Treatment of the critically ill child in low-resource settings

Essential paediatric emergency and critical care

Hans-Jörg Lang

Thesis for the Degree of Doctor Philosophiae (Dr.Philos)
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Abstract

Introduction: In 2019 approximately 5.2 million children died before the age of 5 years. Around 2.2 million children and young people died between the age of 5-24 years. A large number of these deaths are attributable to severe infections associated with respiratory failure or haemodynamic instability and other organ dysfunctions. While social determinants and public health interventions have a major impact on child health, access to essential emergency and critical care on different levels of referral pathways has the potential to contribute to a reduction of preventable mortality and morbidity of critically ill children treated in resource-limited settings.

Aim:

The aim of this thesis is to evaluate essential elements of respiratory support (both non-invasive and invasive), as well as fluid resuscitation in critically children treated in sub-Saharan Africa.

Methods:

Paper 1 describes an observational study conducted between February and April 2014, in a busy paediatric department in Malawi. The use of bubble continuous positive airways pressure (bCPAP) in the treatment of critically ill children (0-59 months) with acute respiratory dysfunction was evaluated.

Paper 2 describes the analysis of a database which prospectively collected data on the outcomes of patients suffering from snake-bites admitted to the intensive care unit of a rural hospital in Northern-Uganda between 2006 and 2017. Particular attention was drawn to patients with acute respiratory failure following neuro-toxic snake envenomation.

Paper 3 describes a re-analysis of data from a large randomised controlled trial conducted between 2009 and 2011 in three East-African countries (the FEAST-study), in a setting with no availability of advanced intensive care treatment. In order to better understand impact of intravenous fluid resuscitation on vital organ functions in critically ill children, “organ-function scores” were developed using data from the FEAST-study. These scores describe respiratory, cardiovascular, and neurological function and were compared with four other patient cohorts of critically ill patients treated in South Africa, Malawi and the UK. Odds of adverse outcome were assessed using logistic regression for each cohort. Among participants of the FEAST-trial the organ function scores were used to identify differences between children treated with fluid bolus (n=2097) as compared to critically ill children receiving maintenance fluids (n=1044). Using FEAST-study data, further analysis were conducted, including evaluation of the impact of fluid resuscitation on Hb levels and plasma biochemistry in conjunction with changes of organ-function scores. Statistical models were used to identify subgroups of patients with certain “clinical phenotypes” differing in response to fluid bolus administration.

Results: In the Malawian study (Paper 1), 117 children (median age: 7 months) with signs of respiratory failure were treated with bubble CPAP. Overall survival was 79/117 (68%); survival was 54/62 (87%) in children with very severe pneumonia but without further organ-dysfunction. Among 19 children with very severe pneumonia (single-organ failure) and negative HIV tests, all children survived. Survival rates were lower in children with respiratory dysfunction associated with further organ failure (e.g., shock) (45%) as well as in children with severe acute malnutrition (SAM) (36%) and HIV infection or exposure (45%).

In the study evaluating treatment and clinical outcomes among critically ill snake-bite victims in northern Uganda (Paper 2) 67 patients (38.5%) were children (<18 years). 60 patients (36.5%)

developed acute respiratory failure requiring invasive mechanical ventilation. Despite limitations in data-collection, study results suggest that neurotoxic envenomation was the most common cause of respiratory failure among study patients requiring mechanical ventilation. Antivenom (at low and probably inadequate doses) was administered to 12.6% of study patients. The median ICU length of stay was 3 days (interquartile range, 2-5) and mortality was 8%. ICU mortality of patients with ARF, requiring mechanical ventilation was 16.7%.

In Paper 3 increasing respiratory, neurological and cardiovascular scores were associated with death among FEAST study patients, and with adverse outcomes for specific scores in the four other cohorts. In FEAST-participants, IV fluid bolus increased respiratory and neurological scores and decreased cardiovascular score at 1 h after the start of IV fluid boluses. Fluid bolus recipients had mean 0·33 g/dL (95% CI 0·20–0·46) reduction in Hb levels after 8 h ($p<0·0001$), and at 24 h had a decrease of 1·41 mEq/L (95% CI 0·76–2·06; $p=0·0002$) in mean base excess and increase of 1·65 mmol/L (0·47–2·8; $p=0·0070$) in mean chloride, and a decrease of 0·96 mmol/L (0·45 to 1·47; $p=0·0003$) in bicarbonate. There were similar effects of fluid bolus administration in three patient subgroups, identified on the basis of their baseline clinical characteristics.

Conclusions: Paper 1 suggests that bubble CPAP can be used efficiently in the treatment of acute respiratory dysfunction in paediatric units in malaria-endemic, resource-limited contexts. The role of non-invasive respiratory support as part of a care package for critically ill children with multi-organ dysfunction needs further evaluation, while children with malnutrition or human immunodeficiency virus infection need particular attention.

Provision of basic intensive care, including mechanical ventilation, was a feasible treatment option for snakebite victims presenting with acute respiratory failure in a rural hospital in sub-Saharan Africa. Acute respiratory failure in this context was associated with neuro-toxic snake-envenomation, without severe acute lung injury and no other associated severe organ-dysfunctions.

Fluid resuscitation using “unbuffered” intra-venous solutions can be associated with severe adverse events: respiratory and neurological dysfunction, hyperchloraemic acidosis as well as reduction of haemoglobin-levels. Using smaller volumes of electrolyte balanced resuscitation fluids may be beneficial in the treatment of critically ill patients with haemodynamic instability, while careful monitoring of haemoglobin-levels and other vital organ functions is required.

Future pragmatic research needs to be directed to optimize a “ comprehensive paediatric critical care package” adapted to resource-limited contexts.

Abbreviations

ACHEI	Acetyl-cholinesterase inhibitors
AKI	Acute kidney injury
APLS	Advanced Paediatric Life Support
ARDS	Acute respiratory distress syndrome
ALIMA	Non-governmental organization – Alliance for International Medical Action
ARF	Acute respiratory failure
AVPU	Coma- score: alert; response to voice; response to pain; unresponsive
bCPAP / BCPAP	bubble CPAP, continuous positive airway pressure
BE	Base excess
BIPAP	Bilevel positive airway pressure
ARV	Anti-retro-viral treatment
BP	Blood pressure
CHD	Congenial heart disease
CHW	Community health worker
COM	College of medicine
CPAP	Continuous positive airway pressure
CPR	Cardiopulmonary resuscitation
CRF	Case record form
CRT	Capillary refill time
CSF	Cerebro-spinal fluid
CVS	Cardio-vascular system
CXR	Chest Xray
DED	Deutscher Entwicklungsdienst/German Development Service
DOPE	Displacement, obstruction, patient, equipment
ED	Emergency department
EECC	Essential emergency and critical care
EPECC	Essential paediatric emergency and critical care
ESICM	European society of intensive care medicine
ETAT	Emergency triage and treatment
FEAST	Fluid Expansion as Supportive Therapy (FEAST) study
FIO_2	Fractional O_2 - concentration in inspired air
GIZ	Gesellschaft für internationale Zusammenarbeit
HAS	Human albumin solution
HB	Haemoglobin
HDI	Human Development Index
HDU	High dependency unit
HFNC	High flow nasal cannula
HHFNC	Heated humidified high flow nasal cannula
HIV	Human immunodeficiency virus
HR	Heart rate
ICU	Intensive care unit
IPC	Infection prevention control
IQR	Inter-quartile range
IRB	Institutional review board
IO	Intra-osseous
IV	Intra-venous
KDIGO	Kidney Disease: Improving Global Outcomes
KCH	Kamuzu Central Hospital
LHF	Lassa hemorrhagic fever
LMICs	Low- and middle-income countries
LPM	Litre per minute
MAM	Moderate acute malnutrition
MAP	Mean arterial blood pressure
MOF	Multi-organ failure
MRDT	Malaria rapid diagnostic test

MSF	Médecins sans frontières
NGO	Non-governmental organisation
NIBP	Non-invasive BP, blood pressure
NIV	Non-invasive ventilation
NIPPV	Nasal intermittent positive pressure ventilation
OI	Oxygenation index
OSI	Oxygenation saturation index
ORS	Oral rehydration solution
PARDS	Paediatric ARDS, acute respiratory distress syndrome
PaO_2	O_2 partial pressure
pCO_2	CO_2 partial pressure, carbon dioxide
PCR	Polymerase chain reaction
PD	Peritoneal dialysis
PEEP	Positive end expiratory pressure
PEMVECC	Paediatric Mechanical Ventilation Consensus Conference
PEWS	Paediatric early warning system
PF-ratio	PaO_2/FIO_2- ratio
PICC-line	Peripherally inserted central line
PICU	Paediatric intensive care unit
PTIF	Peak tidal inspiratory flow
PJP	Pneumocystis jirovecii pneumonia
PMTCT	Prevention of mother to child transmission
POCUS	Point of care ultrasound
POC-test	Point of care test
RBC transfusion	Red blood cell transfusion
RCT	Randomised controlled trial
RESOMAL	Rehydration solution for malnutrition
ROSC	Return of spontaneous circulation
RR	Respiratory rate
RRT	Renal replacement therapy
SAM	Severe acute malnutrition
SARI	Severe Acute Respiratory Infections
SBP	Systolic blood pressure
SCD	Sickle cell disease
SF-ratio	SpO_2/FIO_2 - ratio
SDG	United Nations Sustainable Development Goals
SIMV	Synchronized intermittent mandatory ventilation
SIRS	Systematic inflammatory response syndrome
SpO_2	Saturation from pulse oximetry
SOF	Single organ failure
SOI	Severity of illness
SOP	Standard operation procedures
SSA	Sub-Saharan Africa
SSC	Surviving sepsis campaign
TB	Tuberculosis
UA	Upper airway
U5MR	Under fiver year mortality rate
VALI	Ventilator associated lung injury
VAP	Ventilator associated pneumonia
VSPNA	Very severe pneumonia
WHO	World Health Organisation
WOB	Work of breathing

Preamble

The author of this thesis – Hans-Jörg Lang – completed his medical studies in Freiburg/Breisgau, Germany. During a student elective in a remote district hospital in the République du Benin (Kouande/Atakora, supported by the German development service/DED) he first was exposed to challenges health services face in resource-limited settings. After graduation he conducted most of his post-graduate training in the UK (Bangor/North Wales, Cardiff, Leicester, Birmingham, London), with a short period as interne in France. Before starting his training in paediatric and paediatric intensive care he profited from internships in internal medicine, general surgery, traumatology and anaesthesiology. As medical officer in a district hospital in Northern Namibia he gained further experience (2001-2003; via the German development service/DED). From 2007-2009 he was substantially involved in the preparation of a large RCT (FEAST-study), which was conducted in 6 paediatric units in East Africa. Hans-Jörg Lang was particularly involved in pragmatic training programs in essential paediatric emergency and critical care in four paediatric departments in Uganda, where most of the patients were recruited for this RCT (Mulago Hospital/Kampala, Soroti, Mbale and Lacor-Hospital near Gulu). In cooperation with colleagues from participating paediatric units, training programs included extensive "on the job-training", improvement of patient circuits as well as activities facilitating the integration of study procedures in routine clinical processes. Additionally, during the preparation of the FEAST-trial a small study assessing cardiac function and fluid responsiveness in 30 children with severe malaria was conducted in Kilifi/Kenya. Point of care echocardiography studies and supra-sternal doppler assessments were done by Sophie Yacoub and Hans-Jörg Lang. Paper 2, was conducted in Lacor-Hospital, Gulu in Northern Uganda (one of the sites of the FEAST-study) and arose from persisting contacts to colleagues in this remarkable hospital. From 2011 to 2014 Hans-Jörg Lang worked at Kamuzu Central Hospital (KCH) in Lilongwe/Malawi on a paediatric unit with around 20,000 paediatric admissions per year (employment by the Malawian College of Medicine and the German international cooperation/GIZ). Despite extreme resource-limitations the clinical team managed to substantially reduce paediatric hospital mortality within several months by strengthening different elements of a patient circuit. Particular support was provided by the late Prof. Peter Kazembe (previous head of department of the paediatric unit a KCH and head of the Baylor, HIV-services at this stage). In 2011 the Malawian College of Medicine (Malawian-COM, based in Blantyre) opened a second campus at KCH. In cooperation with Dr. Ajib Phiri (deputy dean of the Malawian COM), the paediatric department in Blantyre, Hans-Jörg Lang

contributed substantially to the start of a 3rd year medical student paediatric course in Lilongwe. In 2014 in cooperation with Dr. Bernadette O'Hare and Dr. Ajib Phiri he contributed considerably to the start of a clinical officer bachelor training program. During his time in Lilongwe two basic observational studies assessing the use of bCPAP in the treatment of children with acute respiratory dysfunction were conducted, including Paper 1.

Since 2015 Hans-Jörg Lang worked for two humanitarian organisations. Via Médecins Sans Frontières (MSF) he supported projects in different countries in Sub-Sahara Africa and Afghanistan. As paediatric advisor for the NGO "The Alliance for International Medical Action (ALIMA), https://alima.ngo/en/news/) the author worked since 2019 in Ebola treatment centres in the eastern part of DR Congo, a large COVID-treatment centre in Guinea and other projects. At the same time he remains involved in training programs, research projects and guideline development. He also holds a lecturer post in the Global Child Health Department of the University Witten/Herdecke in Germany. In the last years he was involved in some activities supported by WHO (Ebola training programs in Tanzania, DR Congo; new inter-agency triage tool, WHO oxygen scale-up project COVID-19[a]).

[a] The author participates in this on-going panel discussion lead by WHO: https://www.who.int/initiatives/oxygen-access-scale-up

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Great thanks and respect for all my colleagues and students I worked with over several years in paediatric departments in different countries. So many colleagues work with amazing dedication in challenging and sometimes overwhelming conditions. My thoughts are with all the critically ill children treated during these periods as well as their parents and families.

Particularly I remember the late Dr. Peter Kazembe, who supported many colleagues, including myself with advice and always positive spirit. Dr. Kazembe was one of the first paediatricians in Malawi. With his dedication, open mind, humour and humanity he is a role model for many, including myself.

Dr. Peter Kazembe (Watts, G., *Peter Nicholas Kazembe.* The Lancet, 2020. **396**; with permission)

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Publications in the thesis

Paper 1

Myers S, Dinga P, Anderson M, Schubert C, Mlotha R, Phiri A, Colbourn T, McCollum ED, Mwansambo C, Kazembe P, **Lang H-J**. Use of bubble continuous positive airway pressure (bCPAP) in the management of critically ill children in a Malawian paediatric unit: an observational study. *BMJ Open Respiratory Research* 2019; 6: e000280.

Paper 2

Lang HJ, Amito J, Dünser MW, Giera R, Towey R. Intensive-care management of snakebite victims in rural sub-Saharan Africa: An experience from Uganda. *Southern African Journal of Critical Care (Online)* 2020; 36: 39-45.

Paper 3

Levin M, Cunnington AJ, Wilson C, Nadel S, **Lang HJ**, Ninis N, McCulloch M, Argent A, Buys H, Moxon CA, Best A, Nijman RG, Hoggart CJ. Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial. *The Lancet Respiratory Medicine* 2019 Jul;7(7):581-593.

Annex 1

Supplement to Paper 3 in *The Lancet Respiratory Medicine* 2019 Jul;7(7):581-593. (This supplement was part of the original submission)

Annex 2

The original FEAST-study: Maitland, K., et al., Mortality after fluid bolus in African children with severe infection. *The New England Journal of Medicine,* 2011;**364**: 2483-95. (The original study on which Paper 3 was based on. H-J. Lang contributed substantially to the set-up of the 4 trial centers in Uganda between 2007 – 2009.)

Introduction

In 2019 approximately 5.2 million children died before the age of 5 years. More than 40% of deaths in this age group were due to deaths during the neonatal period. Around 2.2 million children and young people died between the age of 5-24 years.[1] Children living in "fragile states", exposed to socio-economic challenges, political instability and humanitarian crisis with limited access to essential, good quality health services are at increased risk.[1-3] Most deaths in children and newborns are either preventable and/or treatable. Social, economic and political determinants have a major impact on child health as highlighted in the United Nations Sustainable Development Goals.[4,5] However, public health interventions and essential emergency and critical care (EECC) in health facilities and streamlined referral pathways have the potential to substantially reduce preventable mortality of children, adolescents and adults in resource-limited contexts.[6,7] Pragmatic research projects addressing important clinical challenges can contribute to improved quality of care and guide policy makers towards the set-up of efficient health care systems. Publications presented in this thesis address aspects related to respiratory support and treatment of haemodynamic instability in critically ill children treated in resource-limited countries in sub-Saharan Africa (SSA).

Global Burden of diseases and regional differences

Since 1990 there has been a substantial reduction in child mortality globally.[1] In 1990,12.5 million children under the age of five years died, while in 2019 this had reduced to 5.2 million.[1] A number of low- and middle-income countries (LMICs), for example in South East Asia achieved the United Nations Millennium Development Goal number 4 which was to reduce the under-five mortality rate (U5MR) from 1990 to 2015 by 2/3. However, a number of countries in SSA were less successful in reducing child mortality.[1] In 2019 approximately 50% of all child deaths occurred in SSA.[1] Child mortality is higher in fragile states and among populations exposed to humanitarian crisis (e.g. conflict or post-conflict situations, displaced populations).[1,2] Economic factors play an important role and wealthier countries can spend more on public services and have much lower levels of child mortality, however countries in SSA often have as little as $100 per capita to spend on all sectors including healthcare.[4] Additionally, there are considerable geographical and social inequalities within countries in terms of child mortality.[8]

A large number of deaths in children are attributable to severe infections (e.g., respiratory infections, severe malaria, diarrheal diseases; figure 1).[1] Most severe infections are either preventable and/or treatable,[1,9] but without early, efficient management, severe infections can progress to organ

dysfunction and death. This process can be defined as sepsis,[9] a syndrome caused by severe infections associated with a disease progression potentially leading to multiple organ dysfunctions. Sepsis is not defined as a separate entity in the standard *Global Burden of Disease* estimates,[1,9,10] but is a major cause of morbidity and mortality worldwide and in many low-resource settings is the terminal event of poor and/or delayed management of severe infections. Incidence of sepsis peaks in early childhood and among older adults and the burden of disease related to sepsis is particularly high in SSA.[9]

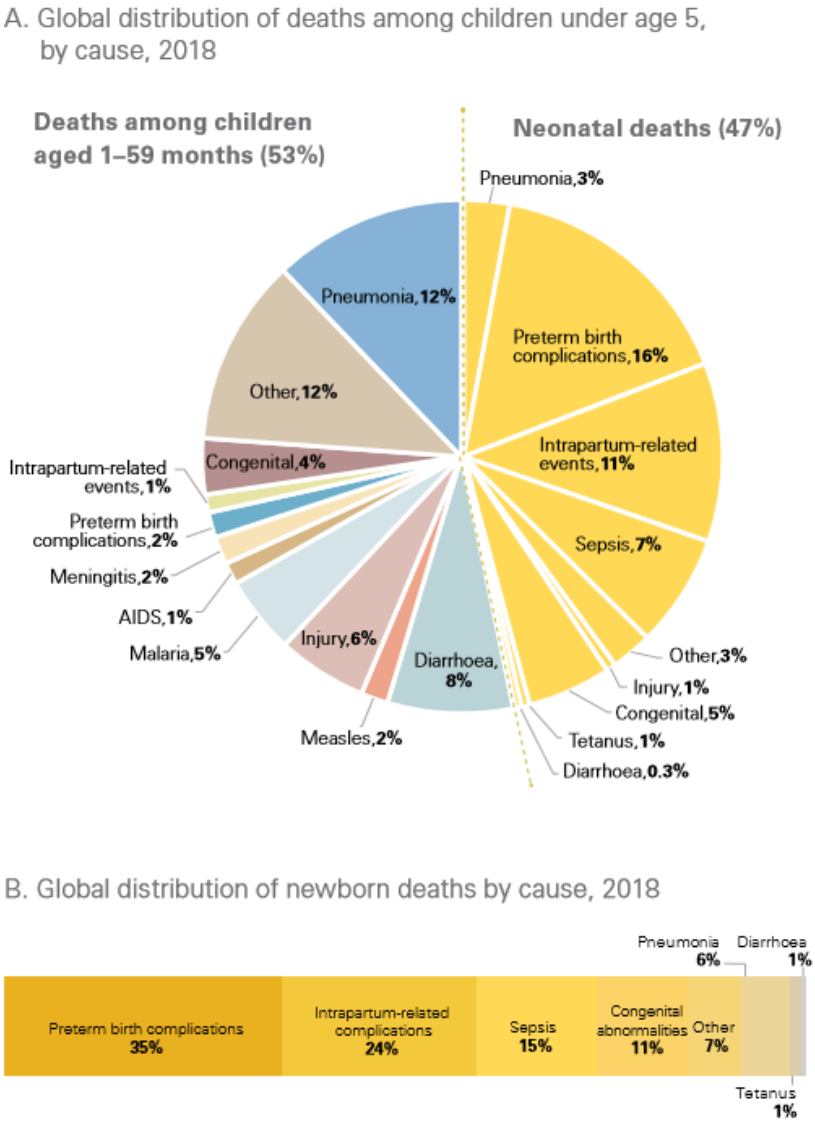

Figure 1. Causes of deaths among children under the age of 5 years.[1]

Malnutrition increases the risk to develop severe infections and worldwide around 50% of deaths in children under age of 5 years are associated with undernutrition.[1] Additionally, the prevalence of human immunodeficiency virus (HIV) infections and tuberculosis (TB) substantially contribute to morbidity and mortality among children and adolescents.[1] In most low-income countries, neonatal mortality did not decline to the same extend as overall U5MR and world-wide, neonatal deaths account for more than 40% of deaths in children under the age of five years.[1]

Maternal health is critical for disability-free neonatal survival,[1] yet maternal morbidity and mortality remains high in resource-limited settings.[11,12] Most causes of maternal deaths are preventable and or treatable e.g.: severe sepsis, post-partum hemorrhage (PPH), eclampsia, complications associated with unsafe abortions.[12] A considerable number of maternal deaths, stillbirths and neonatal complications can be prevented by improving access to essential obstetric emergency care services.[1,12] Complication rates in pregnancy are particularly high in young mothers.[12] Therefore, management of obstetric emergencies in adolescents and young adults is an important aspect of emergency and critical care.

