive care, and cannot be used in emergency departments[169]. Two-dimensional (2D) Doppler echocardiography (ultra-sonography) is one the four techniques (PATD, pulse index, and femoral artery thermodilution catheterisation) recommended for monitoring CO in septic shock by 2007 American College of Critical Care Medicine (ACCM) guidelines[220]. Echocardiography is non-invasive as compared to the other methods and additionally can detect pericardial effusion, evaluate contractility, check ventricular filling, can be used in the emergency department, and good agreement with PATD method[159 410 411]. Trans-oesophageal echocardiography is superior to transthoracic[363] but can only be used in unconscious patients and may give wrong readings if misplaced and positioning requires radiological confirmation. Both require highly skilled operators and a lengthy training is required to attain the requisite skills.

USCOM, a non-invasive CO measuring device that uses continuous-wave Doppler ultrasound, has been developed recently and presents an alternative to echocardiography[189 190 194]. It uses 2.2-3.3 MHz transducer that is place on the suprasternal notch to measure flow through aortic valve and 3rd to 4th left intercostal space parasternally for measuring pulmonary valve flow[193 412]. Each flow represents the velocity time integral (VTI) (calculated from peak flow), defined as the distance travelled by a column of blood for each stroke. Stoke volume =VTI × CSA (cross sectional area of valve). The devise uses sex and height based algorithm to determine the CSA and CO. The systemic vascular resistance (SVR) is calculated form CO divided by mean arterial pressure (MAP) after subtracting CVP. MAP is calculated from the blood pressure that is entered. USCOM devise is easy to learn (operator proficiency achieved after performing 20 measurements), non-invasive, is reliable, and measurements are reproducible[179]. Van Lelyveld-Haas *et al* found acceptable correlation between USCOM and PATD techniques but also detected systematic and variable errors[413]. They studied 25 adult stable ICU patients and compared 263 paired readings. A study of 37 pre-term neonates, with 66 paired measurements, comparing CO obtained using USCOM and 2D echocardiography showed good agreement when compared using Bland-Altman bias analysis (mean transpulmonary CO 0.36±0.19l/min by echocardiogram and 0.37±0.14l/min by USCOM)[414]. However, this study is the first one to compared echocardiogram and USCOM in older children.

A number of studies have been done comparing CO obtained using USCOM and PATD. Tan *et al* found good agreement between CO measurements obtained using USCOM and PATD in 40

measurements obtained in 22 adult patients undergoing mechanical ventilation after cardiac surgery[186]. However they found that the difference between the two methods increased with increased as CO increased. Jain *et al* recorded a total of 120 paired measurements of CI in 31 adult surgical patients and found good correlation between USCOM and PATD readings[296]. Animal study in 6 dogs (319 sets of paired readings) by Critchley reported good agreement in CO obtained by USCOM and transit time ultrasonic flow-probe placed on the ascending aorta[298]. Chand and colleagues, investigating 50 post-cardiac surgery patients, found excellent agreement in CO, CI and SV measured by USCOM and PATD[299]. Some studies have however questioned the validity of USCOM device as compared to PATD. A study by Knirsch *et al* in 24 patients aged <18 years with congenital heart disease without shunt undergoing cardiac catheterisation found poor correlation in CO measurements obtained by PATD and USCOM devices[295]. Knirsch and colleagues however recommend USCOM as useful for monitoring device for trends. In a study comprising a heterogeneous population of postoperative cardiac patients by Chan *et al*[415], they concluded that USCOM had limited clinical utility compared to PATD. They suggested that the Doppler flow signal quality may have been affected by intra-thoracic, patient position and operator learning curve.

This study has provided evidence to support the use of USCOM for haemodynamic monitoring in place of echocardiography and other CO measuring techniques in emergency care settings. Caution is however advised in the measurement of stroke volume. Values of SVI obtained by USCOM were valid as evidenced by the high prevalence of low values in severely ill participants with dehydration. However this study was limited by the small sample size. USCOM device is a valid tool for measurement of haemodynamic parameters in children with febrile illnesses in low resource settings outside the intensive care and in emergency care settings.

8.3. Haemodynamic status and myocardial function in children with severe illness

This study investigated haemodynamic status and cardiac function in children with various disease severities with/out clinical features of shock. The aim was to establish whether children with clinical features of shock present with distinct haemodynamic patterns or characteristics. Haemodynamic parameters included cardiac output/index, stroke volume/index, afterload (SVRI), and contractility (measured as inotropy index). However, the utility of SVRI and inotropy measurements was less satisfactory since both required a CVP reading (a value of zero is assumed in absence of CVP) and thus the data generated on these two values are should be interpreted cautiously since CVP was not measured. Participants with severe disease (S-severe disease alone and SIMP-severe disease plus impaired perfusion) were found to have a significantly lower admission SVI compared to those

without severe disease (NS and NSIMP). Participants with clinical features of shock (NSIMP and SIMP) displayed a complex pattern of shock but predominantly showed hyperdynamic circulation (manifest as a high cardiac index). Hyperdynamic circulation was also the predominant pattern in participants who fulfilled either FEAST or ACCM definitions of shock. Low cardiac index was less common but if present increased the risk of death. At admission children with signs of vasodilatation (low SVRI) was more common in participants with clinical features of shock, including who fulfilled FEAST and ACCM criteria. A combination of high cardiac index plus vasodilatation, also referred to as warm shock[179 180], was also the main presentation in those with clinical features of shock (FEAST and ACCM/PALS). Cold shock[179 180], with a pattern of low cardiac index plus vasoconstriction, was also present in the above groups but was less common.

Children with delayed CRT or derived shock mainly displayed a pattern consistent with warm shock although the numbers were too small to draw definitive conclusions. Delayed CRT is thought to be secondary to vasoconstriction, a compensatory mechanism for global reduction in circulating volume, where flow is diverted to increase flow to vital organs instead of peripheral tissues. Vasoconstriction is also believed to increase afterload resulting in reduction in stroke volume and cardiac out when there is no compensatory tachycardia. Elevated lactate (>3.5mmol/L), elevated creatinine (>80μmol/L), and low urine osmolality (<400mOsm/L) were all associated with abnormal cardiac indices (both high and low) at admission. Therefore abnormal haemodynamic were indicative of both global and end-organ (renal) hypoperfusion. Renal function is more dramatically affected by changes in blood volume since the kidneys receive 70% of cardiac output. Criteria for bolus administration, based on existing guidelines and clinical judgement, mainly identified children with hyperdynamic circulation.

8.3.1. Pathophysiological basis of haemodynamic and myocardial dysfunction in shock

Tissue hypoperfusion secondary to severe sepsis and septic shock is a complex presentation characterised by elements of hypovolaemic, cardiogenic and distributive shock[416]. Early course of sepsis is characterised by increased capillary leak, venous dilatation (increased capacitance), and myocardial depression that may caused by released cytokines (TNF-α, IL=1β and IL=6), nitric oxide, calcium, and mitochondrial dysfunction and apoptosis[156]. These processes result in a fall in stroke volume and ejection fraction and decreased systemic vascular (arteriolar) resistance[179-181]. Compensatory tachycardia (children) and increased ventricular compliance (adults) to maintain cardiac output (index) follows. This early phase of shock is hyperdynamic and is characterised by increased cardiac index and low vascular resistance and has been referred to as ‘warm’ shock.

Clinically it is characterised by fever, bounding pulses, flushed pulses, oliguria and hypotension. Initially patients who failed to respond to fluid resuscitation were classified as having 'cold' or hypodermic shock[180]. However haemodynamic monitoring has showed that patients with cold shock have low cardiac index and high vascular resistance[179]. Whether warm and cold shock patterns are distinct presentations or continuum of the same pathophysiological process is still debatable[156 180]. It has been proposed that they represent different pathophysiological mechanisms[180 220]. Patients with cold shock who receive fluid resuscitation develop hyperdynamic circulation and display the warm type[180]. Clinical signs of cold shock include low/weak/absent pulse volume, cold clammy skin, hypotension, and the patients are described to appear more severely ill compared to those with warm shock. The third haemodynamic pattern that may be seen in shock consists of low cardiac index and low SVRI (cardiac and vascular tone abnormality)[156 179].

The common denominator during the early phases in all forms of shock is the reduction of stroke volume and this study showed a higher prevalence of low SVI in severe disease compared to non-severe disease[159 417]. This is accompanied by compensatory tachycardia to maintain cardiac output and peripheral vasoconstriction to preserve blood flow to the vital centres[159]. This is a complex process because inflammatory mediators released during shock however cause vasodilatation in early cases and vasoconstriction depends on the balance between vasodilators and vasopressors released[157 418]. Children maintain their cardiac output mainly by tachycardia since they have proportionately smaller cardiac mass relative to body surface than adults and cannot significantly increase their contractility[159]. Adults on the other hand are able to achieve hyperdynamic circulation to maintain cardiac output during shock by increasing cardiac contractility and ventricular dilatation hence preserving their stroke volume for some time and warm shock predominate[159 309-311 419]. The similarities in cardiac indices in participants (who have different stroke volumes) could therefore be explained by compensatory mechanisms.