In the age group between 5 and 24 years approximately 2,2 million children and young people died in 2019 of mostly preventable and treatable conditions.[1] Injuries (including road traffic accidents, drowning, burns, and falls) are important causes of morbidity and mortality in children and young people above 5 years.[1] In fact, road traffic injuries are among major causes of morbidity and mortality in older children, adolescents, and young adults,[13] while exposure to violence is particularly relevant in conflict zones.[2,3] Non-communicable diseases (e.g., diabetes, sickle cell disease, epilepsy, malignancies) contribute considerably to disease burden in older children and adolescents.[1,10] Adolescent health takes a central role within the "LIFE COURSE (figure 2)" as outlined in the United Nations Global Strategy for Women's, Children's and Adolescents' Health (2016–2030).[14]

A considerable number of children who survive critical conditions (e.g., cerebral malaria) suffer subsequently from preventable life-long disabilities.[15] Access to essential emergency and critical care (EECC) has the potential not only to contribute to reduction of mortality, but also to the reduction of preventable disability.[7,15,16]

The SARS-CoV2 pandemic is having direct effects on health systems. However, indirect effects of the pandemic such as disruption of food supply chains, reduction in the provision and utilisation

of essential health services as well as effects on allocation of health resources can potentially have a severe impact on maternal and child health, especially in low-income countries.[1,17]

In this thesis, aspects of essential paediatric emergency and critical care will be discussed, with a specific focus on respiratory support and treatment of haemodynamic instability.

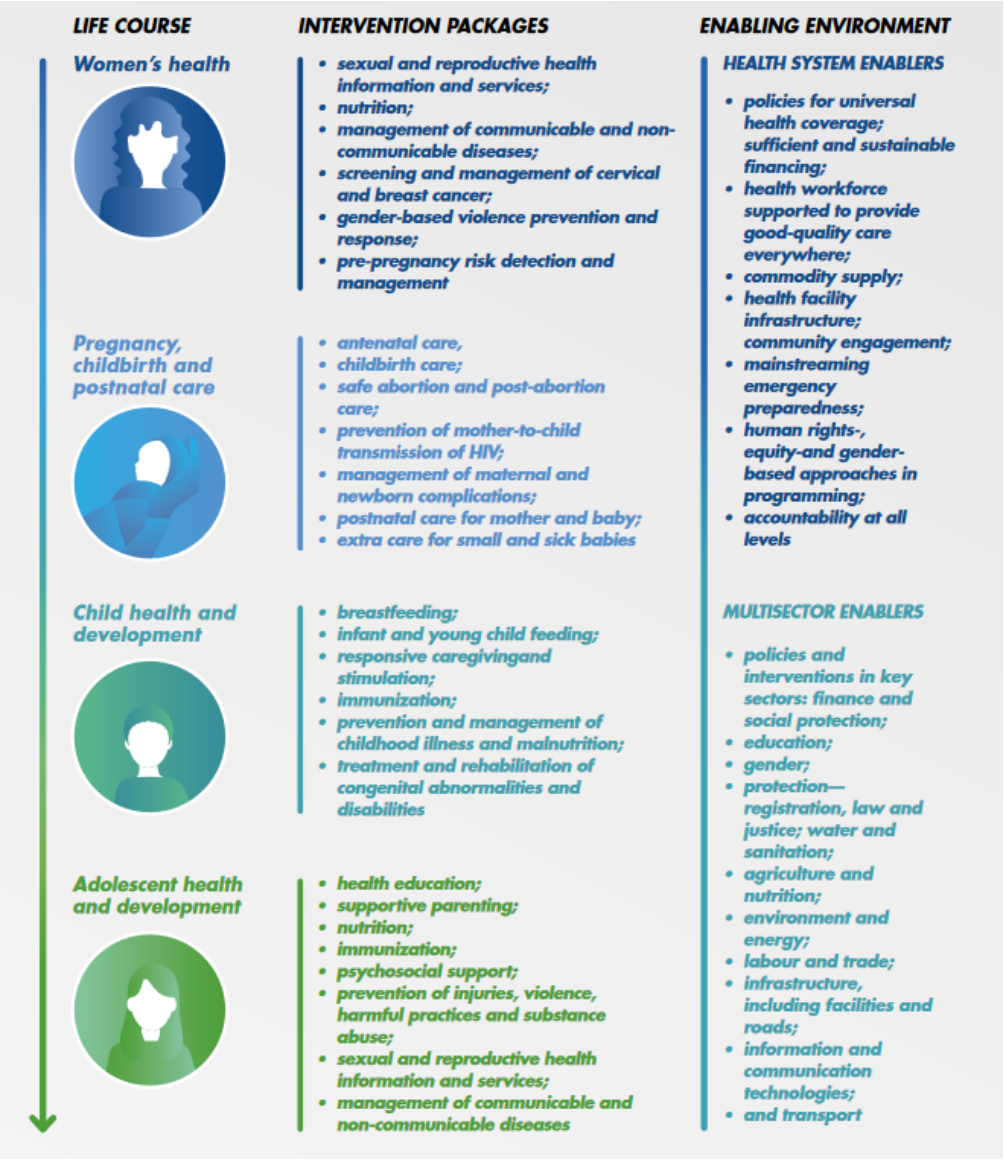

Figure 2. Examples of evidence-based interventions for women's, children's and adolescents' health. (https://www.who.int/life-course/partners/global-strategy/ewec-globalstrategyreport-200915.pdf?ua=1).[14]

Clinical network – access to essential emergency and critical care (EECC)

The international community recognizes the need to urgently reduce preventable child deaths. This objective is outlined in the United Nations Global Strategy for Women's, Children's and Adolescents' Health (2016–2030)[14] and the United Nations Sustainable Development Goals (SDGs).[5] In this context, EECC is an important element of Target 3.8: *To achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.*[5,6,18] EECC has the potential to contribute to reduction of preventable morbidity and mortality in children, adolescents and adults in resource-limited settings.[6,7,19,20] Examples for critical clinical conditions, which can be treated within a referral system, able to provide EECC:

- Children with severe pneumonia and hypoxaemia need access to health facilities who can provide supplemental O_2 and non-invasive respiratory support.
- Children with severe anemia associated with severe malaria need stabilisation of vital organ function, including the possibility to receive a safe blood-transfusion if indicated.
- Patients with prolonged seizures need stabilisation of vital organ functions, seizure control and treatment of underlying causes.
- Sick newborns have higher chances of survival with access to essential newborn care.
- A pregnant adolescent with postpartum haemorrhage needs access to EECC and specifically to emergency obstetric services.

In order to improve access to EECC, a robust referral pathway from communities and peripheral health facilities to district or regional hospitals is crucial.[21-24] The majority of critically ill patients enter and move along this referral pathway. However, access to adequate hospital based emergency and critical care is challenging for a large part of populations in SSA.[23] Additionally, improvement of quality of paediatric care in peripheral facilities and hospitals needs a multi-disciplinary approach, including sustained training programs for health workers.[21,22,25,26]

Strengthening access to EECC on different levels of referral pathways, is also a vital element in outbreak response strategies (e.g., Ebola Viral Disease, SARS-CoV2), in association with infection prevention control (IPC) measures, contact tracing and immunization programs (if available). [27-31]

Pre-hospital care: Community based care, peripheral health facilities and transfer

Pre-hospital care: Community based care & Community health workers

Community health workers (CHWs) can be trained in the recognition of signs of serious illness and can therefore perform "triage" on community level. Early recognition and referral of sick patients, associated with a clear referral mechanism, has the potential to reduce morbidity and mortality. Comprehensive training programs need to be adapted to different contexts and skill levels of CHWs.[32] Participation of civil societies and community leaders is vital in all aspects of community based care.[33]

Pre-hospital care: Peripheral health facilities & "referral health centers"

Services provided in peripheral health facilities are crucial in improving access to essential health services for local populations. By decentralising certain health services, workload in district and regional hospitals can be reduced. Peripheral health facilities play an important role in the initial management of critically ill patients and act as primary referral facility for communities.

The WHO algorithm, integrated management of childhood illnesses (IMCI), guides treatment of common childhood illnesses at the level of peripheral health facilities. Curative care elements are integrated with advice on nutritional care, immunization schedules etc.[34-37] Essential newborn care is part of IMCI algorithms.

In some settings, certain peripheral health facilities can provide basic level of in-patient care and can act as "referral health centers". In this context WHO guidelines outlined in the pocketbook: Hospital Care for Children can complement IMCI-algorithms.[38] These guidelines include emergency triage assessment and treatment (ETAT), pragmatic algorithms designed for initial identification and emergency treatment of critically ill children as well as for children at risk of clinical deterioration. ETAT-algorithms follow international principles of paediatric emergency care.[38-40]

Severely ill children need immediate emergency treatment, prior to transfer to district or regional hospitals. In this context, provision of O_2 can have a major impact on survival chances of children with respiratory dysfunction and needs to be available at this level of a referral pathway.[41] Sustainable energy solutions in combination with O_2-concentrators can facilitate reliable provision of O_2 even in remote settings.[42,43] Portable O_2-concentrators can provide O_2 during transfer of critically ill patients.

Pre-hospital care: Transfer

In many low-resource settings, ambulance services are under-funded or might not even exist. Communities need to find opportunities to move sick patients to a health facility or organize transfer between health facilities. Referral systems are important elements of EECC, which need to be strengthened in many countries.[24,44]. The set-up of "referral health centers" at geographically strategic locations can be beneficial. Communities might be able to transport critically ill patients to local

facilities where initiation of emergency treatment as well as clinical surveillance is feasible for a period of time. Limited "ambulance service capacities" can then target transfers from these "referral health centers" to district/regional hospitals where more advanced emergency and critical care can be provided. Efforts to strengthen referral systems need to be adapted to available resources and contexts. This requires a sustained multi-disciplinary approach (Appendix 1, Table 11).

Hospital based care: Patient circuits – emergency and critical care

District or regional hospitals play a crucial role within referral pathways and are the primary "referral hub" for peripheral health facilities and need to be considered as vital elements of universal health coverage as defined in SDG 3.[5,21,22] In many low-resource settings referral to tertiary hospitals may only be feasible for specialized services of a minority of patients and only if stable enough for transfer. Additionally, tertiary hospitals in many low-resource contexts also cover the function of a district hospital for populations living in closer proximity. Within health facilities set-up of efficient patient circuits is important in order to provide good quality emergency and critical care, including optimized, context-adapted respiratory support as well as treatment of haemodynamic instability.[19,20]

Triage and emergency department

Primary entry point to a hospital is the **emergency department (**ED). WHO in cooperation with other agencies suggests a pragmatic "triage tool" categorizing patients according to severity of illness and/or risk for rapid clinical deterioration.[45] Other triage tools exist (e.g. South African Triage System (SATS; Manchester Triage Group).[46,47] However, the "WHO inter-agency triage tool" is pragmatic and adapted to needs in low-resource settings (figure 3). An efficient triage process ensures rapid evaluation of severity of illness, followed by immediate emergency care in case of life-threatening conditions. In the context of disease outbreaks, evaluation of the risk of presence of a highly contagious disease needs to be integrated in the triage process.

Classification of severity of illness using the triage system recommended by WHO:[45]

Triage: First step in the context of disease outbreaks
Screening of risk factors suggesting presence of a highly contagious disease (e.g., Ebola, Lassa hemorrhagic fever (LHF), measles, Severe Acute Respiratory Infections (SARI; e.g., SARS-CoV2), cholera). This step should not delay evaluation of severity of illness as well as initiation of emergency care. Standard IPC-measures need to be established in order to protect health workers and avoid cross-infection among patients.[30,48]

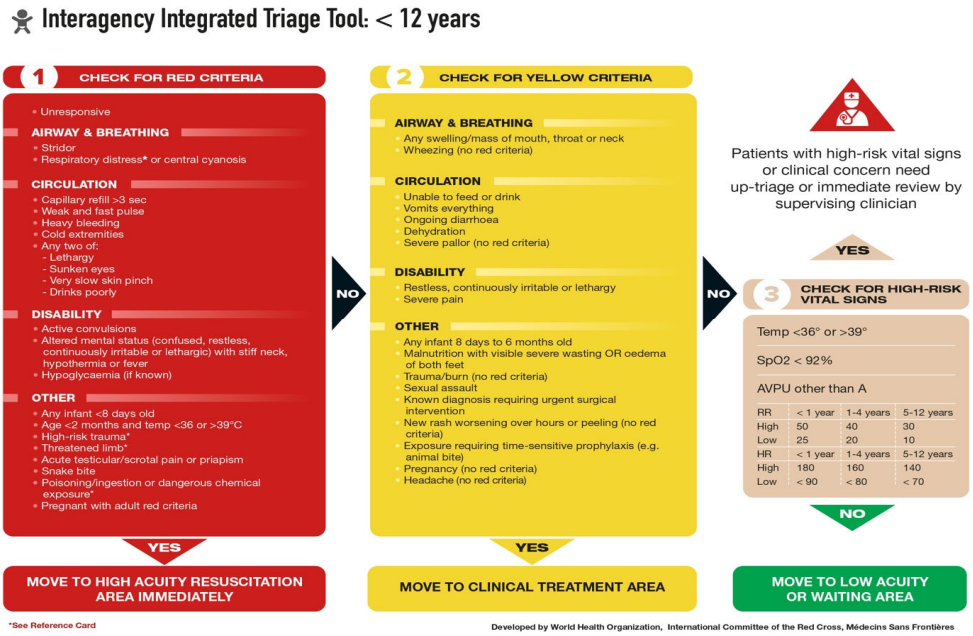

Figure 3. WHO inter-agency triage tool for "routine facility-based care" of children < 12 years. Other elements of this triage tool exist: "routine facility based care" of patients > 12 years (including pregnant women), facility-based mass casualty triage and pre-hospital triage.[45]

Red: Immediate emergency care is needed: Patients require urgent resuscitation and support of vital organ functions in the emergency unit. Simultaneously treatment of underlying conditions is initiated (e.g., sepsis, severe malaria). Pregnant women and newborns need specific attention. Other aspects like limb-saving surgical procedures or the potential of rapid clinical deterioration need to be considered (e.g., poisoning, neuro-toxic snake-bite envenomation).

Yellow/ priority care: The "priority category" commonly presents the largest group of patients presenting for triage. Patients in this category have significant illness and the majority require hospital admission. Efficient treatment needs to be initiated as soon as possible. Particularly vulnerable groups of patients are inherently classified as "priority" e.g.,: young infants, malnourished children, patients referred from other facilities.

Green / non-urgent category: These patients can often be managed in outpatient departments. However, treatment should not be delayed. A number of children classified as "non-urgent" may benefit from observation in a short stay unit. These patients need to be reviewed regularly. In case of clinical deterioration, abnormal vital signs (e.g., SpO_2) or point-of care (POC) tests, patients are re-classified and clinical management needs to be accelerated.

Emergency department (ED)

The set-up and space provided for EDs needs to be considered carefully during construction or rehabilitation of hospital facilities. Anticipation and planning for a variety of situations contributes to resilience of health facilities and the ability of hospital teams to cope with challenging situations e.g.:

- Seasonal variation of clinical activities (e.g., rise of activities during malaria seasons).
- Surges of activities (e.g., mass casualties) and outbreak management (e.g., Ebola, SARI).

Triage zone, ED and critical care units need to be in close proximity in order to optimize communication and support between clinical teams as well as rapid and safe patient transfer. This set-up improves possibilities to cover 24-hour periods with experienced clinical teams.

In many low-resource settings a large percentage of patients admitted to hospitals are children. A designated part of the ED therefore needs to be prepared for paediatric and newborn care. In smaller or medium-sized facilities it is useful to maintain one ED for adults and children in order to facilitate rational use of logistic set-up as well as 24-h coverage of the unit with experienced health workers. Larger hospitals might consider to separate adult and paediatric sections of EDs. Additionally, EDs need to be equipped for the care of specific patient populations e.g.: pregnant women as well as surgical emergencies. Rapid access to operating theatres and obstetric emergency care is needed.

Multi-disciplinary teams are needed to maintain the quality of care in EDs and critical care units including e.g.:[19] biomedical and logistic support, pharmacy, supply chains, laboratory/blood bank, access to imaging/radiology facilities (e.g., point-of-care ultrasound (POCUS), mobile X-ray machines). Health workers need support and adequate working environments. Pragmatic training and management guidelines are important in this context (Table 1, levels of critical care).

Short stay unit

Short stay units are vital elements of efficient patient circuits and should be associated with the ED.[19] As clinical conditions of children can change rapidly, clinical observation periods can contribute to improved safety and quality of care, especially in settings where access to health facilities is challenging. An observation period of several hours allows the evaluation of clinical conditions of patients and their response to treatment (e.g., in children with non-severe pneumonia, non-severe malaria, diarrhea). While reducing risks to miss early signs of clinical deterioration of patients classified as “non-urgent cases”, short stay units can help to reduce the number of hospital admissions of children, who improve after initiation of treatment and an observation period.

Critical care unit

After initiation of emergency treatment, critically ill patients require further care and monitoring. Without critical care units, hospitals will struggle to establish efficient patient flow and adequate quality of care. Dedicated critical care units for children and adults are needed. Realistic levels of paediatric emergency and critical care can be defined (Table 1), taking into account that basic levels of critical care have the potential to serve a large number of severely ill children.[6,20,49] Higher levels of care can be considered if essential elements of services are established in all parts of a patient circuit and if adequate resources and skill levels can be maintained.

Patient circuits and newborn care; Neonatal units

Neonatal care needs to be considered at all levels of a referral pathway.[50] In view of their particular vulnerability, newborns in the first week of life are classified as "emergency/red cases" in the new WHO Inter-agency triage tool.[45] All young infants under the age of 6 months (or practically all breast-feeding children) are classified as "priority/yellow" cases.[45] Patient circuits need to be set-up for the treatment of newborns and young infants. Dedicated context-adapted neonatal units in district and regional hospitals contribute to improved quality of care.[50]

Step down care

Patients recovering from critical illness often benefit from a gradual reduction in levels of monitoring and treatment before they are ready for general ward care. Step down care is best provided in close proximity to the critical care ward. The set-up of a step-down unit is crucial in order to guarantee adequate patient flow, while allowing identification of potential clinical deterioration, which may be missed on standard wards.

Units for young infants

Experience in large paediatric departments in low-resource settings, shows the importance to establish specific clinical zones for young infants (e.g., 1-6/9 months). After stabilisation of vital organ functions, these clinical zones can function as "step-down units" for young infants, while providing better adapted care and protection for this vulnerable group.

Other clinical areas & paediatric early warning systems

Hospitalized children who deteriorate in standard ward areas (e.g., nutritional units, general paediatric or surgical wards) should be transferred back to critical care units after the immediate emergency response. Essential resuscitation equipment needs to be available in any clinical area. The

use of paediatric early warning systems (PEWS) among hospitalized children have the potential to facilitate recognition of early signs of clinical deterioration.[51,52] However, PEWS need to be integrated in clinical processes of paediatric units, including pragmatic training of clinical teams and well defined patient circuits.[52] Care-takers can be integrated in these processes.[53] Health workers need to be trained to rapidly perform clinical assessments of patients, prior to the formal evaluation of vital signs.[54,55] This approach is particularly important in case of high work-loads on paediatric units in resource-limited contexts. Concern of health workers and care takers, regarding the clinical condition of a child should trigger rapid evaluation by an experienced nurse or clinician. Following rapid clinical assessment vital signs are then reviewed, including basic point of care tests (e.g., blood sugar, Hb) as indicated. Further research regarding integration of PEW-systems in different clinical contexts is needed.[51-53]

Outbreak preparedness and "isolation pathways"

Health systems need to be prepared on different levels of referral pathways for identification and treatment of patients with suspected or confirmed highly contagious diseases (e.g., Ebola, Lassa,SARS-CoV2, measles, cholera). Experience from the Ebola epidemic in eastern DR-Congo (2016-2018) shows that good quality EECC can be provided for patients with highly contagious diseases, while respecting principles of patient centered care.[28,29,56b] In this context, efficient set-up of treatment centers is crucial in order to provide EECC, while ensuring visibility and transparency of patient care for relatives and communities.[27-29,57]

Context-adapted levels of essential paediatric emergency and critical care

Essential paediatric emergency and critical care has the potential to reduce hospital mortality considerably.[19,20,49] Training modules and management guidelines recommended by WHO (e.g., ETAT)[38,39] are adapted to resource-limited settings and follow principles of international emergency care algorithms (e.g., advanced paediatric life support/APLS).[40] While ETAT-guidelines are extremely valuable, they are not designed to cover the whole spectrum of knowledge and skills needed to treat critically ill children in district, regional or tertiary hospitals. Table 1 describes suggestions for levels of critical care, which can be adapted to available resources, work-load and skill levels of clinical teams.