The question of whether certain distinct haemodynamic patterns of shock are predominant in paediatric shock remains. In a study in 30 children admitted to PICU, Brierly *et al* demonstrated cold shock in community acquired septic shock and warm shock in hospital acquired septic shock, cold and warm shock [179]. The findings reported here would therefore seem to be at variance with conclusions drawn by Brierly *et al* because of the high prevalence of hyperdynamic circulation (warm shock). However, there were a number of differences between the two studies; the population in that study all had proven bacterial sepsis, had received large volume boluses and fluid refractory by definition hence the need for intensive care management including inotropic support[181]. The findings in this thesis therefore do not contradict the findings by Brierly and colleagues because it involved a

different population (outside the PICU), less sick, and who did not have proven bacterial sepsis. In 50 children with fluid refractory shock admitted to PICU in 3 hospital over a 4 year duration, Ceneviva *et al*[181] reported that 58% had low CI, 20% had high CI plus high SVR, and 22% had both vascular and cardiac dysfunction manifested as low CI plus low SVRI. Ceneviva's findings have been used to support the assertion that cold shock is the predominant pattern of paediatric shock, which differs from the prominence of warm shock found in adults[179]. However, Ceneviva's findings exclude a large group of fluid responsive children present in the study reported in this thesis. Earlier reviews in paediatric septic shock reported a pattern of progression that is similar to adults-warm shock in early cases[180]- and which is consistent with pathogenic mechanisms and these findings. Intense vasoconstriction, with increased peripheral resistance, following vascular leakage is a known prominent pathophysiological mechanism in meningococcal septic shock[420]. Substantial vascular leakage and vasoconstriction has also been reported in dengue shock syndrome[37 421]. The findings in dengue and meningococcal shock may not be generalisable to other infectious illnesses, which present with a distributive shock to substantial venodilatation which is isovolumic, rather than predominance of vascular leakage in their pathogenesis leading to substantial intravascular volume depletion. This current study adds to the description of haemodynamic patterns and myocardial function in children with severe febrile illness at presentation to the hospital.

The study showed a low prevalence but poor survival in participants with low cardiac index, regarded as having myocardial dysfunction. Myocardial depression in common in sepsis and is caused by cytokines and other inflammatory mediators released[156 416 422 423]. This has also been seen in meningococcal shock where IL-6 is associated[155]. Low prevalence of low CI seen this study could be as a result of recruiting children without shock (NS and NSIMP, only 1 case seen) and recruitment of children at earlier stages of shock. The worse outcome in participants with low CI may indicate need for inotropic support and/or additional vasopressor support if accompanied by vasodilatation[416 422]. The finding is consistent with a study which found poor survival in children with low CI admitted to PICU[181]. Myocardial depression is also known to cause failure in resuscitation in burn shock[424]. Ehrhadt *et al*[392] reported that biochemical markers of myocardial dysfunction and cardiac damage complicated severe malaria and were associated with lactic acidosis. They measured N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker of left ventricular function, heart-type fatty acid-binding protein (H-FABP), and creatinine kinase muscle-brain (CK-MB). An echocardiographic study in Kenyan children with severe malaria demonstrated mild-to-moderate myocardial dysfunction (lower stroke volume and high LMPI) and evidence of reduced preload (high

IVCCI), which correlated with the severity of acidosis[393]. A case report has also reported myocardial dysfunction in children with severe malaria using echocardiography[425].

Clinical signs of cold shock were fewer in the study as compared to those of warm shock in concurrence with USCOM findings. Abnormal haemodynamic findings on USCOM were associated with increased risk of death and other markers of tissue hypoperfusion (clinical and biochemical) indicating the prognostic value of USCOM findings taken at admission and prior to any intervention. USCOM measurements are therefore helpful in initiation of therapy, understanding causes of failure of an intervention, and in guiding further intervention for cases of shock that fail initial therapy. Such intervention may include vasopressors, inotropes, vasodilators, and hormone therapies may be required[137 220]. Preferential use of any of these therapies depends on the cause of non-response to initial therapy; reduced arteriolar resistance would require vasopressors, increased vascular resistance requires vasodilators, impaired contractility requires inotropes, and adrenal insufficiency would require steroids[137].