[b] Personal experience in Ebola treatment units supported by the NGO ALIMA in DR-Congo in 2019 and 2020 as well as in Guinea in 2021.

Table 1. Suggestions for the definition of context-adapted levels of critical/intensive care.
These "level of care definitions" include elements, which were suggested for a policy-paper for provision of EECC within projects supported by Médecins sans Frontières-Operational Center Brussels (MSF-OCB). Among other resources, definition of levels of critical care of the paediatric intensive care society in the UK were consulted.[58]

Categories	Enhanced ward care	Basic critical care (Level 1)	Intermediate critical care (Level 2)	Advanced critical care (Level 3)
Emergency care	Emergency management – "ABCDE"			
Upper airway (UA)	Basic care: UA clearance & treatment	Basic care: UA clearance & treatment	Consider use of supraglottic airway / laryngeal mask	Advanced airway management
Respiratory support	Consider supplemental O_2; Nebulized broncho-dilators	Ventilation via self-inflating bag & mask; Supplemental O_2; Nebulized broncho-dilators; Aspiration/drainage of pleural effusion& empyema, pneumothorax	Non-invasive respiratory support: bCPAP; HFNC; Non-invasive BIPAP*	Non-invasive and invasive respiratory support (mechanical ventilation)
Circulation & anaemia	Consider RBC transfusion of otherwise stable patients	IV & IO fluid resuscitation; RBC transfusion	Infusion of inotropes/ vasopressors (low dose rate) via peripheral IV lines; "Midlines" and PICC-lines may be used	Central venous lines or PICC-lines;* inotropes/ vasopressors
Neurological emergencies	Clinical observation; pain treatment	Management of coma and seizures; neuro-protection adapted to contexts		
Fluids, electrolytes & renal function	Maintenance fluids; monitoring of fluid balance	Maintenance fluids and adaptation in case of acute kidney injury (AKI); monitoring of fluid balance	Consider correction of electrolyte imbalances; consider peritoneal dialysis (PD) in some contexts.[59-61]	Renal replacement therapy (RRT)- to consider in certain specialized contexts.
Gastrointestinal system & nutrition	Oral or nasogastric tubes; ORS administration; introduction of enteral nutrition; "safe feeding practices"			Consider partial par-enteral nutrition in some contexts
Infections	Treatment of severe acute infections: e.g., bacterial infections, malaria, viral infections; source control (e.g., drainage of abscesses, pleural empyema, "surgical abdomen"); screening for TB & HIV and management; Management of severe infections adapted to regional epidemiology (e.g.; malaria, leishmaniasis, rickettsia, melioidosis, dengue) Outbreak management e.g.: Ebola, Lassa, SARI, Measles, Cholera			
Co-morbidities & complications	Examples: sickle cell disease (SCD); diabetic-ketoacidosis; management of underlying conditions e.g.: neurological conditions, cardiac dysfunction, chronic renal failure, malignancies			
Obstetric emergencies	Example: post-partum haemorrhage, eclampsia, sepsis			
Haematology	To consider RBC transfusions	RBC transfusion	Consider in some settings fresh frozen plasma (+/- platelet concentrates)	

Monitoring	SpO_2/FIO_2-ratios, RR, HR, NIBP; Input/ output estimation	Frequent vital signs: SpO_2/FIO_2-ratios, RR, HR, manual NIBP; Urine output & fluid balance (avoid urinary catheters if possible	Continuous SpO_2/FIO_2-ratios & HR ; Automated NIBP ; consider multiparameter monitors	Capnography is essential for advanced airway management & mechanical ventilation
Laboratory	POC-tests: Blood glucose; HB; urine-tests, rapid diagnostic tests/RDT (e.g., Malaria, HIV)); CSF examination **Establishment of a blood bank is a key priority!**		Further laboratory tests, depending on contexts: POC-tests: Electrolytes & renal function, blood gases, lactate FBC, coagulation screens, hepatic function; biomarkers	
	Microbiology and virological analysis (biological fluid cultures) – dependent on set-up and available resources			
Imaging – POCUS	POCUS if possible		POCUS To consider mobile XR	POCUS ; mobile X-ray, desirable CT-scan(no priority)
Human resources nurses/patient	1/10-15	1/5-6	1/ 3	At least 1/ 2
	Human resource/patient ratios need to be adapted to contexts. Support and training of nurses is an essential element in provision of ECCC.			
Care assistant/patient	1/10-15	1/5-6	1/3	1/ 2
Clinician-physician/patient	Ward round at least 2/day; immediate availability if needed	Frequent re-evaluation; support from experienced clinician & nurse	Available on the unit: 1/5-10 patients; support from an experienced clinician & nurse	1/ 4–6; supportive supervision by experienced clinician & nurse
Child & parent friendly care	Communication with patients and parents; integration of parents/care-takers in the care of children; psychological support; pain treatment, comfort, early mobilisation, stimulation, play; physiotherapy			
Palliative care	In case of severe illness and futile clinical condition: discussion with clinical teams and care-takers			
Other elements	Infection prevention and control (IPC) packages; antibiotic stewardship programs			

A multi-disciplinary approach is required in order to implement context-adapted paediatric emergency and critical care – examples: Human resources management & training; services for health workers (e.g., adequate & safe working conditions, opportunities to rest, nutrition, WASH).
Health facility logistics (e.g., reliable electricity supply), supply chains & pharmacy, WASH, biomedical equipment & maintenance services.
Context adapted management algorithms and sustainable training programs for health workers. Supportive working and learning environment.

IV: intra-venous; IO: Intra-osseous; BIPAP: bi-level positive airway pressure; PICC: peripheral inserted central catheters; SARI: Severe Acute Respiratory Infections; NIBP: Non-invasive blood pressure; POC-tests: Point of care tests; HB: Hemoglobin

Paediatric critical care in resource-limited contexts: Respiratory support and treatment of haemodynamic instability

Respiratory support and treatment of haemodynamic instability are essential elements of context adapted critical care in low-resource settings.

Respiratory failure: single organ failure (SOF)

Severe respiratory infections are common causes of mortality in newborns and older children.[1,62] Mortality risk increases among children with hypoxaemia.[63,64]

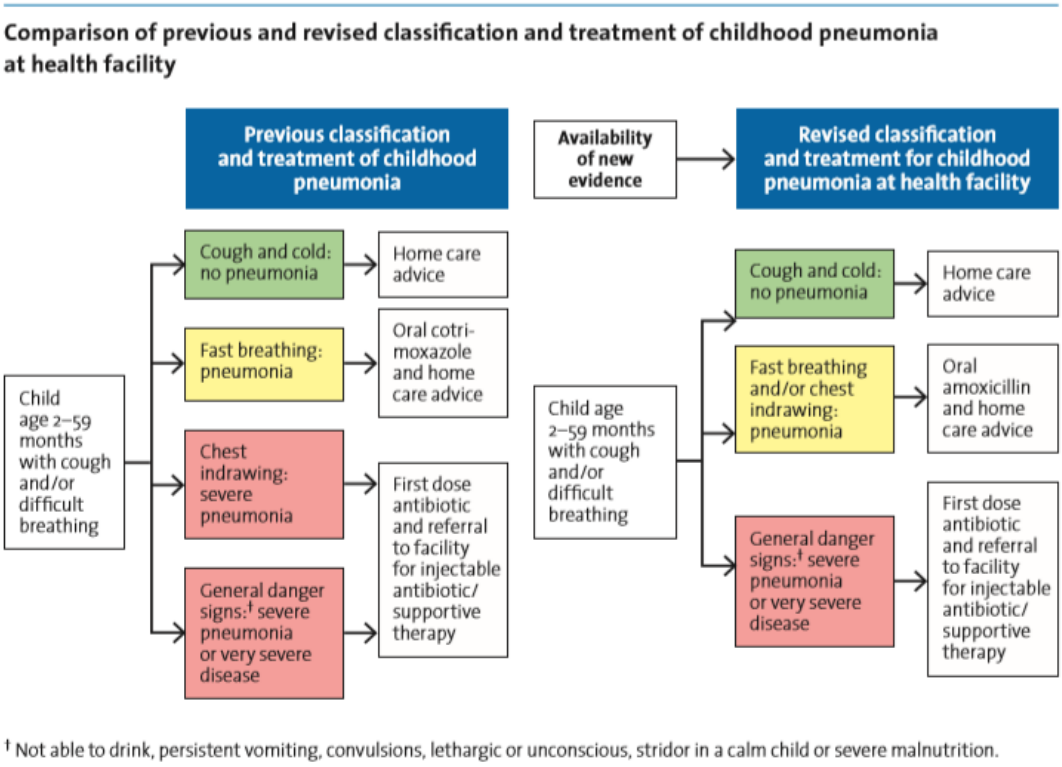

Figure 4. WHO classification of pneumonia, guideline-revision from 2014[38,65]

The 2014 WHO pneumonia-guideline recommends to treat children classified as "non-severe pneumonia" as out-patients, if no additional dangers signs are present.[65] To decide at one time-point if a child with non-severe pneumonia can be discharged or needs hospital admission is challenging, especially in contexts where care-takers have difficulties to return to health facilities in case of clinical deterioration of their children.[66,67] Observation periods of several hours in short stay units can help clinicians to assess potential risk of clinical deterioration. O_2 saturation monitoring by pulse oximetry

(SpO_2) has the potential to improve quality of clinical assessment and improve identification of children with hypoxaemia, who carry an increased risk of mortality.[66,68] Biomarkers can potentially contribute to clinical risk-assessment and rational use of antibiotics in certain settings.[69-71] Additionally, it is important to include care of children above the age of 5 years in efforts to reduce mortality associated with severe respiratory infections.[72]

Health workers in district and regional hospitals need to be aware of different factors associated with signs of respiratory dysfunction and hypoxaemia e.g.:

- Signs of upper-respiratory tract obstruction need to be recognised.[40]
- Foreign body aspiration is among differential diagnosis in children with sudden onset of respiratory symptoms. [40,73]
- Further clinical aspects need to be evaluated: presence of bronchospasm (e.g., asthma), pleural space pathologies (e.g., pleural effusions/empyema, pneumothorax).
- Cardiac causes need to be considered as a differential diagnosis.

Further factors influence risk-assessment and treatment of patients with respiratory problems e.g.:

- Newborns, infants as well as malnourished children need particular attention.[67,74]
- HIV-infection and associated opportunistic infections (e.g., *pneumocystis jirovecii* pneumonia/PJP, tuberculosis) as well as tuberculosis in children without HIV-infection need to be considered.[75,76]
- Children with sickle cell disease (SCD) carry a high risk to develop severe infections, while non-infectious patho-mechanisms can co-exist (sickle cell chest crisis).[77,78]
- Presence of other signs of organ-dysfunctions increase mortality risk among children with respiratory dyfunction.[79-81]

Access to essential elements of critical care on different levels of referral pathways has the potential to improve outcomes of a considerable number of children with respiratory dysfunction. Reliable provision of supplemental O_2 plays an important role in this context.[41,43,63] Reliable provision of O_2 is challenging in many contexts in SSA.[82] At this stage further non-invasive or invasive respiratory support is rarely in hospital settings in SSA.

Multi-organ dysfunction: Respiratory failure in the context of critical illness

Severe infections can lead to a complex systemic inflammatory response syndrome (SIRS), while different infections such as bacteraemia and malaria can coexist.[9,83,84] This disease process can progress to severe organ dysfunction, including acute respiratory distress syndrome (ARDS).[85,86]

Respiratory support is therefore an essential element in the management of critically ill children with single or multi-organ dysfunction.[85] Pragmatic criteria for the definition of paediatric ARDS were defined, considering that in children arterial blood gases are not always available. This is particularly relevant in the management of patients with ARDS treated in low-resource settings.[87-91]

Table 2. Definition of paediatric ARDS/PARDS(Khemani, R.G., et al., Crit Care Med, 2015). [87-89] *Printed with permission. For adults see: ARDS-Berlin definition*[92] *and Kigali-adaptation for low-resource contexts.*[90,91]

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

PARDS definitions:[88] *(1) Invasive ventilation: Use PaO_2-based OI-calculations when available. If PaO_2 is not available, adapt FiO_2 to maintain SpO_2 ≤ 97% to calculate OSI or SpO_2/FIO_2 (SF) ratio.*
(2) For non-intubated patients treated with supplemental O_2 or different modes of non-invasive ventilation use PF-ratio. If PaO_2 not available use SpO_2/FIO_2-ratios
PF: PaO_2/FIO_2; SF:SpO_2/FIO_2; MAP: mean airway pressure (in cmH_2O); OSI: oxygenation saturation index = FIO_2XMAPX100/SpO_2; OI: oxygenation index=FIO_2XMAPX100/PaO_2 (in mmHg)
SpO_2/FIO_2 ratios can also be used to classify severity and risk of mortality among children with PARDS.[88,89]

Provision of oxygen and non-invasive respiratory support in children

Provision of supplemental O_2 and non-invasive respiratory support plays an important role in the care of children with respiratory dysfunction. A study conducted in Malawi showed that use of pulse oximetry in peripheral health facilities and village clinics can help clinicians and CHW to identify children with severe pneumonia and hypoxaemia.[66,68] A study in Papua New Guinea demonstrated that reliable supply of low-flow O_2 can reduce mortality among children with severe pneumonia.[41]

On the other hand, reliable provision of O_2 remains a challenge in many health facilities in sub-Saharan Africa (SSA).[82] However, O_2-concentrators in conjunction with reliable electricity systems are cost-effective and provide a reliable method of O_2-supply in low-resource settings.[93-96] The combination of solar-powered energy systems and the use of O_2-concentrators can be an option to improve O_2-supply in health facilities even in remote settings.[42,43]

Non-invasive respiratory support has the potential to improve outcome of critically ill children managed in low-resource settings. Different forms of non-invasive respiratory support exist: continuous positive airway pressure (CPAP), heated humidified high-flow nasal cannula (HHFNC/HFNC)[c] as well as different modes of non-invasive bilevel positive airway pressure (BIPAP) support.[97-100] CPAP has been used efficiently for the treatment of children with respiratory dysfunction in high-resource settings (e.g. viral bronchiolitis).[101-103] The role of non-invasive respiratory support in the management of septic children with "less severe" paediatric ARDS is also under evaluation in high-resource settings.[98,104]

CPAP is part of standard care on neonatal units in high resource settings, including the use of non-invasive respiratory support in combination with surfactant-therapy in the care of preterm infants.[105-107] It has been shown that bubble CPAP (bCPAP) offers a relatively low-cost alternative to ventilator-delivered CPAP in newborn care.[108] There is growing evidence that the use of bCPAP on neonatal units in middle-income and low-income countries is feasible and safe.[109]

In a previous study conducted in a busy paediatric unit in Lilongwe/Malawi, an improvised bCPAP set-up was used in the treatment of severely ill children with acute respiratory dysfunction.[110d]

Advanced respiratory support – mechanical ventilation

Interventions described as part of level 2 critical care (Table 1) are quality improvement measures, which can realistically be established in certain resource constraint settings (e.g., non-invasive respiratory support). A well-functioning level-2 unit is an essential step in the process to develop a level-3 intensive care unit (ICU). Advanced airway management and mechanical ventilation can be considered in settings where adequately trained clinical teams can treat and monitor patients 24 hours per day. Additionally, interventions associated with a level 3 ICU require considerable investment in logistics (e.g., biomedical equipment, pharmacy supplies).

[c] Heated humidified high flow nasal cannula (HHFNC) and high flow nasal cannula (HFNC) are expressions for the same mode of non-invasive respiratory support. In this thesis the term HFNC is used.
[d] The author set-up this study with colleagues and is last author in this publication.

Background: Snakebite envenomation – the burden of disease

Up to 5.4 million people are annually bitten by snakes with one third to one half experiencing signs of envenomation. It is estimated that world-wide this results in up to 138,000 deaths per year.[111] However, accuracy of epidemiological data is limited due to under-reporting and poor access of snake-bite victims of to healthcare services.[111-113] The burden of snakebites is unevenly distributed over the globe with 95% of cases encountered in low- and middle-income countries (LMIC) in Africa and Asia.[114,115] In those countries, snakebites disproportionally affect rural and economically disadvantaged populations, who often have limited access to essential health services.[116,117] In 2017, WHO recognized snakebite envenoming as a neglected tropical disease.[117-119] Accordingly, snakebite antivenoms are included in WHO's list of essential medicines.[120]

Depending on the snake species, common acute clinical conditions arising from snakebites include neurotoxicity, which can rapidly lead to acute respiratory failure (ARF), abnormal coagulation, shock and further organ dysfunction, as well as local tissue destruction.[121] Multiple factors, such as delayed presentation to healthcare facilities, adversely affect outcome of snakebite victims.[112] Restricted access and high costs are factors limiting the use of antivenoms, particularly in sub-Saharan Africa.[122] [123] However, even in the presence of efficient antivenoms EECC measures are vital in the management of critically ill snakebite victims. In the case of severe neurotoxic snake bite envenomation airway management and respiratory support is particularly important.

Treatment of shock in low-resource settings

Haemodynamic instability is a common complication in critically ill children presenting with severe infections and is associated with a high risk of mortality.[85]

Definition of sepsis and septic shock

Sepsis is a major cause of morbidity and mortality worldwide. Incidence of sepsis peaks in early childhood and among older adults. Health-related burden associated with sepsis is particularly high in African countries south of the Sahara.[9] The International Pediatric Sepsis Consensus Conference (2005) published definitions and criteria for sepsis, severe sepsis, and septic shock in children:[124]

Sepsis = proven or high suspicion of an invasive infection and the presence of a "systemic inflammatory response syndrome" (SIRS).

Severe sepsis = Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions.[124]

New adult definitions and criteria were published in 2016 with "sepsis" defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Sepsis-3).[125] In this consensus the new adult definition "sepsis" equals the previous term of "severe sepsis". "Septic shock" is therefore defined as one of the organ-dysfunctions associated with sepsis: a circulatory and cellular/metabolic dysfunction associated with a high mortality-risk.[125] The "Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children-2020 (SSC paediatric guidelines, 2020)" still uses the 2005 nomenclature for definition of sepsis and severe sepsis.[85,124] Adaptations of the international paediatric sepsis definition are currently debated.[126]

"SSC-paediatric guidelines (2020)" clinical criteria for the definition of septic shock & sepsis associated organ-dysfunction:[85]

Septic shock: severe infection leading to cardiovascular dysfunction (including hypotension and/or impaired organ perfusion plus the need for treatment with vasoactive medication).

Sepsis associated organ dysfunction: severe infection leading to cardiovascular and/or non-cardiovascular organ dysfunction.

***WHO uses clinical parameters to define shock in children (Appendix Table 14):** presence of the three following signs: Cold extremities, CRT > 3 seconds, weak & fast pulses.[38,39]*

Different causes of circulatory failure need to be considered by critical care teams.[40,127]

At this stage, the vast majority of paediatric units in in SSA lack resources to implement all steps of the management algorithm outlined in figure 5.[128] Nevertheless, it is feasible to apply internationally accepted strategies of critical care and implement essential, initial steps of these algorithms. However, interventions need to be reviewed and adapted to resource-limited contexts. Additionally, regional epidemiology of burden of disease needs to be taken into account (e.g., nutritional status of children, prevalence of SCD, severe infections like malaria, dengue). The "European society of intensive care medicine (ESICM) global intensive care" working group describes similar challenges in the management of critically ill adult patients with sepsis managed in resource limited contexts.[129,130]

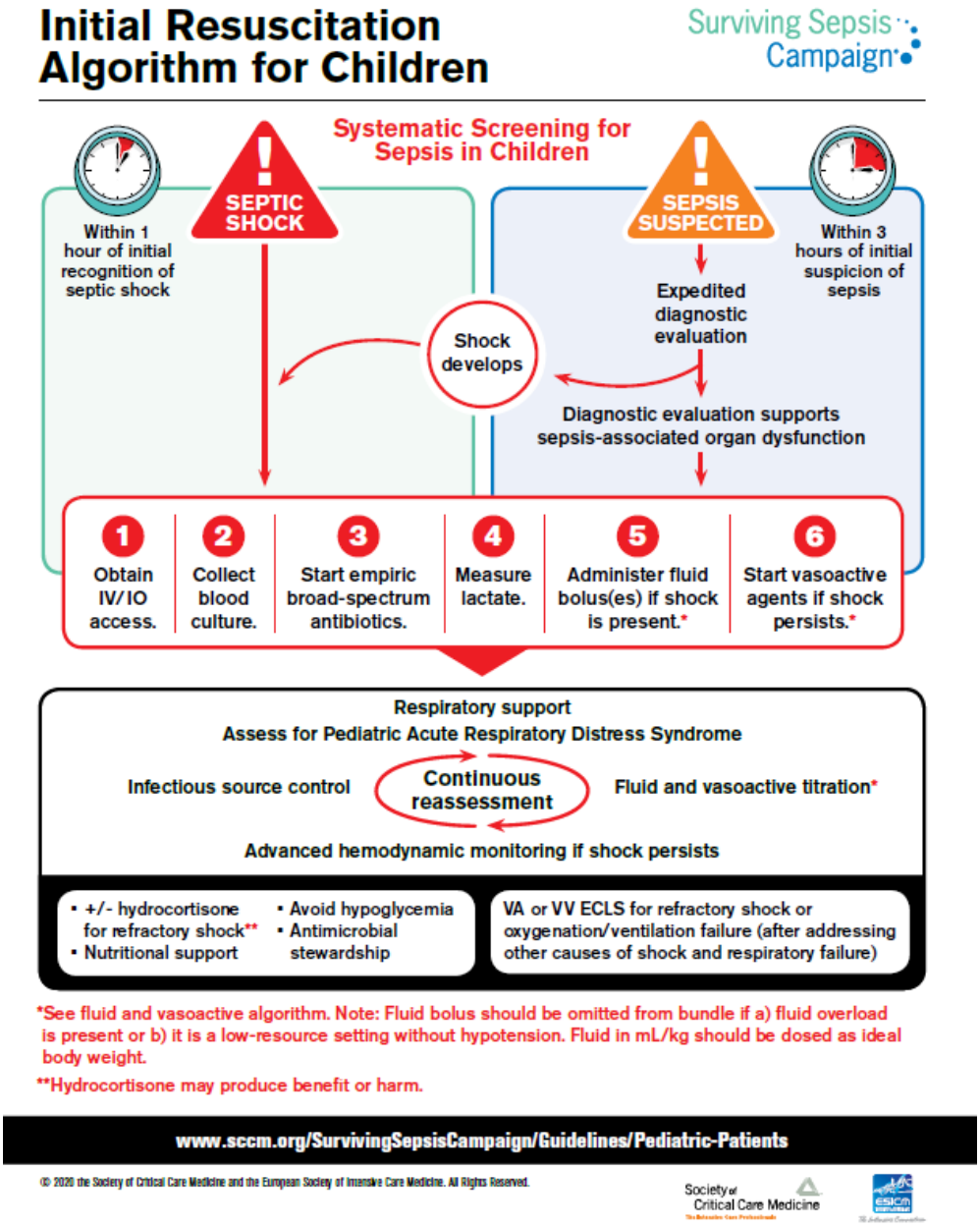

Figure 5. Initial resuscitation algorithms for children: Surviving sepsis campaign (https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients).[85,128] Printed with permission.

Aim and objectives

The aim of this thesis is to evaluate essential elements of respiratory and circulatory support in the care of critically ill children treated in resource-limited contexts.

Specific objectives

In Paper 1 the specific objective was to:

- Evaluate non-invasive respiratory support with bCPAP in the treatment of critically ill children with the following clinical presentations:
    - Children with respiratory dysfunction (as single organ dysfunction).
    - Children with respiratory dysfunction in the context of multi-organ dysfunction (e.g., severe malaria/sepsis).
    - Children with respiratory dysfunction and associated co-morbidities e.g.: severe acute malnutrition, HIV-infection.

In Paper 2 the specific objectives were to:

- Evaluate the clinical outcomes of critically patient snake-bite victims, including patients with acute respiratory failure due to muscle paralysis following neuro-toxic snake envenomation.
- Describe the characteristics of an intensive care unit in a resource-limited settings using invasive respiratory support.

In Paper 3 the specific objectives were to:

- Review the impact of IV fluid resuscitation on respiratory, cardio-vascular and neurological function among critically ill children with haemodynamic instability.
- Describe the effects of normal-saline and human albumin solution (HAS 5%) as resuscitation fluids on electrolyte and acid-base balance.
- Evaluate the benefits and risks of fluid resuscitation among patients with haemodynamic instability and different clinical phenotypes (e.g., neurological dysfunction, severe anaemia, respiratory dysfunction).

Methods

Study settings

Table 3. Overview of the methods and set-up of the main publications of this thesis.

Publication	Study setting	Study design	Patient numbers	Participants' description
Paper 1: Use of bubble CPAP in the management of critically ill children in a Malawian paediatric unit.	Paediatric Department, Lilongwe/ Malawi	Observational study	117	Critically ill children with respiratory dysfunction
Paper 2: Intensive care management of snakebite victims in rural sub-Saharan Africa: An experience from Uganda.	Intensive Care Unit; Northern Uganda	Observational study	174	60 patients with ARF requiring mechanical ventilation following neurotoxic snake-bite envenomation
Paper 3: Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial.	6 paediatric departments in East Africa	Re-analysis of a randomised controlled trial with contribution from additional studies	3170[a]	Critically ill children with haemodynamic instability. Not children with SAM and/or severe dehydration
Annex 1: Supplement to Paper 3, describing additional details of methods and results.				
Annex 2: Original publication (FEAST-study) on which a big part of the analysis described in Paper 3 was based on.[131]				
[a]*FEAST, patient numbers: 3141 patients in stratum A and 29 patients in stratum B (details in text)*				

Country information

The studies in this thesis were conducted in the following countries: Malawi, Uganda, Kenya and Tanzania, table 3. In addition, patient cohorts from Malawi, the United Kingdom and South Africa were included in Paper 3. Table 4 gives basic country information regarding the human development index (HDI) situation and child mortality in 1990 and in 2018.[1,132,133] The data highlight the considerable reduction in child mortality in Malawi, Tanzania, Uganda, Kenya and South Africa. The data also show that neonatal mortality did not decline to the same extent as mortality rates in children above the age of 1 month. Health interventions for children above the age of 5 years and adolescents need the same attention as activities targeting the well-being of younger children.[1]

The economical situation of a country has a major impact on child health.[4] Regarding child mortality and access to essential health services considerable regional differences within LMICs exist.[8] In order to further improve child health, interventions at different levels of societies and health

systems are needed.[5] Improving access to essential paediatric emergency and critical care on different levels of referral pathways is important in this context.[6,24,44]

Table 4. Child mortality between 2019-2018: Malawi, Uganda, Kenya, Tanzania, South Africa, UK. Human development indices (HDI) from 2019 are documented. https://data.unicef.org/dv_index/; http://hdr.undp.org/en/countries

Country		Neonatal mortality per 1000	Infant mortality per 1000	U5MR per 1000	Proportion neonatal death rate/U5MR	CMR 5-14 years per 1000	HDI position in 2019
Malawi	1990	50	139	239	22 %	40	172
	2018	22	35	50	46 %	14	
Uganda	1990	39	109	185	23 %	32	159
	2018	20	34	46	44 %	15	
Kenya	1990	28	68	107	26 %	18	147
	2018	10	31	41	48 %	10	
Tanzania	1990	40	100	166	25 %	30	159
	2018	21	38	53	41 %	13	
South Africa	1990	20	46	59	34 %	8.1	*113*
	2018	11	28	348	32 %	5.5	
United Kingdom	1990	4.5	7.9	9.3	48 %	1.8	*15*
	2018	2.6	3.6	4.3	60 %	0.8	

*Neonatal mortality: death during the first 28 days of life; Infant mortality: deaths between birth until 1 year of age; U5MR: under five mortality rate-includes neonatal mortality; CMR: Child mortality rate; *HDI: Human development index – position among 189 countries in 2019.*

Paper 1: Study setting, Patient circuit and bubble CPAP device

Paper 1: Study setting

This was an observational study of all children 0–15 years treated with bCPAP between 26 February and 15 April 2014 conducted in the paediatric department at Kamuzu Central Hospital (KCH) in Lilongwe, Malawi. KCH is one of the 4 central hospitals in the country with more than 700 beds. The paediatric department has around 300 official beds, including paediatric surgery and the neonatal unit. In 2014, the department had approximately 20 000 admissions of children between the ages 2 months –15 years. It was conducted during the peak of the malaria season in March and April 2014. During this period more than 2500 children with different levels of severity of illness (SOI) were admitted per month.[49] A re-organisation of the patient circuit in this paediatric unit contributed to a reduction of paediatric hospital mortality (reported mortality in 2010: around 7%).[134] Since 2011, further quality improvement measures were put in place and a further reduction of mortality was achieved. During the study period in 2014 hospital mortality in the paediatric unit in KCH was approximately 4%.[49] Similar mortality rates were reported from the paediatric unit in KCH in 2015.[135]

Paper 1: Patient circuit of the paediatric department in Lilongwe/Malawi

In this large hospital in Lilongwe the adult ED functioned separately from the paediatric triage and patient circuit. Paediatric patients were initially screened in a triage/admission zone, situated in close proximity to the paediatric department. Critically ill children were immediately managed in a "4-bed resuscitation zone". This area was directly connected to a "critical care/emergency zone" (approximately 16–18 beds), where further essential critical care was provided. During extremely busy times several patients had to be placed in one "bed-space". In an additional "treatment room" less severe "priority cases", who needed hospitalization received initial treatment before further care was continued in the different clinical areas of the paediatric department.

In a 6-bed "high dependency unit (HDU)", closer observation of selected critically ill children could be offered. The number of HDU beds was insufficient for the management of the large number of hospitalised critically ill children. This deficiency could be partially compensated by the introduction of the "critical care/emergency zone". Close proximity of essential elements of the patient circuit (triage, resuscitation zone, critical care zone and HDU) allowed health workers to work as a team and adapt to different levels of work-load. Senior supervision by at least one consultant on site for 12 hours/day was assured. Consultants on-call arrangements were made to cover 24 hours/day.

A step-down unit allowed observation of patients, who improved clinically during the treatment in the HDU or emergency/critical care zone, but who still needed closer surveillance. The introduction of a step-down unit for young infants (<6-9 months) contributed to improved quality of care for these particularly vulnerable children and reduced work-load in other clinical areas. All newborns born in KCH and almost all newborns admitted via triage and the emergency zone were treated in a dedicated neonatal unit.

Despite resource-limitations, the paediatric department tried to strengthen crucial elements of an efficient patient circuit. Centralisation of basic critical care enabled a limited number of staff to provide best possible care to an extremely large number of critically ill children.

Paper 1: Support of children infected with HIV

The unit's policy was to offer HIV testing and counselling to every hospitalised child. However, because of high workload and limited numbers of HIV counsellors not all hospitalized children were tested. Of note is the remarkable support by the late Dr. Peter Kazembe, head of Baylor College-HIV services and previous head of the paediatric department at KCH.[136] His team contributed to good quality support for children infected with HIV as well as children with malignancies (e.g., Burkitt's

lymphoma). This included ambulatory care and in-patient support during day-time working hours and week-days (e.g., initiation and adaptation of anti-retroviral treatment/ARV).[137] Support of Baylor-College also included clinical advice from a paediatric cardiologist for a period of time.

Paper 1: Bubble CPAP device

The low-cost bCPAP devices used in this study are modified O_2-concentrators with a maximum air/oxygen flow of 16 liters/min (LPM) (maximum O_2-flow: 8 LPM, maximum air flow: 8 LPM). FiO_2 can be determined by adjusting the ratio of O_2/air flow. Blended flow is humidified and warmed using the heat produced by the compressor of the device. Pressure is determined by the distance of the distal part of the expiratory limb of the ventilation circuit below the water surface of a water bottle ("resistor"). These bCPAP devices were reviewed by an independent biomedical team in Sweden and performed similarly to bCPAP devices used in high resource settings.[138] It is important that new bCPAP systems follow the conventional set-up for bCPAP in order to guarantee pressure stability and low flow resistance withing the system (figure 6).[138-140] In case not enough "bCPAP set-ups" were available, O_2-cylinders were used to provide O_2-flow required for provision of bCPAP. With this set-up, FiO_2 could not be adapted but O_2-flow could still be humidified. Patients were switched to dedicated bCPAP devices whenever a set-up was available.

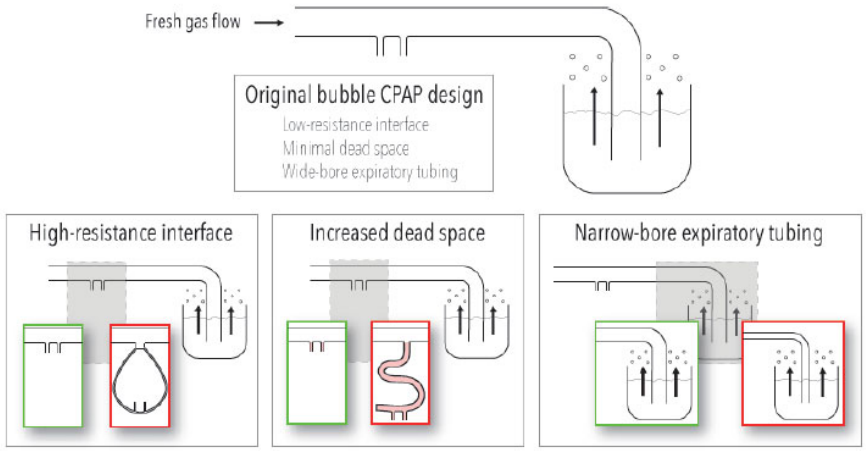

Figure 6. Designs of bubble CPAP-systems need to follow the conventional set-up.[140]
Deviation from the original set-up of bCPAP need to be avoided e.g.: High resistance interfaces, increased dead space created by "Y-connections" leading to the interface, high resistance expiratory tubing. Figure from: Baldursdottir, S., et al., Basic principles of neonatal bCPAP: effects on CPAP delivery and imposed work of breathing when altering the original design. Archives of Disease in Childhood - Fetal and Neonatal Edition, 2020.[138,139]

Paper 1: Study design and participants

Paper 1 describes an observational study evaluating clinical outcomes among children treated with bCPAP between 26. February and 15. April 2014 in the paediatric department at Kamuzu Central Hospital (KCH) in Lilongwe, Malawi. Most newborns were treated on a dedicated neonatal unit. A small number of newborns born outside KCH, received respiratory support with bCPAP on the paediatric unit. Only these newborns were included in the study.

Critically ill children (0-15 years) were initiated on bCPAP if, after initial resuscitation, they were found to have severe respiratory distress and/or hypoxaemia with or without further organ dysfunctions (e.g.; shock, severe anaemia, altered level of consciousness). BCPAP was initiated in the "emergency/ critical care zone" or HDU depending on bed availability.

Very severe pneumonia was diagnosed by the presence of either SpO_2 <90%, severe respiratory distress (severe chest indrawing), danger signs such as inability to drink or breast feed or reduced level of consciousness. The term "very severe pneumonia" used in this study corresponds to the classification "severe pneumonia" as defined by revised WHO pneumonia guidelines from 2014.[65] Multiorgan failure (MOF) was defined as respiratory dysfunction associated with further organ dysfunction at the time of bCPAP initiation: cardiovascular dysfunction (including severe anaemia) or neurological dysfunction. Severe anaemia was defined as an Hb <7 g/dL or clinically when POC-testing of Hb was not available. Neurological dysfunction was defined as a Blantyre Coma Scale ≤3 or status epilepticus.[38]

HIV status was defined as "infected" if a child <2 years had a positive DNA PCR test or a child ≥2 years had a positive rapid test. A child was considered to be HIV exposed if there was a positive rapid test for a child <2 years or a documented maternal positive test, but no DNA PCR had yet been performed. Malaria was diagnosed by a malaria rapid diagnostic test (MRDT). All children with malaria receiving bCPAP were considered to have severe malaria in view of their respiratory dysfunction.

Nutritional status was described as either normal, moderate acute malnutrition (MAM) or severe acute malnutrition (SAM) according to WHO guidelines.[38] The following conditions were classified as comorbidities: congenital heart defects diagnosed by point of care echocardiography, neurological disorders, SCD, malignancies or clinically suspected tuberculosis.

Paper 2: Study setting and level of critical care

This study was conducted on the ICU in St. Mary's Hospital, Lacor (Lacor Hospital) in Gulu, Uganda between January 1, 2006 and November 30, 2017. Lacor Hospital is a private, non-profit (former mission) hospital located in the north of Uganda serving approximately 700,000 inhabitants in a poor, post-conflict region. During the time of the study, the hospital had 476 beds and six operation theatres. The hospital ran an 8-bedded ICU for critically ill adults and children with eight trained nurses and four assistant nurses (nurse: patient ratio per shift, 1:4-8). One anaesthetic officer and physician shared the medical responsibility for the ICU patient (Table 5). This team was assisted by a senior anaesthetist from 2002 until 2016. Data from this ICU were reported previously.[141]

The paediatric unit of Lacor Hospital was one of the study sites of the FEAST-study (Paper 3).[131] During the preparation of the FEAST-study the author worked intermittently on the paediatric unit and the ICU of Lacor-hospital between 2007 – 2009.

Paper 2: Study design and participants

This observational study was designed as a retrospective analysis of a prospectively collected database which included all patients admitted to the ICU of Lacor-hospital between January 1, 2006 and November 30, 2017. 174 (2.5%) out of 6,976 patients admitted to the ICU were treated for snakebite envenomation and were included in the study.

Paper 3: Study setting

Patients recruited and treated in the following study sites were included in the analysis of this publications: Paper 3 is a review of the FEAST study published in 2011.[131] In this study 3170 children with signs of respiratory distress and/or reduced level of consciousness and signs of circulatory impairment were recruited and treated in 6 paediatric departments in Uganda, Kenya and Tanzania (Table 6). Results of four further studies describing treatment of critically ill children with signs of haemodynamic instability and/or neurological complications were used to compare physiological derangements among study patients of the FEAST-study. These additional four studies were conducted in paediatric units in Malawi, South Africa and the UK.

Table 5. Essential characteristics of the ICU at Lacor Hospital.[141]

General ICU-admission criteria were applied for snake-bite victims: Instability of vital organ- functions requiring immediate intervention Presence of abnormal vital signs/clinical concerns requiring close observation & treatment Post-operative care in case intensive care and/or close observation is required	
Beds & Nurse/ Patient ratio	8 permanent beds; additional beds could be added if needed 1 nurse for 4-8 patients
Doctors/ Clinical officers	One anaesthetic officer & admitting physician share medical responsibility for ICU patients Supportive supervision by a senior anaesthetist from 2002–2016
Monitoring	Pulse oximeters: 2 ; Non – invasive blood pressure machines: 3 Multi-parameter monitors: 1; 12 lead –ECG: 1 ; Capnography was not available.*
Equipment examples	Basic resuscitation equipment; equipment for advanced airway management Ventilators capable of providing intermittent positive pressure ventilation (Glostavent; Diamedica, Bratton Fleming, UK): 3 O_2-concentrators: 3; O_2-cylinders: limited supply
Management options	**Routine resuscitation measures** **Respiratory care:** Basic and advanced airway management O_2 supplementation via nasal prongs or face mask; nebulisation Mechanical ventilation, NIV was not available during the study period Insertion of chest drains/aspiration of pleural effusions **Circulation:** Fluid management & blood transfusions; peripheral and central line insertion; occasional use of adrenaline or dopamine infusions; no use of arterial lines **Neurological emergencies e.g.:** Management of comatosed patients & status epilepticus; neuro-toxic snake-bite envenomation **Medication:** Following national guidelines & WHO list of essential medications;[120] essential antibiotics (no Carbapenems, Amikacin or Vancomycin); anti-malaria treatment according to WHO guidelines[142] **Snake anti-venom:** Due to limited resources, insufficient supply of anti-venom was available **Nutrition:** Enteral nutritional support; partial parenteral nutrition was used occasionally **Renal replacement therapy:** Peritoneal dialysis (PD) could be performed at the end of the study period on rare occasions; PD was not used in study-patients described in Paper 2
Laboratory	POC-tests: MRDT were available later during the study period, blood sugar, urine analysis Blood films, Hb & Full blood count Analysis of cerebro-spinal fluid (CSF); rapid tests for: HIV, Hepatitis B&C, Syphilis Sputum: Tuberculosis smears (no Gen-Xpert was available during the study period) **Not routinely available:** electrolytes, blood gas analysis, renal or liver function tests, clotting tests, blood or CSF cultures.
Blood Bank	**Blood bank:** rapid and safe blood transfusion services. **Not available:** Tranexamic acid, fresh frozen plasma, platelet concentrates
Imaging	Portable X-ray. Ultrasound by a radiologist (no routine availability of POCUS)
Protocols	General principles of anaesthetics and critical care were followed. WHO and international management guidelines were applied. WHO snake-bite protocols [121] were followed with available resources.
Training	Nurses, anaesthetic officers receive regular on the job training and coaching. Lacor hospital offers training programs for nurses & anaesthetic clinical officers, recognized by the Ugandan MoH.
The hospital has supportive non-clinical departments: logistics & biomedical team, pharmacy & supplies. Lacor-hospital has a reliable electricity system.	
***** Capnography needs to be considered as an essential monitoring-parameter in mechanically ventilated patients.[143]	

Table 6. Basic information of study sites described in Paper 3.
Six units in East Africa were part of the FEAST-study http://www.feast-trial.org/; 4 additional study studies were used to compare description of physiological derangements among FEAST-study patients.