8.3.2. Changes following bolus infusion in children with shock

A sub-group of participants in this study received fluid boluses and an assessment of the haemodynamic changes following infusion was made. The assessment was restricted to participants with severe disease and signs of shock (SIMP) since they fulfilled the shock definition applied in the study. In the SIMP, bolus infusion was more commonly administered to participants who had more features of disease severity at admission compared to those who did not receive a bolus. It was therefore inappropriate to compare haemodynamic changes in following bolus infusion in bolus recipient versus non-recipients even in the sub-group with shock (SIMP). However, for those receiving boluses changes in stroke volume and cardiac index following bolus were still informative. They showed a fall in cardiac index, albeit non-significant, but an increase in SVI over the course of 24 observations hours. Fall in cardiac index over the course of 24 hours was expected owing to the resolution of tachycardia. Resolution of tachycardia may be due to a number of reasons including improvement in stroke volume or resultant from control of fever. A concurrent increase in SVI in the same group implies that the fall in cardiac index was not simply due to resolution of tachycardia but probably secondary to improvement in any of four determinants of stroke volume (afterload, preload, contractility, or compliance/diastolic function). A reduction in heart rate may result in increased time for ventricular filling leading to improved end-diastolic volume, stroke volume and cardiac output/index. Participants with shock who did not receive a fluid bolus (who were less severely ill) however showed greater increase in SVI over the course of 24 hours, despite similar

reduction in cardiac index. The difference in the trend of SVI between the two groups, in bolus recipients and non-recipients in SIMP group, could either indicate worse myocardial function or adverse response in any of the four determinants of stroke volume in those who received fluid bolus. The difference in changes in SVI was not explained by dehydration since this trend was seen even after exclusion of participants with gastroenteritis.

This study shows that severely ill children with febrile disease and those with features of shock present with a complex haemodynamic pattern complex pattern which may determine the choice and outcome of treatment for shock. Measurement of biochemical markers of cardiac function and damage such as NT-proBNP, H-FABP, and CK-MB may improve understanding of the causative mechanisms in those with low CI (myocardial impairment) and poor response (modest increase in SVI) to fluid resuscitation in those with signs of shock. Detailed echocardiography studies such as the one done by Yacoub *et al* may be necessary in the wider group of children with severe febrile illnesses and shock. Further investigation will be needed following the FEAST trial[41] results which showed increase risk of death in children with shock treated with fluid bolus compared to no bolus.

8.4. Safety of colloids for fluid resuscitation in children with severe malaria and shock

The study investigated the safety of colloids following previous trials conducted in Kilifi which showed that hypovolaemia was an important complication of severe malaria in African children[21]. The studies also showed that resuscitation using 4.5% human albumin solution (HAS) resulted in better survival compared to 0.9% saline[19-21]. The studies were small is size and without ideal randomisation. The aim of the study was to establish whether synthetic (non-albumin) colloids, which are relatively cheaper, have similar efficacy and safety profile compared to that of HAS for treatment of shock in children with severe malaria. The results would have been more informative if the definitive trial (FEAST trial)[41], now completed, had shown that HAS resulted in better survival compared to saline. The FEAST trial has since found that treatment of shock using bolus (albumin or saline) increases the risk of death when compared to control. Nevertheless the results of these trials provide valuable information for the safety of these products, in a previously untested population, that may be of use in case new applications for these products are identified.

8.4.1. Safety of gelatin colloid: Gelofusine

Similar resolution of acidosis and clinical features of features of shock (primary outcome) was seen in children receiving HAS or Gelofusine. Many participants remained acidotic (defined by base excess) despite the resolution of other clinical features of shock. This study was not powered to detect effects of HAS and Gelofusine on survival but the results suggested that fluid resuscitation

using HAS resulted in better survival, particularly in cases complicated by coma - a group that was thought to most likely to derive greatest benefit. In children with coma receiving Gelofusine, mortality was significantly greater than those receiving albumin ((6/23; 26%) versus (1/25; 4%), respectively, risk ratio=2.1[1.3, 3.3]). Gelofusine and HAS were equally effective in treating shock and correcting acidosis without complications such pulmonary oedema or raised intracranial pressure. However, acute fatal neurological complications were greater in children receiving Gelofusine (4/44, 9%) compared to HAS (1/44; 2.4%), risk ratio=1.7[1.0, 2.7], p=0.17. There was also one suspected allergic reaction in a child who received Gelofusine. The reaction occurred after concurrent administration of benzylpenicillin and therefore the relationship to the study fluid was uncertain. Neurological sequelae were marginally more common in survivors receiving albumin in this and previous trials [426] but the rates were comparable to previous rates reported in survivors of cerebral severe malaria [427-430]. There were no episodes of gross bleeding or coagulation abnormalities.

Fluid resuscitation with either Gelofusine or HAS resulted in reduced mortality compared to historical controls which had mortality rates of 28-41%, with greatest mortality in the group where acidosis or its clinical correlate, deep breathing, is complicated by coma [3 17 285 286]. Mortality in children who received was lower than in those who received Gelofusine. Mortality in the gelatin arm was comparable to saline arms seen in the previous trials.