Name	Department	Level of critical care (Table 1)	Further details
Mulago Hospital, Kampala; Uganda	ED and paediatric department	Level 1 unit	A large paediatric unit in an urban context, with considerable resource challenges Paediatric admissions: > 15.000/year
Mbale Hospital; Uganda	ED and paediatric department	Level 1 unit	Paediatric department in a regional hospital, with considerable resource challenges Paediatric admissions: > 10.000/year
Soroti Hospital; Uganda	ED and paediatric department	Level 1 unit	Paediatric department in a regional hospital with considerable resource challenges. Paediatric admissions: approximately 4000/year
Lacor-hospital, Gulu; Uganda (see also Paper 2)	ED and paediatric department	Level 1 unit	Paediatric unit in a regional hospital in Northern Uganda, with resource-limitations, but additional external funding. Hospital beds (total, adults and paediatrics): 476 Paediatric admissions: > 10.000/year
Kilifi, Kenya; District hospital associated with KEMRI-Wellcome Trust Research Program	Paediatric department and research unit	Level 1 unit with very good staffing level	Paediatric unit in a district hospital, with a well-organized "level 1" paediatric critical care unit. Paediatric admissions: approximately 4500/year[144]
Teule, Tanzania; District Hospital	Paediatiatric department	Level 1 unit	Paediatric unit with considerable resource-limitations; Paediatric admissions: approximately 3500-5000 /year
Further cohorts of patients, who were included in the analysis of Paper 3			
Queen´s Elizabeth Hospital; Malawi	Paediatric department and Research Unit	The research unit is a level 1 unit with good staffing level	A large paediatric department with a well-functioning emergency department Paediatric admissions: > 15.000/year
Red Cross Children´s Hospital, Cape Town, South Africa*	ED and PICU	Level 3 unit	A department with high workload, but high-level of expertise.
St. Mary´s Hospital; London; UK*	ED and PICU	Level 3 unit	Emergency and critical care unit in a high-resource setting.
United Kingdom meningococcal cohort	Paediatric EDs & PICUs in the UK	Level 3 units	Emergency and critical care units in a high-resource setting.

*Unpublished data

Paper 3 : Study design and participants

Background – original FEAST study[131]

In Paper 3 data from the FEAST-study were re-analyzed. Data from 4 additional studies were integrated in the analysis: Two published paediatric studies of critically ill children (meningococcal disease in the UK, and cerebral malaria in Malawi)[145,146] together with data from two unpublished cohorts (one from South Africa, the other from St. Mary's hospital in London, UK).

In the original FEAST study 3170 patients with fever, respiratory distress and/or prostration/reduced level of consciousness and signs of impaired perfusion were enrolled between 13. January 2009 and 13. January 2011.[131] In "Stratum A" 3141 were randomly assigned to either maintenance fluids only (4 mL/kg per hour; n=1044), or to receive IV fluid boluses of 20 mL/kg human albumin solution (HAS) 5% (n=1050) or normal saline (n=1047) in the first hour. A further 20 mL/kg of resuscitation fluids were administered if signs of impaired perfusion persisted.[131] Children initially assigned to "Stratum A" developing severe hypotension during the course of the treatment received 40 ml/kg boluses of study fluid (normal saline in the control group).[131] In "Stratum B" patients were classified who presented with hypotension (systolic blood pressure of <50 mm Hg in children younger than 12 months of age, <60 mm Hg in children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of age). Children in "Stratum B" were randomly assigned to receive 40 ml/kg of HAS bolus or normal saline. Only 29 patients were enrolled in this group (13 received HAS boluses; 16 received Saline boluses).[131]

Of note, initial boluses were increased in "Stratum A" from 20 to 40 ml/kg (60 ml/kg in "Stratum B") after a protocol amendment in June 2010.[131] This is an important information, as 40ml/kg is a high volume of resuscitation fluid administered to critically ill children in settings without possibility to provide non-invasive or invasive respiratory support or infusions of vaso-active drugs.

Children with SAM (weight/height – z-scores <-3)[38] and patients with signs of severe dehydration were not included in the FEAST-study.[131] WHO defines specific fluid management-regimens for these particular patient groups.[38,39]

Vital signs were assessed in surviving children at 1 h, 4 h, 8 h, 24 h, and 48 h after starting IV fluid bolus in the HAS and normal saline groups, or after randomisation in the control group (Paper 3 Annex 1 p 21). Hb levels and plasma lactate were measured at baseline, 8 h, and 24 h. Base excess, pH, and electrolytes were measured at baseline and at 24 h.[131]

Further clinical details of the FEAST-study have been described in different publications.[131,147,148] FEAST-data were the main source of the secondary analysis of results presented in Paper 3.

Paper 3: Objectives and set-up of the re-analysis of the FEAST-trial data

In view of un-resolved questions raised by the FEAST-trial, authors of Paper 3 believed that a review of data from this RCT would be beneficial. This review reflects an important scientific process, which can contribute to improvements of a comprehensive approach to the care of critically ill children with haemodynamic instability treated in malaria-endemic, resource-limited contexts.

Paper 3 postulated that increased mortality in patients receiving IV fluid boluses was associated with adverse effects of fluid resuscitation on respiratory function, cardiovascular function as well as O_2 carrying capacity or neurological function. In this context biochemical and acid base haemostasis of IV fluid bolus recipients was affected as well.

To test this hypothesis "organ function-scores (physiological scores)" were developed in order to measure essential parameters describing severity of respiratory, cardiovascular and neurological function. For this purpose, sequential vital sign data from the FEAST-study were evaluated. These "organ function scores", evaluated at "baseline" for patients recruited in the FEAST-study were then compared with the severity of organ-dysfunction and clinical outcomes in four other cohorts of critically ill patients treated in Malawi, South Africa and the United Kingdom (paper 3).

For FEAST-patients, further analysis were performed in order to detect sequential changes in organ function within the first 48 hours of admission. In addition, effects of the actual volume of administered IV resuscitation fluid was evaluated. Additional important clinical derangements were considered in the analysis process: Hb levels, electrolyte and acid-base derangement (paper 3).

In order to better understand the impact of fluid resuscitation, subgroups of patients presenting with comparable "clusters of patho-physiological phenotypes" were defined (paper 3).

Comparison of organ function scores with further 4 cohorts of critically ill patients

In paper 3 "Organ-function scores" (respiratory, neurological and cardio-vascular scores) at baseline in the FEAST-study cohort were compared with cohorts of critically ill patients with different degrees of severity of illness (SOI) and causes of disease. Additionally, different levels of critical care could be provided for patient cohorts treated on a research ward in Blantyre Malawi (level 1 unit with relatively high health worker to patient ratio)[146] as well as EDs and PICUs in South Africa and the United Kingdom/UK (level-3 ICUs; Table 1).[145]

Cohort from Malawi (2010-2011)

In a Malawian cohort, between 4. June, 2010 and 5. June, 2011 448 children were admitted to Queen Elizabeth Central Hospital, Blantyre, Malawi, and reported in a study describing children with severe neurological insults associated with cerebral malaria (including the presence of malaria associated retinopathy).[146] Results of serial magnetic resonance imaging (MRI) of the brain and clinical variables were related to outcome.

Cohort from South African (2013 – unpublished data)

In a South African cohort, 61 children receiving fluid resuscitation for presumed sepsis and acute gastroenteritis at Red Cross Children's Hospital, Cape Town, South Africa were recruited between 1. February, 2013 and 1. June, 2013. Vital signs and other clinical details were documented on admission to hospital and related to outcome (need for intensive care admission or death).

Cohort from UK – meningococcal disease study (1997-1999)

In a UK meningococcal disease study 148 fatal cases and 354 survivors with meningococcal sepsis in England and Wales were enrolled between 1. December, 1997, and 28. February, 1999. The cohort has been described previously.[145]

Cohort from an emergency department in London/UK (2014-2015 – unpublished data)

In the St Mary's (London/UK) cohort, vital sign data and outcome (need for hospital or ICU admission) were collected for 18.863 children attending the ED from 10. June, 2014 to 9. March, 2015.

Table 7. Description of FEAST-study[131] & 4 additional studies, used to evaluate "organ-function scores" (Paper 3).[145,146]

The following study sites where part of the FEAST-study[131]						
Participating unit	**Recruitment**	**Recruitment criteria**	**Further details/Intervention**[a]	**Data collected**	**Patients**	**Outcomes: No (%)**
Mulago Hospital, Kampala; Uganda Mbale Hospital; Uganda Soroti Hospital; Uganda Lacor-Hospital/Uganda Kilifi, Kenya Teule, Tanzania	13. 01.2009-13. 01.2011	**Inclusion criteria:** Fever OR signs of respiratory distress, OR prostration AND signs of impaired perfusion **Exclusion criteria:** SAM; severe dehydration; Non-infectious causes of critical illness; Contra-indications for fluid bolus (e.g. heart disease)	**"Stratum A"** randomization: Control group: maintenance fluids; bolus - 20 mL/kg HAS, first hour; bolus - 20ml/kg normal saline, first hour - Further 20 mL/kg if signs of impaired perfusion persist after first hour - In case of hypotension: 40-ml/kg bolus of study fluid (saline in control group) **"Stratum B":** Children with severe hypotension were randomly assigned to receive 40 ml/kg of HAS or Saline bolus.	Vital signs: 1 h, 4 h, 8 h, 24 h, 48 h after randomization Basic laboratory tests: Hb, Lactate, Urea & electrolytes, MRDT[b]	**Total: 3170** **Stratum A: 3141** HAS: 1050 Saline:1047 Control: 1044 **Stratum B: 29** HAS:13 Saline:16	Primary outcome: Mortality at 48 h: **Total: 315 (9.9%)** **Stratum A** Bolus group (HAS & Saline):220 (10.5%) Control group: 76 (7.3%) **Stratum B: 18 (62.1%)** **Secondary outcomes:** Mortality or neurologic sequelae by 4 weeks.
Analysis of 4 further patient cohorts were included in the analysis of Paper 3						
Participating unit	**Recruitment**	**Recruitment criteria**	**Further details/Intervention**	**Data collected**	**Patients**	**Outcomes; No (%)**
UK-meningococcal cohort	01.12.1997–28.02.1999	Neisseria meningitidis culture or PCR positive or purpura fulminans without other cause	Emergency and critical care in a high resource settings	Vital signs, clinical & laboratory data	502	Death and clinical sequelae: 148 (29%)
Queen´s Elizabeth Hospital; Malawi	04.01.2010 – 05.06 2011	Blantyre coma score ≤2; Plasmodium falciparum parasitaemia; malaria associated retinopathy	Essential emergency & critical care (level-1; see *Table 1*) Research unit with good nurse& clinician to patient ratio.	Vital signs, clinical & lab. data, serial MRI-brain scans	448	Death or neurological sequelae: 106 (24%)
Red Cross Children Hospital, Cape Town[c]	01.02.2013 – 01.06.2013	Septic shock or severe gastroenteritis & clinician's decision to give fluid resuscitation	Emergency and critical care in a high resource settings	Vital signs, clinical & laboratory data	61	Death or intensive care admission: 20 (33%)
St. Mary´s Hospital/London[c]	10.06.2014 – 09.03.2015	ED presentation	Emergency and critical care in a high resource settings	Vital signs, clinical & laboratory data	18 863	Admission to hospital ward or PICU: 1933 (10%)

[a]The initial boluses were increased in stratum A from 20 to 40 ml per kilogram (60 ml per kilogram in stratum B) after a protocol amendment in June 2010.
FEAST definition of hypotension: systolic BP of <50 mm Hg in children <12 months, <60 mm Hg in children 1 to 5 years of age, and <70 mm Hg in children > 5 years.
[b]MRDT=Malaria Rapid Diagnostic Tests; [c]unpublished data

Training and benefit for the study population

Paper 1 Bubble CPAP: training & benefit for the study population

Patients admitted to the paediatric unit at KCH in Lilongwe benefited since the end of 2011 from different activities. The Malawian College of Medicine (COM; based in Blantyre/Malawi)[149] opened a second campus at KCH, in Lilongwe in 2012:

- In 2012 a part of the Malawian medical student training program was moved to KCH. This included a clinical paediatric rotation for 3rd year students.
- In 2014 the clinical part of a clinical officer bachelor training program was started at KCH.[26]

In the context of these training programs experienced paediatricians were integrated in clinical care on the unit.[149-153] Additionally, clinical officers enrolled in the bachelor-training program contributed as "middle grade clinicians" to improved quality of care. The author worked as a paediatrician in KCH from end of 2011 to 2014 and contributed substantially to the start of the paediatric rotation of medical students as well as the initiation of the bachelor training program for clinical officer.[26]

BCPAP was established as a routine form of non-invasive respiratory support on the paediatric unit. In this context bCPAP was integrated in continuous "on the job training" and tutorials for nurses, clinical officers, post-graduate trainees and students. In 2012 a first CPAP-study was conducted on the unit, using an improvised bCPAP-set-up.[d 110] Quality of care improved between 2012 and 2014, while work-load remained extremely high. The conduction of the observational CPAP study described in Paper 1 contributed to improved surveillance of critically ill children.

Paper 2 Mechanical ventilation: training & benefit for the study population

A senior anaesthetist contributed over several years to continuous on-the-job training on the ICU at Lacor-hospital. A formal training program in anaesthesia was initiated for clinical officers. Essential critical care skills were included in this training program.

Routine documentation of essential clinical data of critically ill patients enabled the ICU-team to establish an on-going audit process. Data of this documentation have been published in a previous study.[141] Paper 2 is a result of this audit-process. These activities contributed to improvements of clinical practice on the ICU.

Of note, Lacor-hospital was one of the FEAST-study sites. In this context the hospital's paediatric department benefited from training in essential paediatric emergency and critical care (EPECC).[131]

Paper 3 Fluid resuscitation: training & benefit for the study population

FEAST- study sites in Uganda, Kenya and Tanzania benefited from the following interventions:

- Formal ETAT- trainings[38] were conducted in participating units in Uganda and Kenya prior to the start of recruitment of patients. On the job training/coaching in aspects EPECC took place during the preparation of the RCT and during the recruitment phase.
- Patient circuits were optimized, especially in the Ugandan study sites Soroti, Mbale and Lacor-hospital. These activities contributed to improved triage, emergency and critical care. Study procedures were integrated in routine processes of the participating units.
- Additional nurses and doctors recruited for the RCT were responsible for identification, recruitment and treatment of study patients, including further specific study procedures (e.g., consent, documentation). These colleagues were integrated in clinical teams of participating units and contributed to general paediatric care.
- Some essential equipment and consumables were financed via the FEAST-study budget (e.g., O_2 concentrators, SpO_2 monitors, NIBP-machines, basic resuscitation equipment).

All patients treated on the participating units benefited from these activities. The author substantially contributed to these processes between 2007 and 2009 (page 12 of the initial publication).[131]

Patients recruited in the Malawian cohort in Queen´s Elizabeth Hospital were treated on a specific research unit: A well-equipped level 1-unit (Table 1) with a good nurse to patient ratio and senior supervision. Patient cohorts in the studies conducted in Cape Town and London/UK were recruited in well-equipped high-resource settings.

Data collection

Paper 1 Bubble CPAP: data collection

A case record form (CRF), an observation chart and a patient register were used for data collection. Data were entered into an Excel database. Collected data were based on essential clinical observation and information used in routine practice. Data-collection performed for study purposes therefore contributed to improved quality of patient surveillance on the unit. This study was done in a routine clinical setting and did not have a target sample size. The sample included most patients treated with bCPAP between 26 February and 15 April 2014. Only isolated, CPAP-runs of short duration (less than 12 hours) might have been missed. Of these isolated cases, all children survived as all files of children, who died on the unit were screened specifically.

Paper 2 Mechanical ventilation: data-collection

This observational study was designed as a retrospective analysis of a prospectively collected database which included all patients admitted to the ICU of Lacor-hospital between January 1, 2006 and November 30, 2017. From this database, all patients admitted to the ICU because of snakebite envenomation were included into the analysis. No exclusion criteria were applied. Selected data of 139 study patients were included in a previous analysis reporting admission diagnoses, use of mechanical ventilation and outcome of critically ill patients treated at the study ICU.[141]

Paper 3 Fluid resuscitation: Randomization and data-collection

The initial FEAST- study was conducted between 13 Jan 2009-13 Jan 2011.[131]

FEAST-study: randomization

Randomization procedures for the FEAST-trial were conducted by the trial statistician at the Medical Research Council Clinical Trials Unit, London/UK. Each clinical trial center received a list of trial numbers and the randomly assigned intervention. Randomization procedures were introduced at each study site.[131]

FEAST-study: data collection

Children recruited in the study followed the same patient circuit as any other child treated in the participating units. Study procedures (e.g., recognition critical illness, immediate initiation of emergency treatment, consent procedures and randomization) were integrated in routine processes of the units. Also “study interventions” assigned by the randomization process and data collection were integrated in essential critical care management. This process of integration assured that data-collection and trial monitoring was well accepted by communities, health professionals and contributed to the quality of study procedures.

A structured CRF was completed at defined time-points:

- Vital signs were documented at following time points in the CRF: baseline, 1 h, 4 h, 8 h, 24 h, 48h and in addition essential clinical interventions, including trial interventions.
- Hb, plasma lactate was measured at baseline, at 8 h, at 24 h and base excess, pH and electrolytes were assessed at baseline and at 24 h.

Adverse events were recorded and reported to the Clinical Trials Facility in Kilifi, Kenya, within 2 days. Documentation of study procedures (e.g., identification of patients, consent, randomization, trial interventions), data collection as well as recording of adverse events were reviewed regularly by visiting trial monitors. 4 weeks after recruitment a neurological assessment was performed by an

independent clinician. In case neurological sequelae were detected a further assessment was conducted at 24 weeks.[131]

Statistical analysis

Paper 1 Bubble CPAP: statistical analysis

A CRF, an observation chart and a patient register were used for data collection. Data were entered into an Excel database. The proportion of bCPAP cases who survived by risk group, sex, age, complications, HIV status and treatment methods were described. Univariable logistic regression to determine if the odds of bCPAP survival were higher in particular subgroups was conducted. In view of the relatively small number of recruited patients no further multivariable analysis could be conducted. Additionally, the following analysis is described: survival and death (treatment failure) by HIV status, severe malnutrition and the presence of organ-dysfunction other than respiratory failure including shock, malaria, anaemia (MOF). This study was done in a "real life" clinical setting without dedicated funding and did not have a target sample size. All analyses were done in Stata V.14.2 for Mac (paper 1).

Paper 2 Mechanical ventilation: statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics (former PASW), (IBM Software 20.0; IBM, Vienna, Austria). We compared survivors and non-survivors as well as patients presenting with different snakebite envenoming syndromes (paralysis/neurotoxicity; coagulopathy/ shock/hemolysis; extensive tissue damage) using the Chi^2-, Mann-Whitney U-rank sum, and Fisher's Exact test, as appropriate. *P*-values <0.05 were considered to indicate statistical significance (paper 2).

Paper 3 Fluids resuscitation: statistical analysis

Statistical methods of re-analysis of FEAST trial data were complex and were led by an experienced statistician. For more details, please see the methods section of paper 3 and annex 1.

Paper 3 represents a hypothesis-based reanalysis of FEAST data. The primary hypothesis was that IV fluid bolus administration is associated with considerable changes in cardiovascular, respiratory and neurological function as well as O_2-carrying capacity, biochemical and acid-base status.

The secondary hypothesis of paper 3 was that if these changes are detectable, they can explain the excess mortality in the IV fluid bolus intervention arms of the FEAST study.

To evaluate these two hypothesis, multiple analyses were conducted in paper 3 in order to describe if organ-function at baseline had an impact on risk of mortality in the different intervention arms. Additionally, further analysis were conducted to detect changes in organ-function over time (48 hours) and to assess on how actual volume of IV resuscitation fluid impacted on organ-function and clinical outcome. In this context further clinical derangements potentially associated with IV fluid bolus administration were evaluated e.g.: Hb levels, electrolyte and acid-base changes as well as lactate levels.

In order to better understand the impact of fluid resuscitation on clinical outcomes of patients with different clinical presentation, subgroups of patients presenting with comparable "clusters of patho-physiological phenotypes" were defined.