Effects on coagulation factors were not measured, therefore, whilst there were no gross effects witnessed, micro-disturbances in coagulation may have been missed. Gelofusine was neither superior to saline or albumin for treatment of shock in children with febrile illness. Further exploration of Gelofusine for treatment of shock is therefore not warranted.

8.4.2. Safety of dextran and starches

Bolus infusion of either 6% hydroxyethyl starch 130/0.4 (HES) or 6% dextran 70 (Dextran) resulted in similar resolution of clinical features of shock. There was evidence of a better resolution of acidosis and respiratory distress in children receiving HES compared to Dextran; however, in the absence of any other superiority on outcome and the small patient numbers, this finding is of uncertain significance. Respiratory distress is a clinical marker of metabolic acidosis [3 286] and their concurrent better improvement seen with use of HES suggests that this is unlikely to be a chance finding. The two arms (HES and Dextran) had similar baseline characteristics so differences were not explained by unbalanced randomisation. One child who received dextran was reported by the carer to have worsening of pre-existing epilepsy at follow-up and was classified as having neurological sequelae.

There was no evidence of renal impairment in children treated with HES as shown by falling creatinine levels and good urine output over 24 hours of monitoring. There were no occurrences of gross bleeding or effects on coagulation seen in the trial. This was the first trial to have generated safety and efficacy of these two fluids for treating children with severe malaria complicated by metabolic acidosis.

Overall mortality was low (5%) in this study including children in the high risk group but this should be interpreted cautiously and may not be strictly comparable with overall mortality in the previous trials (≈10%)[19-21 141]. The results of this trial should not be interpreted as an indication that resuscitation with either HES or Dextran result in better survival compared to either saline or Gelofusine since this trial recruited less severely ill children because children with hypotension and children who required emergency interventions were excluded in this trial but were included in previous trials. Ethics committee had concerns about allergic reactions to dextran that had been seen in a trial in dengue[40] and therefore specified the need for prior informed consent. Higher risk children, included in the previous trials, were not enrolled into this trial. Nevertheless, the 92% survival of the high risk group (enrolled participants with coma and acidosis) and the minimal neurological events is reassuring about the safety of the two intervention fluids.

The relative better efficacy of HES compared to Dextran should be interpreted with consideration of experiences of using HES in other conditions. In dengue shock syndrome, children receiving HES were found to have less requirement for a rescue colloid and faster cardiovascular recovery when compared to those randomised to Dextran during the initial stages of shock[40]. The findings are supported by a study in adults with severe dengue sepsis[431]. The effects of the two fluids on markers of coagulation reported in the dengue trial are reassuring[40]. Dengue is especially a condition where coagulopathy manifests in the pathophysiology and the absence of coagulopathy in patients receiving colloids somehow allays some of the long standing fears of increased risk of coagulopathy in recipients of dextran. The VISEP trial, comparing medium molecular weight starch (HES 200/0.5), 10% pentastarch, and modified Ringer's lactate in adults with sepsis[248] reported an earlier normalisation of central venous pressure/oxygen concentration in the pentastarch group. However this outcome was compromised by higher number of dose-related episodes of renal failure (doubling of creatinine levels), requirement for renal replacement therapy and poorer survival over a 90 day follow up duration [248] in pentastarch group. A subsequent meta-analysis concluded that larger doses of starches in general result in an increased incidence of acute renal failure and late death [249]. The technology for manufacturing has evolved to counter long standing safety concerns[432] and recent evidence suggests that newer generation of medium molecular weight starches such as HES 130/0.4

do not increase the incidence of acute renal failure[433 434]. The higher concentration (10%) starches have a higher water-binding capacity resulting in reduced renal flow[247], are incompletely metabolised with storage in the kidney, the mechanism thought to be responsible for acute renal damage[247 435]. Volumes prescribed in this trial were modest and were not witnessed to cause renal injury but it is uncertain if there were any long term effects on renal function owing to the short follow-up period (30 days).

Further exploration of HES bolus treatment may have been warranted if the FEAST trial had showed a superior survival benefit of fluid boluses compared to no bolus and HAS was superior to normal saline. With respect to HAS, Dextrans would be less favourable for further exploration owing to higher incidence of allergic reactions, it's prone to contamination during manufacturing process and concerns over renal impairment.

8.5. Safety of isotonic fluid for treatment of shock in children with severe malnutrition

Strict adherence to the WHO fluid management protocol (using HSD/5D) in the pilot phase and RCT phase indicate a very high mortality when applied rigorously (mortality=100%) and with some modifications to allow a lower risk group to be investigated and delayed initiation of feeding (mortality=58%). The FIM trial compared equal volumes of RL and HSD/5D. HSD/5D more frequently failed to correct shock, evidenced by presence of oliguria in 50% of survivors to 24 hours compared to 25% in RL arm. Cautious fluid resuscitation using low dose isotonic solutions (Ringer's lactate (RL) and albumin (HAS)) were shown to be safe, with moderately better resolution of haemodynamic indicators of shock including urine output. Overall, there was no significant improvement in survival. Cardiogenic failure, determined by evidence of pulmonary oedema, was not observed for any of the fluid resuscitation strategies.

The high mortality (over 50%) and inadequate correction of shock in all study arms resulted in a decision to prematurely terminate the trial following consultation with the external safety monitors. The regimens employed in the trial design were a compromise, opting for modest volume fluid expansion, and did not employ internationally accepted practice in the non-malnourished children due to concerns of cardiogenic failure and volume overload. As the trial proceeded, the absence of any clear evidence of pulmonary oedema coupled with the high mortality raised concerns on the rationale for withholding standard international paediatric practice guidelines. It was thought that the data generated would be sufficient to provide a sound scientific background for designing further trial using appropriate volumes to correct hypovolaemia.

In subgroup of children with kwashiorkor, in whom the concern of fluid overload and heart failure were mainly founded, outcomes were comparable to children with marasmus even in those receiving isotonic fluids and in the sub-group with dehydrating diarrhoea. This is consistent with recent findings in a Bangladesh study where children with severe malnutrition and cholera received up to 100ml/kg of isotonic fluid (cholera saline) within 6 hours[436]. Although cholera represents a special case with disproportionately huge fluid loses, the findings of both these studies challenge the notion that children with severe malnutrition have myocardial dysfunction together with sodium (and water) retention[437] rendering them susceptible to cardiogenic failure and inability to cope with rapid volume expansion using isotonic fluids[438].

The widely held concerns date back to studies from 1960^{s} and 1970^{s} demonstrating in children with severe malnutrition a state of reductive adaptation and a hypocirculatory state, which recovers on nutritional rehabilitation [439-445]. The conclusions were drawn from radiographic studies showing reduced cardiothoracic ratios on x-rays, autopsy studies showing diminished heart size, and histological changes such as interstitial oedema and myocardial atrophy[446 447]. Others have observed that the heart is reduced in size in concordance with the skeletal musculature[443 444] and both systolic and diastolic functions are well preserved, thus response to fluid expansion should be sufficient[448 449]. Few studies have drawn on modern technology and contemporary understanding of paediatric critical illness to study myocardial status and response to fluid expansion. The other concern is that children with severe malnutrition have increased total body sodium concentration, increased water retention, and impaired kidney function [450-453] but these have not been substantiated by studies in highly clinically-defined patient cohorts. Sodium and water retention are a common compensatory mechanism in severe illness with circulatory impairment and in the absence of physiological studies it is difficult to interpret these findings which underpin the scientific rationale advanced for the current WHO fluid resuscitation guidelines. In this trial pulmonary oedema (cardiogenic failure) or fluid overload were not observed.

The FIM trial, together with recent trial in malnourished Bangladeshi children, provide new findings that add to the scientific literature and extend the debate fluid resuscitation in children with severe malnutrition[27 31 32 124 266 438]. The high mortality, persistence of shock and oliguria suggests that shock is not fully treated and further investigation is warranted. The FEAST trial, which examined fluid resuscitation in well nourished children showed better survival in participants treated with control (maintenance fluid only) compared to bolus infusion[41]. Children with malnutrition and/or diarrhoea were excluded and thus the results can not be directly extrapolated to malnourished children. Nevertheless, a review of the present malnutrition fluid resuscitation guidelines is warranted since a

large number included in the FIM trial had hypovolaemia secondary to diarrhoea. The FIM trial showed persistence of many signs indicating systemic hypoperfusion warranting further analysis.

A recent study in rats have showed unpredictable relationship between macrocirculation (measured by cardiac output and resolution of other features of shock) and microcirculation[407]. In that study, the authors reported that a number of animals showed markers of tissue hypo-perfusion despite recovery of macrocirculation. The solution to better treatment of shock in this population may therefore lie beyond merely normalising parameters systemic circulation to a better understanding of tissue perfusion and strategies to improve it. Newer techniques for monitoring haemodynamic response to fluids, which are easy to learn, non-invasive, reliable and reproducible can be easily used in low resource settings are currently avaialable[179]. These techniques offer assessment of myocardial function at presentation together with monitoring of haemodynamic response to fluid expansion. The resuscitation approach used in this trial should be evaluated using these newer techniques while also incorporating monitoring for tissue perfusion. Colloids and crystalloids are now known to have similar survival benefit in well-nourished children but this should not exclude further evaluation of colloids in children with severe malnutrition due to their pathophysiological differences.