Table 8. Study overview (Paper 3).
Simplified description of the main steps of the statistical analysis (Figure 1; Paper 3)

Steps of the statistical analysis	Description
Development of "Organ-function/physiological scores	"Organ-function/physiological scores" were developed to describe respiratory, neurological, and cardiovascular function based on vital sign data in FEAST.
Comparison of organ-function scores between FEAST & 4 additional patient cohorts	Scores were used to describe severity of illness (SOI) in the FEAST-cohort (focus on stratum A; n=3141) & 4 additional cohorts at baseline. The 4 additional cohorts represent critically ill patients with different degree of SOI, different causes of illness, treated in different contexts in terms of available levels of care.
Pre-planned analysis, focusing on the FEAST-cohort	
Calculation of sequential organ-function scores	Organ-function scores were calculated at different time-points in the FEAST-cohort (baseline, 1 h, 4 h, 8 h, 24 h 48 h) to describe changes of physiology and impact of fluid boluses on organ-function.
Effect of fluid boluses on organ-function scores, Hb, acid-base, biochemistry	Among FEAST-participants effect of fluid bolus was assessed on sequential organ-function scores after admission (first 48 h). Further parameters were included in the analysis e.g.: Hb levels, electrolytes, acid-base & Lactate
Identification of patients with larger changes in organ-function & blood parameters	In a further step, the proportion of patients with larger, more clinically important changes in organ-function scores and blood parameters were compared in a secondary analysis.
Impact of fluid bolus volume on organ-function scores & blood parameters	Effect of IV fluid bolus volume (< 30ml/kg or >30ml/kg) on organ-function scores, Hb, and biochemical parameters was assessed in a further analysis.
Identification of clusters of comparable "clinical phenotypes"	Organ-function scores were used in conjunction with further parameters (Hb, biochemistry) to identify clusters of patients with comparable physiological derangements at baseline. Three main clusters of "clinical phenotypes" were identified. Clinical outcomes and response to fluid bolus was evaluated.
Post-hoc analysis	
Multivariate analysis of effects of fluid boluses on clinical outcomes	Combined contribution of effects of bolus on time to death was assessed in a post-hoc analysis using a multi-variant model. Response to IV fluids was reviewed in order to explore how multiple simultaneous physiological changes caused by IV fluid bolus were associated with excess deaths in bolus recipients. The following covariates were used for these analysis: organ-function scores, Hb levels, biochemistry values (chloride, bicarbonate, base excess).

Paper 3: Fluid resuscitation – development of "physiological/organ-function" scores

Respiratory score

To assess severity of respiratory dysfunction, respiratory rate (RR) and SpO_2 were used. Vital signs were normalised using published age-adjusted normal values (Paper 3 Annex 1, pp 3-6). The contribution of SpO_2-measurements were "weighted" in order contribute adequately to the "respiratory score" in relation to changes in respiratory function.

Respiratory score=(respiratory rate – mean respiratory rate for age) + 5 × (100 – SpO_2).

If measured RR was less than mean RR for age, the term (RR – mean RR for age) was set to zero, so that only increased RRs contributed to the score.

Use of SpO_2/FIO_2-ratios could have strengthened the value of the score.[87-91] However, in the FEAST-study no reliable FIO_2-values were documented. Additionally, some participating units struggled to ensure reliable provision of O_2 as suggested by WHO.[93]

Cardio-vascular score

Physiological responses to developing cardiovascular dysfunction are initially aimed at maintaining BP in order to assure perfusion of vital organ functions with vasoconstriction and increasing HR. If these compensation mechanisms fail, adequate perfusion of vital organs decreases. Age-adjusted degree of tachycardia as well as the degree of hypotension was combined. Together with a weighted value of capillary refill time (CRT) these essential clinical data were used to form a measure of cardiovascular dysfunction as follows (Paper 3 Annex 1, pp 3-6):

Cardiovascular score=(heart rate – mean heart rate for age) + (mean systolic blood pressure for age –systolic blood pressure) + 25 × (capillary refill time).

If measured HR was less than mean HR for age the term (HR - mean HR for age) was set to zero. If systolic blood pressure (SBP) was higher than mean SBP for age the term (mean SBP for age - SBP) was set to zero.

Integration of Hb levels could have strengthened this cardio-vascular score. In some research settings determination of cardiac-output index and oxygen delivery can be of added value.[154]

Neurological score

Raised intracranial pressure is associated with decreasing level of consciousness and potentially with bradycardia, and hypertension (the latter two are components of Cushing's triad).[155] The following parameters were combined to a "neurological score": weighted level of consciousness measured on the AVPU (Alert, Verbal, Pain, Unresponsive) scale (alert=0; responds to verbal

stimulus=1; responds to painful stimulus=2; unresponsive=3)[40] and age adjusted degree of hypertension, and age adjusted degree of bradycardia (Paper 3 Annex 1, pp 3-6) .

Neurological score=(SBP – mean SBP for age) + (mean HR for age – HR) + 25 × (AVPU coma scale).

If SBP was lower than the mean SBP for age, the term (SBP - mean SBP for age) was set to zero, so that only increased SBP contributed to the score. If HR was greater than the mean HR for age, the term (mean HR for age - HR) was set to zero, so that only decreased HR contributed to the score.

Potential weakness of the score e.g.: Not all patients with increased intra-cranial pressure will develop hypertension, especially if a patient presents with haemodynamic instability. Additionally, a potentially time-limited period of hypertension might not have been recognised during the FEAST-study. However, the impact of the AVPU coma score may compensate for this potential weakness.

In the FEAST-cohort, scores were calculated at baseline and 1 h, 4 h, 8 h, 24 h, and 48 h. From the cohorts from Malawi, South Africa and the UK only baseline data were used for the analysis.

Consent and IRB approval; ethical considerations

Paper 1 CPAP: consent & IRB approval

Ethics approval was provided by the Malawian National Health Sciences and Research Committee, protocol number 941. As the study describes routine clinical management (non-invasive respiratory support) of critically ill patients, patient consent for publication was waived. Authors have not declared a specific grant for this research from any funding agency. There were no competing interests of the authors (paper 1).

Paper 2 Mechanical ventilation: consent & IRB approval

Analysis of the ICU data was approved by the institutional review board (IRB) of Lacor-hospital. This study evaluates routine patient care on the ICU. Due to the retrospective design of the study, written and oral consent was waived. Data of 139 study patients were included in a previous publication. Similar IRB approval procedures were applied in this context (paper 2).[141]

Paper 3 Fluid resuscitation: consent & IRB approval

All studies were approved by the IRB of the relevant centers. Details of recruitment procedures, consent procedures, ethics, and institutional approvals for the FEAST, meningococcal, and Malawian cerebral malaria studies have been reported.[131,145,146] Access to the FEAST trial data was provided after a formal request to the trial study group. Data collection for the South African sepsis cohort and

St Mary's Hospital/London cohort were approved by relevant research ethics committees of University of Cape Town and UK. In agreement with these approvals, written informed consent was taken only for participants from whom additional data or samples were obtained beyond those necessary for routine care. Data from each study were made available with agreement of the relevant study investigators. Analysis of factors affecting outcome in each study were covered by the ethics approval of each study (paper 3).

Study oversight of the initial FEAST study

Ethics committees at Imperial College, London, Makerere University, Uganda, Medical Research Institute, Kenya, and National Medical Research Institute, Tanzania, approved the protocol. An independent data and safety monitoring committee reviewed interim analyses two times per year.[131]

Endpoint review committee of the initial FEAST study

An endpoint review committee, reviewed all deaths, neurologic sequelae and adverse events. Members of this committee were unaware of the management assigned to individual patients during the randomization process.[131] Of note, the endpoint review committee had limited diagnostic means to determine causes of death (e.g., no routine point of care lung ultrasound or echocardiography or imaging options of the central nervous system were available). Accuracy of determination of causes of death or adverse events was therefore limited.[e]

Patient consent in a clinical trial, assessing critical care in a resource-limited setting

An informed consent process assured voluntary participation of patients in this clinical research. International guidelines exist to protect patients recruited in emergency and critical care research.[156,157] In order assure that the consent process does not delay time-critical emergency interventions a system of deferred consent was used in the FEAST trial.[131] In this context the consent process was started during the initial emergency treatment with a verbal assent. After the initial stabilisation of the child this process was completed by an informed consent conversation, while considering potential cultural and language barriers.[158,159]

[e] The author was part of the endpoint review committee.

Research in paediatric emergency and critical care: assurance of patient safety

Paper 1 bubble CPAP: Assurance of patient safety

The following measures contributed to quality of care and safety in relation to the observational study presented in Paper 1:

- bCPAP is a recognised form of non-invasive respiratory support for children and newborns. Already in 2012 bCPAP was introduced on the paediatric unit in Lilongwe as part of routine care in children with respiratory dysfunction.[d110]
- The device used in the study followed standard set-ups of a bCPAP system. In a biomedical review conducted in a respiratory laboratory of Karolinska Hospital, Stockholm/Sweden, it performed similarly to a bCPAP system, used in high resource settings.[138]
- A pragmatic "on the job" training program accompanied the introduction of bCPAP.
- In the given context of an extremely busy paediatric unit, participation in the observational study was associated with additional attention to clinical monitoring and surveillance.

Paper 2 Mechanical ventilation: Assurance of patient safety

Medical devices used for mechanical ventilation in the ICU of Lacor Hospital were routinely used for anaesthesia and intensive care in multiple countries and by a number of humanitarian organisations. Advanced airway management and mechanical ventilation was routinely practiced on the ICU and in operation theatres of Lacor Hospital. Experienced clinicians were involved in the care of critically ill patients. A senior anaesthetist routinely supported the clinical team.

The database, from which data were extracted for this study (Paper 2), was routinely used on the ICU and enabled the clinical team to maintain an ongoing audit process.

Paper 3 Fluid resuscitation: Assurance of patient safety

During the preparation of the RCT and during the time of recruitment, the "paediatric emergency triage assessment and treatment training team" as part of the clinical trial team invested enormous efforts to integrate study procedures in routine processes (page 12 of the original publication):[131]

- Patient circuits were reviewed in partnership with the institution's clinical teams and administration.
- On-going capacity building in combination with the introduction of some biomedical equipment and consumables ensured that all study patients received essential emergency and

critical care adapted to available resources. Health workers recruited specifically for the FEAST-trial actively participated in clinical care of all patients treated on the units.

In this context, the participating paediatric departments generally benefited from quality improvement measures associated with the conduction of the FEAST-trial.

For further details regarding information related to study oversight (independent data and safety monitoring committee), please see Annex 2, the original FEAST publication.[131]

Results – Main findings

Paper 1 Bubble CPAP: Results and main findings

Paper 1: Clinical outcomes

Of note is the good clinical outcome of children with "very severe pneumonia (VSPNA)" and no other severe organ dysfunctions (single organ failure, SOF). All 19 children with VSPNA who were HIV negative and had no additional comorbidities or organ dysfunctions survived (five children in this group had suspected TB). Additionally, 40 from 42 (95%; 95% CI 84% to 99%) children with VSPNA (unknown or negative HIV status) and no comorbidities and no other organ dysfunction survived (paper 1).

In children with respiratory failure and further organ dysfunctions (e.g., shock with and without severe anaemia, reduced level of consciousness (multi-organ failure, MOF) survival was lower (45%), than in those with SOF and no comorbidities (86%; $p<0.0001$).

Additionally, survival was significantly lower in children with SAM (36%) as compared to patients with no severe malnutrition (81%). Survival was also lower in children with confirmed HIV infection or exposure (45%), compared to those with negative HIV-status (81%) or with unknown HIV-status (68%). 61% of children with SAM had more than one organ dysfunction (e.g., signs of shock). A more detailed sub-analysis was not possible because of the relatively small number of recruited patients (N=117) (paper 1).

Among the 117 patients presenting with respiratory failure, four had congenital heart disease CHD)

- Atrio-ventricular septum defect (AVSD): 2 children (1 with clinical features of trisomy 21)
- Ventricular septum defect (VSD): 1 child
- Persistent ductus arteriosus (PDA): 1 (this child had features of trisomy 21)

If clinical signs suggesting CHD were noted (e.g., a heart murmur, no improvement with routine treatment) POCUS was used to perform basic echocardiography at the bedside. Ultrasound-scans

were initially performed by the author. During the study period the clinical team had the chance to confirm echocardiography findings with the support of a trained paediatric cardiologist, who was affiliated with Baylor College HIV-services.[137]

Three of the 117 children described in Paper 1 had signs of neuro-disability: (cerebral palsy (1), hydrocephalus (1), suspected neuromuscular disorder (1) (paper 1).

Paper 1: Technical details & complications

Of the 117 patients, 13 experienced complications related to bCPAP-treatment, including nasal obstruction(2), blocked nasal prongs (2), interruption of O_2-supply from depleted cylinder (2), lesions of the nasal septum (7) and aspiration of enteral feeds (1). Some patients had more than one complication. The number of treatment failures among those experiencing complications was 3/13 patients (paper 1).

There were no statistically significant differences in survival by bCPAP delivery devices. However, the clinical team tried to use dedicated bCPAP set-ups, whenever possible. O_2-cylinders providing O_2-flow for bCPAP were only used if no dedicated bCPAP were available or as back-up in case of power cuts (paper 1).

The average air/O_2-flow set at the start of the bCPAP use was 9.1 liters/min (SD 2.0, range 5–16). The mean age of patients was 7 months (IQR: 2-15 months) and the mean weight of patients was 6.4 kg (unpublished dataset of Paper 1). In a bCPAP system air/O_2-flow needs to meet the peak tidal inspiratory flow (PITF) of patients, which in infants less than 6 months is around 1.7 L/min.[160] This approach is similar to the practice recommended in the use of High-flow Nasal Cannula (HFNC) humidified air/O_2 systems.[161,162]

The average starting bCPAP pressure was 6.7 cm H_2O (SD 1.0, range 4–9). This pressure level is similar to the CPAP pressures recommended to achieve adequate reduction of work of breathing (WOB) in studies evaluating the treatment of children with bronchiolitis.[101,103]

Paper 2 Mechanical ventilation: analysis and main findings

Of the 6 976 patients admitted to the ICU during the study period, 174 were treated for snakebite envenomation (2.5%). More than a third of the patients were younger than 18 years (n=67; 38.5%).

Non-survivors more frequently presented with coagulopathy, shock or haemolysis than survivors. Invasive mechanical ventilation was used more often for treating non-survivors than survivors. Complications were documented for more non-survivors than survivors. Antivenom (at low and probably inadequate doses)[121,163] was administered to 22 patients (12.6%). The median (IQR) length

of ICU stay was 3 days (interquartile range: 2 – 5 days) and overall mortality was recorded as 8% (n=14) (paper 2).

More detailed information on clinical symptoms at presentation could be determined from the ICU-database for 40 patients (23%). The need for invasive mechanical ventilation and subsequent ICU mortality differed among snakebite victims who presented with clinical symptoms.

Sixty patients developed acute respiratory failure (ARF) requiring mechanical ventilation (n=60; 34.5%). Among these patients, clinical symptoms were documented in more detail in 16 cases. Neurotoxicity (fasciculation/paralysis) was the most commonly documented indication for advanced respiratory support (87.5%). However, it should be noted that in absence of any other documented complication, it is most likely that in this study ARF in patients requiring mechanical ventilation was associated with a neurotoxic snakebite syndrome. Antivenom could be administered only to 10 (16.7%) of the 60 mechanically ventilated patients. Three of these patients died (33.3%). Of the 50 ventilated patients who did not receive antivenom treatment, seven died (14%). There was no statistical difference in mortality between mechanically ventilated patients with or without antivenom therapy (p=0.35; Fisher's exact test) (paper 2).

The ICU mortality of patients requiring mechanical ventilation was 16.7%. Of the 60 patients who required mechanical ventilation, 17 (28.3%) were younger than 18 years. Six of these 17 children with ARF died (35.3% mortality). 2 of the 17 children requiring ventilation were younger than 5 years, both of whom died. Of the 43 patients older than 18 years who required mechanical ventilation, four died (9.3% mortality). The difference in mortality rates between children and adults requiring mechanical ventilation was statistically significant (p=0.02; Fisher's exact test) (paper 2).

Length of ICU stay (Paper 2; Fig. 2A) and mortality (Paper 2 Fig. 2B) were significantly higher in patients requiring mechanical ventilation than in those who did not need invasive respiratory support.

Paper 3 Fluid resuscitation: analysis and main findings

Comparison of severity of organ-dysfunction: FEAST-study and four other cohorts

For the interpretation of results it is important to note that in the FEAST-study risk of mortality at 1 hour after randomization was similar in the three study groups (1.2% in the albumin-bolus group, 1.1% in the saline-bolus group, and 1.3% in the control group).[131] After 1 hour, increased mortality was documented in patients receiving normal saline or HAS boluses as compared with the control group.[131] Most deaths among FEAST-study participants occurred before 24 h (259 of 297 deaths (87%) in stratum A), while only a small number of patients died after 48 h.[131]

In the FEAST study, the median organ-function scores were 105 (IQR 86–124) for cardiovascular function, 53 (IQR 37–79) for respiratory function, and 25 (IQR 8–47) for neurological function.[f] Patients in FEAST had significantly higher values of all organ-function scores than the cohort of patients from the ED in St Mary's Hospital/London. Respiratory scores at baseline of the FEAST-cohort was significantly higher than in all other cohorts (p<0·0001; Paper 3 Annex 1 p 9). As expected neurological scores were highest in the Malawian cerebral malaria cohort (median score 75, IQR 55–78; Paper 3 Annex 1 p 9).[146]

Cardiovascular scores of patients evaluated in the FEAST-study were similar to those in the meningococcal gram-negative sepsis cohort from the UK (median score 100, IQR 69–157; Paper 3 Annex 1 p 9).[145] Organ function scores in FEAST were highest in the first hours following admission, and decreased over the next 48 hours (Paper 3 Annex 1 p 9). It is important to note that patients who subsequently died had significantly higher respiratory and neurological scores than survivors at all timepoints up to 24 hours (Paper 3 Annex 1 p 9). Cardiovascular scores were significantly higher in patients who died than in survivors at baseline. 1 h after administration of initial IV fluid bolus (if received) cardiovascular scores were not significantly different between survivors and fatal cases. However, after 4 hours or later cardiovascular scores were significantly higher in patients who died than in survivors (Paper 3 Annex 1 p 9).

In FEAST, odds of death for each ten unit increase in baseline organ function score was 1·09 (95% CI 1·07–1·11) for respiratory score, 1·26 (1·21–1·31) for neurological score, and 1·09 (95% CI 1·05-1·14) for cardiovascular score (all p<0·0001; Paper 3 Annex 1 p 22). In all four cohorts ten-unit increases in baseline scores was at least associated with a trend towards increased risk of adverse outcomes (Paper 3 Annex 1 p 22).

These results suggest that the defined organ function scores are a valuable tool to describe severity of illness (SOI) at baseline and in the FEAST cohort in sequential assessments over the following 48 hours.

Effect of IV fluid bolus on sequential organ function scores & laboratory parameters

In paper 3 linear regression analysis was used to calculate mean differences, adjusted for baseline values, between those randomly assigned to receive IV fluid bolus or no bolus in the FEAST-study. This analysis was conducted in order to evaluate effects of IV fluid bolus administration on organ

[f] Increasing scores in paper 3 describe worsening organ function.

function scores, biochemical parameters and Hb levels. HAS and normal saline IV fluid bolus groups were combined, as they had similar effects on mortality in FEAST.[131]

Mean respiratory score was 3·45 (95% CI 0·90–6·01; p=0·0080) higher at 1 h and 2·3 (0·31–4·3; p=0·024) higher at 4 h in IV fluid bolus recipients than in those who received no bolus, but there was no significant difference between groups at 12 h (table 2, Paper 3). Fluid bolus administration was associated with increased mean neurological scores at 1 h by 2·64 (95% CI 0·76–4·52, p=0·0060) and there was no significant difference at 4 h and 12 h (table 2, Paper 3). In contrast, fluid bolus decreased the mean cardiovascular score at 1 h by 2·17 (95% CI 0·57–3·78, p=0·0080; table 2, Paper 3). However, later there was no significant difference in cardio-vascular scores between bolus and no-bolus groups at 4 h and 12 h.

In a further post-hoc analysis, HAS and normal saline groups were analysed separately (paper 3 Annex 1, p 23). Only at timepoint 8 h the respiratory score increased more in HAS recipients than in patients receiving normal saline. Otherwise there were no significant differences between FEAST study patients who received normal saline or HAS IV fluid boluses (Paper 3 Annex 1 p 23).

Overall, after 4 h, there were no significant differences in organ function scores compared to earlier time-points (table 2, Paper 3).

IV fluid bolus administration was associated with decreased mean Hb concentration at 8 h by 0·33 g/dL (95% CI 0·20–0·46, p<0·0001), which affects O_2 carrying capacity (table 2, Paper 3).

No change in blood lactate was documented in association with IV fluid bolus administration at 8 h or 24 h. However, fluid bolus was associated with a decrease in mean plasma bicarbonate by 0·96 mmol/L (0·45 to 1·47, p=0·0003), a decrease in mean base excess by 1·41 mEq/L (0·76 to 2·06, p<0·0001), and an increase in mean chloride by 1·65 mmol/L (95% CI 0·47 to 2·83, p=0·0070) in patients surviving to 24 h (table 2, Paper 3).