This study had many methodological limitations but it is the first randomised controlled trial comparing isotonic fluids to one of the hypotonic fluids recommended by WHO for treatment of shock in children with severe malnutrition. Volume expansion using isotonic fluids were at least as safe as hypotonic solutions recommended in the current guideline since cardiogenic failure did not complicate their use. Shock was not corrected for all of the fluid strategies and further research investigating various fluid resuscitation strategies is warranted.

8.6. Evidence base of current paediatric fluid resuscitation guidelines in children with shock in severe febrile illnesses

This review critically appraised currently available evidence for fluid resuscitation in paediatric shock in severe infection. The initial searches (up to September 2008) only retrieved nine trials with insufficient evidence to support the preferential use of either colloids or crystalloids. One more relevant trial, the FEAST trial[41], was published after the initial search. The FEAST trial found similar survival in children resuscitated with 0.9% saline and 5% human albumin solution. However, the FEAST trial also found that children with impaired perfusion treated will no bolus (control) had better survival, 3.3% reduction in absolute mortality, when compared to either saline or albumin bolus infusion. The FEAST trial was large pragmatic randomised controlled trial which enrolled 3170 children with severe febrile illnesses and clinical features of shock across six hospitals in East Africa.

It was the largest trial conducted anywhere in the world comparing the survival benefit of using a colloid to a crystalloid bolus for resuscitation in children. It was adequately powered to definitively address the question of overall morality with use of either fluid versus no bolus (control) and also in subgroups such as malaria positive and malaria negative (classified here as sepsis). Following the publication of the FEAST trial results, meta-analysis of all the existing paediatric trials (ten) is in agreement with the findings of meta-analyses in adults[27 32 316], which have also found similar survival benefit in resuscitation using either colloids or crystalloids. The meta-analysis also found increased mortality in children resuscitated with fluid bolus compared to no bolus. This was an unexpected finding and radically challenges the current practice of treatment of shock using bolus infusions especially in resource-poor settings.

The FEAST trial results and subsequent meta-analysis presented in this thesis is still a subject of varied interpretation[454-457] but the significance and implications of the results are not in doubt. First it gives a definitive answer on the similar survival benefit in children resuscitated using either albumin (colloid) or saline (crystalloid). Secondly, it shows that fluid resuscitation using boluses is harmful compared to no bolus in children with shock secondary to severe febrile illnesses within resource poor settings. This finding however excludes shock in children with severe dehydration secondary to gastroenteritis and dengue shock syndrome (DSS) who were excluded from this trial. The implications to the management of meningococcal shock where colloids have been shown to be beneficial in small observational studies within intensive care settings are debatable because the FEAST trial did not enrol children with meningococcal shock[229 230]. Although the FEAST trial results are surprising, it is the first trial that compared treatment of shock using bolus infusions to control (maintenance only). Current practice of bolus infusion in septic shock has been influenced mainly by observational studies where different volumes of boluses were given and in studies comparing one bolus infusion another. The practice has also borrowed heavily from the treatment of haemorrhagic shock and shock secondary to severe dehydration (gastroenteritis) despite the different aetiologies and pathophysiological mechanisms from septic shock.

Three questions emerge as a result of the FEAST trial findings; Firstly, why the finding in FEAST trial has not been seen in resource rich settings where fluid resuscitation is common; Secondly, possible explanations for the harm caused by bolus infusion in African children and; Thirdly, whether children in Africa respond differently to fluids compared to children in resource poor settings. Children with shock in resource rich setting receive bolus treatment with either isotonic crystalloid or colloid during transport, at the emergency department, or within intensive care. Children with fluid refractory shock are admitted to the PICU and receive other therapies such as inotropes,

vasopressors, steroids, vasodilators, or hormonal therapies as deemed necessary[137 220]. Mechanical ventilation is available for children who require ventilation support. It is currently unknown how use of the other therapies modifies the outcome of bolus infusion in children within resource rich settings. Lack of control group also makes comparison with the FEAST results difficult. Bolus infusion leads to increase stroke volume and cardiac output, following the Starling curve, which increases global blood flow and oxygen delivery[407]. However, responses to improvement of macrocirculation may be different in various organs and improvement in macrocirculation is not always accompanied by improvement of microcirculation (end-organ perfusion)[458 459]. Even when there is improved microcirculatory flow, this may be accompanied by increased arteriovenous shunting rather than re-establishment of flow through occluded microvasculature which results in persistence of impaired perfusion at the tissue levels (end-organs)[460]. Fluid bolus may also lead to re-perfusion injury, trans-location of microbes from poor-perfused bowel, increased availability of oxygen radicals and increased oxidative stress, all factors that may explain the results of the FEAST trial. Participants who received maintenance may not have had the additional stress induced through bolus.