To assess if IV bolus administration was associated with larger changes of organ dysfunction and laboratory markers in some patients, proportions of patients in different sectors of the distribution of each variable between fluid bolus and no fluid bolus groups were compared (figure 7[g]; Paper 3 Annex 1 p 10). Patients who received IV fluids bolus had an increased risk of a large or very large increase in respiratory score and neurological score at 1 h, and of a large or very large decrease in cardiovascular score at 1 h (figure 7[g]). Changes of respiratory score associated with fluid bolus

[g] Figure 7 corresponds to figure 2 in paper-3.

administration persisted at 4 h (Paper 3 Annex 1 p 10). When absolute values of organ function scores at 1 h and 4 h were evaluated, instead of changes from baseline, a bigger proportion of the IV fluid bolus group had high respiratory and neurological scores compared to the no bolus group. However, a smaller proportion of IV fluid bolus recipients had high cardiovascular score (Paper 3 Annex 1 pp 11, 12).

Larger decreases from baseline in base excess and bicarbonate, and larger increases in chloride were associated with fluid bolus administration (figure 7:[g] D–F). Important, at 8 h a greater proportion of bolus recipients had very low Hb concentration (<7·5 g/dL and <5 g/dL) (Paper 3 Annex 1 p 11).

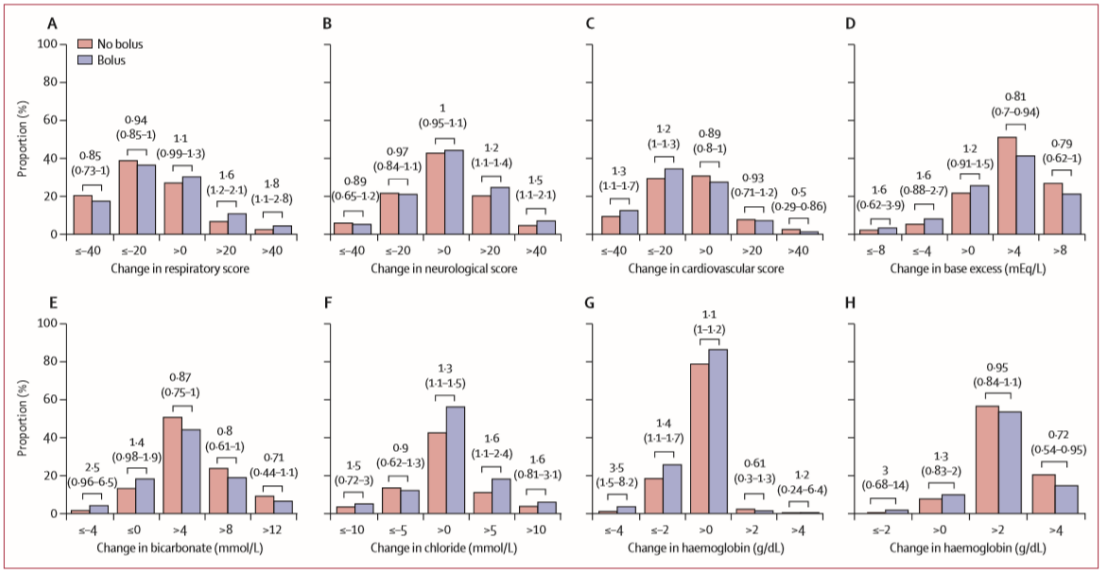

Figure 7. Changes in physiological scores and blood-tests associated with IV fluid bolus (Paper 3)

This figure corresponds to figure 2 in Paper 3. The proportion of individuals in FEAST with different magnitudes of change from baseline in physiological scores and blood-tests are shown according to whether they were randomly assigned to receive no fluid bolus (red bars) or fluid bolus (blue bars). Panels A–C show changes in physiological scores between baseline and 1 h after starting fluid infusion. Panels D–F show changes in biochemical measures from baseline to 24 h. Panels G and H show change in Hb concentration from baseline to 8 h in non-transfused (G) and transfused (H) participants. Negative values indicate decrease from the baseline, and positive values indicate increase from baseline. Values above the bars show relative risk (95% CI) for comparison of proportions between bolus and no bolus groups.

Effect of fluid bolus volume on organ-function, Hb levels and biochemistry parameters

A further analysis conducted in paper 3 evaluated effect of low- or high- IV volume bolus on distribution of organ function scores and blood test parameters. At 4 h first vital sign observations were documented after administration of high-volume boluses was completed. At this time-point higher respiratory and neurological scores in patients who received high volume bolus (≥30 mL/kg)

were recorded (Paper 3 Annex 1 p13). However, distribution of cardiovascular scores at 4 h was similar in low and high- IV volume bolus recipients (Paper 3 Annex 1 p 13). In patients receiving high-IV volume bolus lower base excess and bicarbonate, higher chloride, and lower Hb levels (but only in non-transfused patients) were documented (Paper 3 Annex 1 p 13). Results were similar when changes from baseline were evaluated for these parameters (Paper 3 Annex 1 p14).

Signs of hyperchloraemic acidosis & respiratory function

Changes of acid-base status and electrolytes observed in FEAST participants suggest that administration of IV boluses of HAS or normal-saline can be associated with an hyperchloraemic metabolic acidosis (paper 3). To explore this aspect further, a post-hoc analysis was done to evaluate the effect of IV fluid-bolus administration on pH and respiratory compensation. Of 2082 FEAST participants with pH measurements at baseline, 719 (35%) had acidosis (pH<7·35; Paper 3 Annex 1 p 15). Mortality rate among patients presenting with a baseline acidosis was much higher than for patients with pH $\geq$ 7·35. Among survivors in the IV fluid bolus group, relative risk of being acidotic at 24 h was 1·4 (95% CI 1·0–1·9) compared to the no bolus group. There was a significant negative correlation between chloride and pH, with a stronger effect of chloride on pH in the IV fluid bolus group (Paper 3 Annex 1 p 15).

Low pH could suggest that respiratory compensation mechanisms had been overwhelmed (paper 3). In this context respiratory response at early timepoints was evaluated, when the majority of deaths occurred in acidotic patients. RRs were increased at baseline and 1 h, relative to normal age ranges. SpO_2 decreased more in bolus recipients at 1 h, whereas there were no differences between bolus and no bolus groups in terms of changes in RR (Paper 3 Annex 1 p 15).

Documentation of SpO_2/FiO_2 ratios[87-89] potentially allows more subtle evaluation of change in respiratory function associated with fluid management and/or transfusion. In this context POC-lung ultrasound can be of benefit to detect changes in extra-vascular lung water.[164,165]

Evaluation of critically ill patients presenting with comparable "clinical phenotypes"

In paper 3 three clusters of patients recruited in the FEAST-study with comparable "clinical patho-physiological phenotypes" were identified on the basis of baseline characteristics (Figure 8[h]). Cluster 1 (n=1991) had the least derangement in physiological scores, Hb levels, and lactate. Cluster 2 (n=795) included patients with severe anaemia (Hb concentration <5 g/dL), high lactate and high

[h] Figure 8 *corresponds to Figure 3 in paper-3.*

cardiovascular scores. Cluster 2 also had greater base deficit, lower bicarbonate, and high chloride concentrations (Paper 3 Annex 1 p 7). Cluster 3 (n=384) was characterised by extremely high respiratory and neurological scores, but better maintained Hb levels. The clusters differed markedly in mortality (figure 8[h]). In cluster 1, six (1%) of 658 participants in the non-bolus group died, and 51 (4%) of 1327 died in the bolus group. In cluster 2, 37 (14%) of 264 patients in the non-bolus group died, and 108 (21%) of 518 died in the bolus group. Mortality was highest in cluster 3: 32 (26%) of 122 participants in the non-bolus group died, and 59 (23%) of 252 in the bolus group died. Analysing all study participants, a negative correlation between Hb levels and lactate concentrations could be demonstrated (Spearman r=–0·56, p<0·0001; figure 8 C[h]).

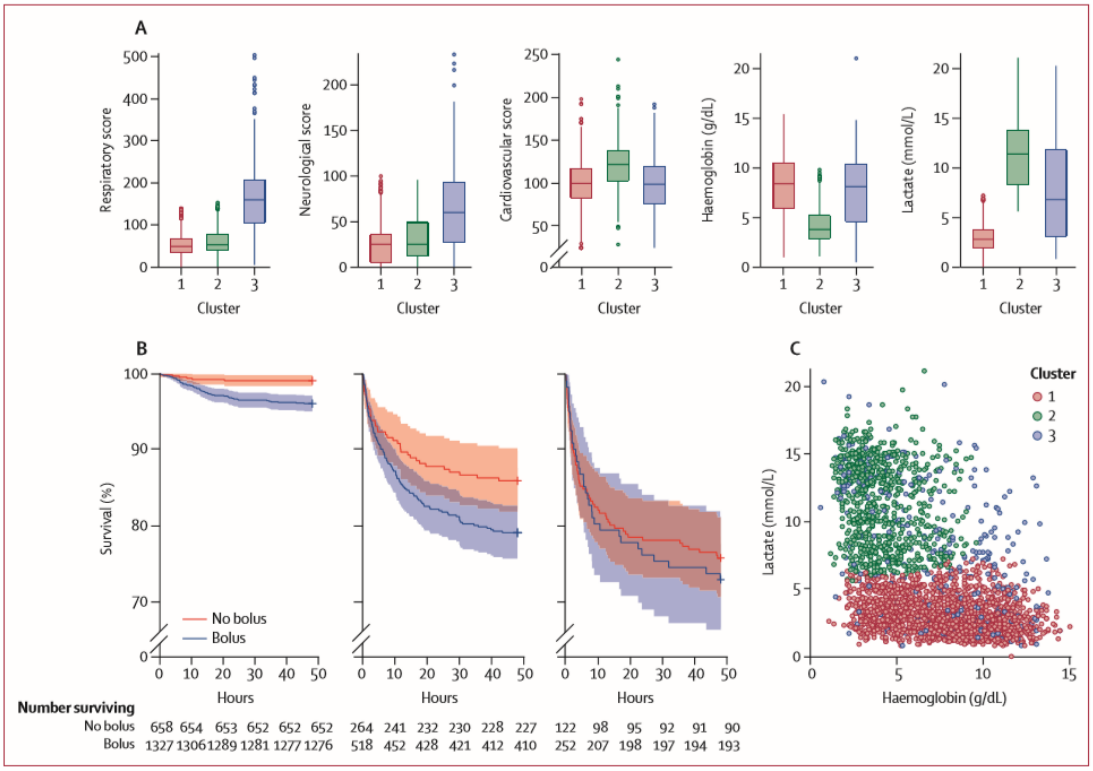

Figure 8 Bayesian cluster analysis of FEAST-data.
This figure corresponds to figure 3 in Paper 3: (A) Distribution of organ-function scores, Hb levels and lactate concentrations by cluster. Boxes show median (coloured line) and IQR; whiskers extend up to 1·5 times IQR. Cluster one, n=1991; cluster two, n=795; cluster three, n=384. (B) Survival curves for no bolus (red line) or bolus (blue line) recipients in each cluster in FEAST stratum A. Cluster-1, bolus n=1327, no bolus n= 658; cluster-2, bolus n=518, no bolus n=264; cluster-3, bolus n=252, no bolus n=122. Dotted lines indicate 95% CIs. (C) Correlation between baseline Hb and lactate concentrations (Spearman p<0·0001, r=–0·56) with individual participants coloured by cluster.

Summary of characteristics of the three identified clusters of clinical phenotypes
Cluster 1 [red] n=1985: *Characterised by least derangements in physiological scores, lactate and Hb levels; relatively low mortality risk.*
Cluster 2 [green] n=782: *Patients with low Hb levels and high lactate levels; high mortality risk.*
Cluster 3 [blue] n=374): *Patients with abnormal neurological and respiratory function; close to normal Hb levels; very high mortality risk.*

Associations between IV bolus administration and respiratory score, neurological score, Hb levels, and blood biochemistry in clusters 1 and cluster 2 were consistent with those seen in FEAST overall (Paper 3 Annex 1 pp 24–26). The association between bolus and changes in blood parameters and organ function scores in each cluster are described in detail in Paper 3 Annex-1 (pp 25–27).

Impact of multiple physiological changes on clinical outcomes

Authors of Paper 3 rationalized that multiple physiological changes associated with "un-buffered" IV bolus administration interact. These fluid induced effects in combination might explain the higher mortality observed among IV fluid bolus recipients in the FEAST-study. In this context it is important to highlight that in the FEAST-study risk of mortality at 1 hour was similar in the three study groups (1.2% in the albumin-bolus group, 1.1% in the saline-bolus group, and 1.3% in the control group).[131] After 1 hour increased mortality was documented in patients receiving normal saline or HAS boluses as compared with the control group.[131] Most deaths among study participants occurred before 24 hours (259 of 297 deaths (87%) in stratum A).[131]

Among patients recruited in the FEAST-study vital signs were documented in the study CRF at: baseline, 1 h, 4 h, 8 h, 24 h and 48 h. Hb levels and plasma lactate were measured at baseline, 8 h, and 24 h, while base excess, pH and electrolytes were measured at baseline and 24 h.[131] Therefore limited biochemistry and Hb values were available for analysis in the first hours after recruitment. However, these initial hours were decisive for clinical outcomes in a large number of critically ill children.

A multivariate analysis was performed in order to explore in more detail complex physiological mechanisms during the first hours of critical care management (Paper 3 Annex 1 pp 6-8). This analysis was based on respiratory, neurological and cardiovascular scores evaluated at 1 hour in the IV bolus and non-bolus group. Biochemistry values and Hb levels were affected by administration of normal saline and HAS and potentially had considerable impact on organ function. These values were therefore crucial for the multivariate analysis. However, besides at baseline these values were not measured during this important, early critical care period. In this context, for the assessment of

patients in the non-bolus group base excess, bicarbonate, chloride at baseline values were used for the multivariate analysis (Paper 3 Annex 1 pp 6-8 & Table 9).

In the bolus group, in order to account for changes in the blood-test parameters associated with administration of normal saline and HAS, which were not measured at 1 h, values were adjusted by the observed mean shifts at 24 h in biochemical results (base excess -1.41 mmol/l, bicarbonate -0.96 mmol/l, chloride +1.65 mmol/l) and at 8 hours for Hb levels (-0.32 g/dl) (Paper 3 Annex 1 pp 6-8) . This calculation represents a conservative estimation of changes of blood-test parameters in the bolus group at 1 h in comparison with baseline values. Patients who were treated with IV fluid boluses, but died in the first 24 hours after recruitment are likely to have had the most severe derangements potentially associated with administration of normal saline or HAS boluses (paper 3). For this reason an additional estimation of biochemical values at 1 h was conducted, using baseline values and data derived from the literature (Paper 3 Annex 1 pp 7, 8, 28-31; Table 9). Results of these two different estimations are shown in Table 9. For bolus and non-bolus groups, Hb level used for analysis were based on baseline levels and the 8 h levels of the data-set from the FEAST-study.

A principal component analysis using organ-function scores at 1 h and estimated biochemistry and Hb levels at this time-point (Table 9) showed that the distribution of fatal cases was distinct from survivors, while risk of mortality and derangements of covariates were related to effects of IV fluid bolus administration (Paper 3 Annex 1 p 18, figure 9).

Table 9. Estimation of biochemistry and Hb levels used for post-hoc multi-variate analysis at time-point 1 h. In the non-bolus group baseline & 24 h levels were used. For the bolus group two different estimations were considered: 1) estimation based on baseline & 24 h data; 2) estimation based on baseline levels & calculations derived from the literature. Only samples with complete measures for all covariates were used for this analysis (N=1901) (Paper 3 Annex 1 pp 6-8).

	No-bolus group; 1 h estimations derived from baseline & 24 h levels	**1) Bolus group; 1 h estimations derived from baseline & 24 h levels**	**2) Bolus group; 1 h estimations derived from baseline & literature**
Base excess mEq/l	+ 0,217	- 1,025	- 5
Chloride mmol/l	+ 0,011	+1,577	+ 10
Bicarbonate mmol/l	+ 0,194	- 0,66	- 5
Hb g/l baseline & 8 h level*	+ 0,03*	- 0,339*	
*Change in Hb level was derived only from FEAST-data, and not from literature values. Data were available at baseline and 8 h.			

Multiple further analyses were conducted to evaluate if changes induced by IV fluid bolus administration on different covariates at 1 h could explain the increased mortality among bolus recipients in the FEAST-study. In addition to a model using baseline variables, four sets of covariate analysis representing the 1 h time point were conducted (Paper 3 Annex 1 pp 6,7,8 ,28-31).

Covariate set 1

The first set of covariate analysis contained the three organ-function scores at 1 h and integrated levels for base excess, chloride, bicarbonate based on the levels observed at baseline and 24 h in bolus and non-bolus arms. A linear change in the levels from 1 to 24 h was assumed in this context. Hb levels used for analysis were based on baseline levels and the 8 h values in FEAST.

Covariate set 2

In this set of covariate analysis organ-function scores and Hb estimate were used for analysis as in set 1. Additionally integrated in the analysis were levels for base excess, chloride and bicarbonate in the bolus arm based on estimates of effects of on "un-buffered" IV fluid bolus (e.g., normal saline) on these biochemistry results derived from peer-reviewed literature. Estimates in the no bolus arm were the same as those used in covariate set 1.

Covariate set 3

The third set of the multivariate analysis evaluated individual components of the organ-function scores and used blood levels as described in covariate set 1.

Covariate set 4

In this analysis individual components of organ-function score were evaluated as in covariate set 3. Additionally biochemistry levels (base excess, chloride, bicarbonate) were estimated using results from the literature as described in covariate set 2.

In all four sets of multivariate analysis the impact of fluid boluses as an additional explanatory covariate was integrated in the statistical evaluations (paper 3).

Baseline values of the different covariates could predict mortality in the bolus and non-bolus group, but could not completely explain the degree of mortality in the bolus recipients in the FEAST-cohort. Subsequent analysis of covariates used estimates to predict 1-hour post-bolus biochemistry values in bolus recipients. When these estimates at the time-point 1 hour were integrated in covariate analysis no longer significant differences in terms of mortality prediction between bolus and non-bolus group could be determined (Paper 3, figure 4; Paper 3 Annex1, p32).

Overall, results of the post-hoc analysis demonstrates that after fluid bolus administration, respiratory and neurological scores as well as base excess were the major determinants of increased mortality risk using the two different methods of post bolus biochemical value estimations (Paper 3; figure 4A & 4B Paper 3 Annex 1 pp 6-8). When individual components of each score were included in the models, post bolus SpO_2, AVPU score and base excess made the largest contribution to explain excess mortality in bolus-recipients (Paper 3, figure 4C, 4D). Effects of fluid bolus administration on

chloride levels, bicarbonate and base excess suggest that a hyperchloraemic acidosis was associated with "un-buffered" normal saline and HAS administration, which potentially contributed to excess mortality in the fluid bolus group in the FEAST-study. These findings were summarised in a physiological model proposing how adverse effects of IV fluid bolus could increase mortality (Paper 3; figure 5).

Paper 3 describes complex interactions of different physiological mechanisms as well as impact of fluid resuscitation on vital organ functions in critically ill children with haemodynamic instability. Clinical outcomes of critically ill patients can potentially be improved by a comprehensive, critical care package, adapted to realities in resource-limited settings.

Discussion

Paper 1: Non-invasive respiratory support/bCPAP

bCPAP: Treatment of children with single organ failure (SOF)

Quality and safety: Feasibility to introduce bCPAP on a busy paediatric unit in Malawi

Paper 1 is an observational study describing treatment and clinical outcomes of 117 children with acute respiratory dysfunction treated with bCPAP in a large paediatric unit in Lilongwe/ Malawi. Among HIV-negative children with acute respiratory dysfunction and no further organ failure (single-organ failure/SOF) treated with bCPAP, mortality was low (mortality: 0%). These results correspond to outcomes reported from a RCT conducted in a paediatric critical care unit in Bangladesh where the study mortality rate was 4% among children with respiratory dysfunction (SOF) treated with bCPAP, while mortality among patients treated with low-flow O_2 was significantly higher, 15%.[166] A previous study conducted in the paediatric unit in Lilongwe among critically ill patients with respiratory dysfunction using an improvised bCPAP set-up describes improvement of physiological parameters (respiratory rate, SpO_2) after commencement of bCPAP.[d110] Safe introduction of CPAP was also described in other paediatric units in SSA (e.g., Ghana).[167,168]

These results suggest that non-invasive respiratory support has the potential to contribute to improvements of critical care in resource-constraint settings. However, the experience outlined in Paper 1 emphasizes the importance to introduce bCPAP in conjunction with sustained efforts directed to improve quality of essential paediatric hospital care e.g.:

Despite considerable resource limitations, important elements of a patient circuit were strengthened on the paediatric unit in Lilongwe (e.g., triage, emergency care). Electricity supply was relatively

reliable during the study period allowing safe use of bCPAP set-ups. In case of power-cuts and problems with the back-up generator, O_2-cylinders could be used.