Certain conditions were not covered in the FEAST trial and there is justification for continuing with existing fluid management guidelines. In DSS there is conclusive evidence that colloids are better than crystalloids for treating shock in severe cases but both have similar efficacy in moderate DSS [37-40]. There is no definitive trial in DSS where mortality is the primary endpoint. The tempo of dengue shock is much slower, where shock develops over many hours or days due to haemoconcentration consequent upon severe capillary leak[175-177]. This is in contrast to shock in sepsis and possibly malaria which progresses rapidly with a high risk of early mortality [177]. In addition, there is the potential risk of brain swelling in sepsis and malaria[461-463] in those with impaired consciousness, whereas neurological complications are rare in DSS.

Earlier studies conducted from Kilifi in children with severe malaria indicated a superior survival benefit with human albumin solution (HAS) compared to saline or other colloid (gelofusine). It is therefore of interest to explain why the results of the definitive FEAST trial were very different from these earlier studies. First of all, the early studies were small in size ,conducted at a single site, and one study did not have ideal randomisation and therefore may have overestimated treatment effect due to HAS [464-467]. Secondly, these studies used HAS with higher concentration of sodium (150mmol/L) as compared to the HAS used in the FEAST trial (136mmol/L) and it would be possible that the beneficial effect seen earlier was a result of the use of a solution with sodium concentrations above the plasma level. While this interpretation may be tempting, a recent randomised trial failed to show any benefit in adults with traumatic brain injury but without shock

treated with hypertonic saline compared to normal saline[468]. Combining the effect of an increased oncotic pressure of the colloid together with supra-physiological sodium levels has not been previously considered. Before the results of the FEAST trial, the single trial in children with sepsis[332] was too small to detect differences in mortality but showed that a larger volume of crystalloid was required to achieve same resuscitation endpoint as colloid. This study was however done in the PICU, there was no control group, and not powered to detect survival benefit.

The systemic review contained in this thesis has highlighted a number of realities. First, that there are surprisingly few trials in the paediatric population examining fluid resuscitation strategies. Fluid resuscitation is a very common practice in modern paediatrics especially in resource rich setting, but recommendations are largely based upon consensus or expert opinion rather than results of definitive studies or meta-analysis. In the recent surviving sepsis campaign review, the evidence for the paediatric recommendations were classified as 2C (weak evidence, based on retrospective review or expert opinion)[137]. Second, of the ten trials reviewed, all have been conducted in resource poor countries, despite fluid resuscitation practice being much less common. Given the findings in this review and the results of the FEAST trial it there should be a debate on how the results impact on fluid resuscitation practice in resource settings, where no similar trial has been done. International paediatric treatment guidelines, largely based on observational studies, recommend 60mls/kg of isotonic resuscitation fluid given in the first hour of development of shock and this is reported to result in a nine-fold reduction in mortality[196 259 260]. It has also been reported that every hour that hypovolaemia is left uncorrected leads to a doubling of mortality[196 260]. However, none of these studies involved randomisation and many other concurrent therapies were given.

Currently there are no recommendations on the optimal fluid (crystalloid or colloid) for resuscitation. Differences in the physiological derangements, speed of the development of shock, complications and pre-intervention case fatality rates frustrate the development of a single fluid resuscitation strategy appropriate for all contexts. The crystalloid-colloid debate has been ongoing globally [30 31 265 266 469 470] but with FEAST results, it would seem that the debate should now shift to the appropriateness of bolus treatment in the first place, especially in resource poor settings. This review only considered published studies and this was a major limitation but the funnel plot was symmetrical on visual inspection of and this showed that it was unlikely to have missed some grey literature.

This review shows that treatment of shock in children with severe infections using bolus infusions of either saline or albumin is harmful compared to no bolus (control). This review also shows conclusive

evidence that like in adults, treatment of shock using saline and albumin result in similar survival. In severe DSS colloids are superior to crystalloids for treatment of shock but both have similar efficacy in moderate DSS. The findings of this review and meta-analysis are applicable to the management of shock in children with febrile illnesses in SSA and other resource poor settings where the informative studies have been done. It excludes management of shock in conditions such as gastroenteritis, trauma, burns, and malnutrition were not critically reviewed. There are no trials comparing crystalloids versus colloids or bolus versus control (no bolus) in children with shock and febrile illnesses in resource rich settings. Studies investigating bolus versus control need to be done in resource-rich settings because the results reported here may not be directly transferable.

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