A number of health workers previously developed competencies in the use of bCPAP,[110] while continuous inter-professional on-the-job training in essential paediatric critical care was conducted. Training programs associated with the Malawian College of Medicine (e.g. medical student training, bachelor training program for clinical officer)[26] contributed to improvements of clinical competencies among health workers. In this context senior clinicians participating in medical education were involved in routine, clinical supportive supervision.

bCPAP: Treatment of children with multi-organ failure (MOF)

In Paper 1 a cohort of children with a high mortality risk is described. In view of resource limitations, children with the most severe clinical presentations benefited from non-invasive respiratory support via bCPAP. No severity of illness (SOI) scores were used in this study, which limits the possibility to compare clinical outcomes with other patient cohorts. In this context, the use of SpO_2/FIO_2 ratios could have helped to better define severity of respiratory dysfunction.[89]

Critically ill children with acute respiratory failure and further organ dysfunctions (e.g., haemodynamic instability) had a significantly higher mortality risk, than children with SOF (45% survival among children with MOF). SAM and/or HIV infection or exposure was also associated with lower survival rates. Of note, 17 out of 28 children with SAM presenting with respiratory dysfunction treated in this study had further organ dysfunctions (e.g., signs of shock).

Malnutrition and HIV have been identified as important risk factors associated with increased mortality among hospitalised children treated in SSA.[135,169-171] Another study conducted in Blantyre, Malawi among children with respiratory dysfunction treated with bCPAP also identified HIV-infection as an important risk factor for mortality.[172]

An increased mortality risk among children with severe acute respiratory infections associated with additional organ dysfunctions (e.g. haemodynamic instability) has been reported in further studies conducted in resource-limited contexts.[74,173] A survival rate of 45% was described in a study from Papua New Guinea among 64 children with respiratory dysfunction treated with bCPAP. This patient cohort was characterized by the presence of important risk factors, similar to patients described in Paper 1 (e.g., septic shock (12.5 % of patients), anaemia (20.3%), signs of heart failure (28.1%), HIV infection (17.2%), SAM (7.8%).[173]

A RCT conducted in a district hospital in Malawi did not show any benefit of bCPAP treatment as compared to supplemental O_2 in the treatment of high-risk children with signs of severe pneumonia.[174] Different factors might have contributed to this outcome e.g.: severity of illness and co-morbidities of enrolled patients (e.g., HIV-infection/exposure, SAM, multi-organ dysfunction), lack of daily supervision by senior physicians, aspects related to the bCPAP system used in the study.[174]

Mortality rates for children with sepsis reported in the literature from high resource settings ranges from 4% up to 50%, depending on severity of illness, associated risk factors as well as geographical location.[85] Refractory shock and/or associated multi-organ dysfunction (e.g., neurological complications, AKI) are factors associated with high mortality risk.[85] In this context, many of the reported deaths among children with severe sepsis occur in the first 48-72 hours of onset of critical care treatment.[85,175-177] Acute respiratory distress syndrome (ARDS) is a common complication among critically ill children with severe infections.[87,88] Khemani et al describe a mortality risk of more than 35% among mostly mechanically ventilated children with severe ARDS (e.g. SpO_2/FIO_2 ratio < 150). The majority of these patients had further organ-dysfunctions and/or other risk factors.[89]

These results emphasize the importance of early identification of signs of critical illness and initiation of efficient treatment in order to reduce risk of disease progression towards severe multi-organ failure.[85] Therefore, essential pediatric emergency and critical care needs to be improved on different levels of referral pathways in resource-limited settings.[24] Non-invasive respiratory support (including bCPAP) has the potential to play an important role in this context. However, limitations of non-invasive respiratory support in the care of children with multi-organ-dysfunction need to be taken into account.[173]

bCPAP: Respiratory dysfunction and co-morbidities

Respiratory function and HIV infection or exposure

The majority of HIV-infections among children can be avoided by efficient prevention of mother to child transmission (PMTCT). Despite considerable improvements in countries in sub-Saharan Africa (including Malawi), a considerable number of HIV-infected, pregnant mothers are not enrolled in PMTCT programs or are not retained in these programs during follow-up.[178,179]

Early infant diagnosis of HIV and early initiation of anti-retro-viral treatment (ARV) in children is part of the WHO strategy to prevent progression to advanced HIV-disease and death.[180] Critically ill children with HIV exposure and/or proven HIV-infection carry an increased mortality risk, in high and in low-resource contexts.[169,181,182] Experience from South Africa also indicates that outcomes of

critically ill HIV-infected children can improve considerably with adequate critical care management, pro-active treatment of opportunistic infections and initiation of ARV-treatment.[183] Therefore, HIV testing and counselling needs to be integrated in routine practice of paediatric critical care units. Presumptive diagnosis of HIV-infection in young children needs to be considered in certain emergency situations until HIV-status can be reliably determined.[38,75] This approach is particularly relevant in children with ARF requiring supplemental O_2 or non-invasive respiratory support. Besides treatment of potential bacterial respiratory infections, rapid initiation of presumptive treatment for *pneumocystis jirovecii* pneumonia (PJP) needs to be considered:

- High dose cotrimoxazole according to WHO guidelines.[38]
- Steroids were found to be beneficial in the management of HIV-infected children with potential PJP in a study conducted in Malawi, in a setting where co-infection with cytomegalovirus and other opportunistic infections cannot be excluded.[76]

Tuberculosis needs to be considered in all children with confirmed or suspected HIV and respiratory failure. POCUS offers opportunities to improve quality of clinical diagnosis of TB in adult patients with HIV. This approach is particularly important in settings with limited access to other forms of imaging and microbiological diagnostics.[184] Even with additional microbiological diagnostic options a definitive diagnosis is achieved only in a certain percentage of children with actual TB.[75,185] In case of clinical suspicion a pro-active approach to presumptive TB-treatment is needed.[75,185] Additionally, in HIV-negative children with respiratory dysfunction, TB is among the potential differential diagnoses. Especially in malnourished children screening for TB needs to be part of routine clinical evaluation.[38,185]

Respiratory dysfunction and cardiac conditions

4 out of 117 children with signs of respiratory dysfunction described in paper 1 had congenital heart disease (CHD), highlighting the fact, that acquired or congenital cardiac conditions need to be considered as a differential diagnosis among children requiring non-invasive respiratory support treatment in resource limited settings.[186,187]. POCUS can play an important role in diagnosis and management of these children.[154,164] More specific diagnosis and management of acquired and congenital heart diseases should be performed with the input of clinicians trained in paediatric cardiology.[164,186,187] Paper 1 was not set-up to draw more specific conclusions in this context.

Respiratory dysfunction and neuro-disability

Three of the 117 children described in Paper 1 had signs of neuro-disability. Experience from PICUs in high-resource settings shows that children with neuro-disability present a considerable proportion of patients requiring prolonged PICU admission in case of critical illness, including the need for respiratory support.[188] If units in low-resource settings improve options of respiratory support, health facilities need to prepare for the care of children with particular needs.

Respiratory dysfunction and further co-morbidities: Sickle cell disease (SCD), malignancies

SCD considerably contributes to paediatric morbidity and mortality in SSA. SCD needs to be considered as an important co-morbidity in critically ill children presenting with respiratory dysfunction and other associated clinical features (e.g., severe anaemia, cardio-vascular dysfunction, neurological complications).[77,78] In the clinical setting, in which the presented bCPAP-study (Paper 1) was performed access to reliable SCD-testing was limited. Point of care-SCD tests are important and pragmatic diagnostic tools in emergency and critical care settings in SSA.[77] Access to good quality supportive care can improve outcomes among critically ill children with SCD.[78] Reliable O_2-supply and non-invasive respiratory support plays an important role in this context. Improved critical care for children with SCD needs to be linked to comprehensive follow-up arrangements.[77]

In the cohort described in Paper 1 no patients with malignancies were included. However, context-adapted supportive care, including non-invasive respiratory support has the potential to improve outcome of some children with malignancies presenting with an acute illness.[189] [190]

bCPAP: Technical aspects of bubble CPAP devices

In order to explore the full potential of bCPAP and prevent complications certain technical and clinical aspects need to be taken into account.

Air/ O_2-flow used in bCPAP set-ups

Air/O_2 flow used in bCPAP devices needs to match "peak tidal inspiratory flow (PTIF)" of patients in order to prevent the risk to impose additional work of breathing during the respiratory cycle. In this context the same principles apply as in high flow-nasal cannula (HFNC) set-ups.

Milesi et al performed spirometry measurements in 44 children (< 6 months of age; median weight: 4.3 kg (interquartile ranges: 3.5-5.0kg) treated with HFNC for acute viral bronchiolitis. PTIF in these young children was 1.68 liters/min/kg (95% CI: 1.51-1.85; min-max: 0.67-3.00 liter/min/kg). In this study PTIF did not correlate with clinical signs of respiratory distress, respiratory rate, required FIO_2 or pCO_2.[160] Additional studies also suggest that optimal HFNC flow rate to reduce work of breathing in infants and young children is approximately 1.5-2.0 liter/min per kg.[161,162] Similar flow rates needs

to be used in bCPAP set-ups. Additionally, the air/O_2 flow in bCPAP set-ups needs to be adapted to assure continuous "bubbling" at the level of the resistor through-out the respiratory cycle to compensate for leaks at the level of the interface or associated with mouth opening. A study conducted in newborns treated with bCPAP documented required air/O_2 flow of > 2 liters/min per kg, while flows needed to be increased with increasing pressure settings.[191]

The bCPAP device used in Paper 1 had a maximum flow of 16 liters/min (8 liters air/min and 8 liters oxygen/min). This device is therefore able to provide adequate flows for children with a weight up to around 11-12 kg, if required flows are estimated for children above 6 months of around 1.5 liters/min per kg. Similar bCPAP devices with a maximum flow of 20 liters/min are available and are a better option. However, also these bCPAP devices should only be used in children weighing up to 13-14 kg in order to match patient's inspiratory demands. In the study presented in Paper 1, the mean age of the patient was 7 months and the mean weight was 6.4 kg (unpublished data).

Like in HFNC-treatment, nasal prongs used in bCPAP set-ups needs to cover around 75% of the nostrils and should not completely seal the nostril, in order to allow entrainment of ambient air, in case provided air/O_2 flow does not match PTIF. If ambient air is entrained during peak inspiratory phases it needs to be assumed that FIO_2 of the actually inspired air/O_2 will be different during these phases, than the FIO_2 set at the bCPAP machine. Using interfaces sealing the nostrils, like suggested in a bCPAP-study conducted in northern Uganda,[192] can expose patients to flow restriction during phases of inspiration when the provided air/O_2 flow does not match peak inspiratory flow demands. In an RCT conducted in a district hospital in Malawi the maximum flow of 10 liters/min of bCPAP set-ups used for the care of children with respiratory dysfunction might not have been sufficient to match PTIF of children weighing more than 6-7 kg. In this study at times non-vented nasal masks were used as interfaces which might not have allowed entrainment of ambient air during phases when inspiratory demands were not matched.[174]

Future research can help to better determine optimal air/O_2 flow needed in bCPAP, especially in older children. bCPAP devices able to provide higher flows, matching peak inspiratory demands of older children (>13-15 kg) may be beneficial. In order to provide optimal support by bCPAP it is important that set-ups follow the conventional set-up for bubble CPAP (see figure 6) in order to guarantee pressure stability and low flow resistance withing the system. Alterations of known principles of bCPAP set-ups can be associated with increased imposed work of breathing.[138,139]

Humidification of the air/oxygen flow used in bCPAP devices

WHO recommends to use heated humidification in children requiring O_2 flow of >4 liters/min via nasal cannula for more than 1-2 hours.[39] High air/O_2 flow used in bCPAP or HFNC devices needs to be warmed and humidified (conditioned) to avoid drying of nasal secretions, maintain mucosal integrity and muco-ciliary function of the upper and lower respiratory tract.[39,193] Cold "bubble humidification devices" may have limited efficiency to humidify air/O_2 flow.[194]

Studies using specific simulation techniques show that during normal spontaneous inspiration of newborns, an important part of the warming process of inspired ambient air takes place in the anterior part of the nasal cavity.[195] Nasal airflow dynamics is an important element in the use of nasal bCPAP or HFNC.[196] In this context mouth leaks and flow rates need to be considered in the evaluation of flow dynamics of nasal air/O_2 flow.[197] Additionally, the degree of humidification and temperature of air/O_2 flow also depends on the ambient temperature.[198]

Humidifier and humidification fluid needs to be changed daily or during each shift in order to prevent nosocomial infections. The humidifier in the bCPAP set-up used in Paper 1 is warmed by the heat of the compressor of the bCPAP-set-up. However, further efforts need to be undertaken to optimize affordable options for warming and humidification of air/O_2 flow in bCPAP devices.

Oxygen concentration

In healthy children an SpO_2 >95% and PaO_2 between 80 and 100 mmHg should be expected.[98] While hypoxaemia and associated reduced O_2-delivery is associated with an increased mortality risk,[199,200] there is increasing evidence that extreme hyperoxia should be avoided in critically ill adults and children.[98,201,202] WHO ETAT guidelines (2016) recommends an SpO_2 target $\geq$ 94% in the treatment of critically ill children with more than one organ-dysfunction.[39] In children with severe pneumonia or acute viral bronchiolitis and no other organ dysfunctions (SOF) SpO_2 levels $\geq$ 90% are acceptable according to WHO recommendations.[39] These recommendations were followed in the Paper 1: SpO_2 targets were in general $\geq$ 94%. In children with SOF SpO_2 > 90-92% were accepted. FIO_2-levels could be titrated accordingly if dedicated bCPAP set-ups were used. However, in view of the high-workload and limited number of available SpO_2-monitors, SpO_2 could often only be monitored intermittently.

The European Society for Paediatric and Neonatal Intensive Care/ESPNIC initiated a consensus conference of international experts in paediatric mechanical ventilation (Paediatric Mechanical Ventilation Consensus Conference (PEMVECC) in 2017.[98] According to PEMVECC SpO_2 targets

for critically ill children with non-cardiac paediatric ARDS (PARDS) are based on previous recommendations (Paediatric Acute Lung Injury Consensus Conference):[98,203] SpO_2 between 92 and 97% when PEEP <10 cm H_2O and 88–92% for PEEP ≥10 cm H_2O.

Particularly in preterm infants hyperoxaemia should be avoided in order to prevent development of retinopathy of prematurity. SpO_2 targets recommended for term and preterm newborns are in the range of 90-95%.[204,205]

During cardio-respiratory resuscitation (CPR) of children high FIO_2 levels should be used (for newborn resuscitation see specific guidelines). After resuscitation (return of spontaneous circulation/ROSC) FIO_2 can then be titrated according to SpO_2 targets. [127,206]

A pilot RCT conducted in the UK ("Oxy-PICU") tested feasibility and safety to conduct a larger trial comparing a restrictive SpO_2-target (88-92%) with a more liberal peripheral O_2-saturation target (>94%). No significant difference between the two patient groups was documented.[207] Recruitment for the larger Oxy-PICU RCT is ongoing.[208]

A recent RCT evaluating different SpO_2 targets in critically ill adult patients highlights the great care that must be taken when evaluating modification of existing SpO_2 targets in critically ill patients.[209] This trial randomized adult patients with ARDS to a conservative O_2 arm (target SpO_2 88% to 92%) or a liberal O_2 arm (target SPO_2 ≥96%). The data and safety monitoring board of this RCT stopped investigations early because of safety concerns and a low likelihood to be able to determine a significant difference between the study groups in terms of primary outcomes (mortality at 28 days). Results of the RCT determined a trend to a higher mortality risk in the conservative O_2-study group.[209] The surviving sepsis campaign expert panel suggests SpO_2 targets between 92-96% in adult patients treated for severe ARDS due to COVID-19 disease.[202] The group strongly advices against increasing FIO_2 to target SpO_2 > 96%. The panel also issues a strong recommendation to avoid SpO_2 levels < 90% in critically ill adult patients with severe ARDS.[202]

SpO_2 targets suggested by WHO for children with respiratory dysfunction with and without further organ dysfunction are a pragmatic interpretation of existing evidence.[39,210] Research evaluating SpO_2 targets among critically ill children conducted in low-resource settings needs to take into account important factors e.g.: Hb levels, cardio-vascular function, neurological complications (e.g. cerebral malaria).[210,211] Especially in malaria endemic areas, a considerable number of critically ill children present with low baseline Hb levels (see FEAST-study),[131] resulting in reduced O_2-carrying capacity and potentially reduced O_2-delivery.[210] Severe anaemia is

associated with increased mortality risk among critically ill children in malaria-endemic regions (Paper 3).

It is important to note that SpO_2 levels can overestimate measured arterial oxygen saturation especially in SpO_2 ranges < 90%.[212] A prospective, observational study conducted in 5 paediatric intensive care units in North America showed a close correlation between SpO_2 and arterial O_2-saturation in ranges between 91% and 97%. However, this relation is less reliable in the range of oxygen saturation levels below 90%. In these ranges SpO_2 can overestimate arterial oxygen saturation levels considerably.[212]

In order to follow WHO and international guidelines, bCPAP and other devices used for non-invasive respiratory support need to have the option to adapt FIO_2, in order to achieve recommended SpO_2 targets with the lowest FIO_2 required.[39,98] SpO_2 levels should be monitored and maintained as currently suggested by WHO and international guidelines.[39,85,98,210,212]

CPAP pressures

Studies conducted in children with acute viral bronchiolitis demonstrate that pressures of 6-7 cm H_20 are associated with optimal decrease of work of breathing (WOB) in this clinical condition.[101,103] Average pressures used at the start of bCPAP treatment in Paper 1 was 6.7 cm H_2O. bCPAP pressure were mostly kept $\leq$8 cm H_2O and weaned gradually if clinical condition allowed. Baro-trauma and air leaks using bCPAP-pressures in these ranges seem unlikely.[100] In case of acute clinical deterioration in the setting described in Paper 1, children could be evaluated using POC-lung ultrasound.[164] Mobile CXRs were not available during the study period.

Interfaces

Well-adapted interfaces are needed to provide efficient respiratory support via bCPAP devices. These interfaces should have the following characteristics:

- Internal diameters of nasal prongs as well as connected inspiratory and expiratory tubing should be of adequate size in order to function with minimal flow resistance.[138,139,213]
- bCPAP nasal prongs, as in HFNC, should not occlude more than around 75% of the nostrils in order to allow entrainment of ambient air in case inspiratory flow demands are not completely matched.[160,162] Leaks can be compensated by increasing air/O_2 flow.
- Design of interfaces and connected tubing should allow easy and quick connection on the child´s head and face. No damaging pressure should be exerted on facial skin, nasal septum, alae and mucosa. Any traction (e.g., via air/O_2-tubing) on interfaces needs to be avoided.

- Nasal masks are additional options.[214] However, design of masks, associated tubings and air/O_2 flow provided by the bCPAP device need to ensure that inspiratory phase is unrestricted.

Further research in design of good quality, affordable interfaces is needed in order to optimize efficacy of bCPAP systems as well as patient comfort and safety.

Electricity supply

The paediatric department in Lilongwe in 2014 had a relatively reliable back-up generator, in case of interruptions of the electricity supply via the national grid. In clinical zones where O_2-concentrators are operated, electrical back-up systems needs to be put in place.[93] Otherwise safety of O_2-therapy and non-invasive respiratory support cannot be guaranteed. Essential biomedical equipment needs to be identified (e.g., O_2 concentrators, bCPAP set-ups, monitors, emergency light) and needs to be connected to reliable electricity supply sources. Units needs to try to establish additional O_2-back up systems. Portable O_2-concentrators with in-built batteries or O_2 cylinders can bridge electrical supply interruptions.

Sources of oxygen

In case not enough dedicated bCPAP set-ups were available, O_2-cylinders were used to provide O_2-flow required to provide bCPAP. With this suboptimal set-up, FiO_2 could not be adapted but O_2-flow could still be humidified. However, humidification of O_2-flow was not warmed. Patients were switched to dedicated bCPAP set-ups whenever such a device was available. No significant difference in outcomes in children treated with the different bCPAP set-ups were documented. However, the authors of Paper 1 strongly recommend to use dedicated bCPAP set-ups.

The use of O_2-cylinders as source of supplemental O_2-therapy or O_2 supply for bCPAP has considerable disadvantages: Logistics required to guarantee reliable O_2 supply via cylinders needs to be well organized. Failures assuring safe and continuous O_2-supply can be associated with serious risks for critically ill patients.[93]

Studies suggest that the use of O_2-concentrators with adequate electricity back-up for provision of O_2 in low-resource settings is a cost-effective option.[93,96] Reliable, affordable O_2-supply is a major challenge in many settings in SSA.[82] Deficiency to match O_2-demands in resource-limited contexts has been highlighted during the SARS-CoV2 pandemic.[215-217ai] Renewable energy solutions (e.g. solar

[i] The author was one of the clinicians interviewed for this newspaper publication: https://www.theguardian.com/global-development/2020/aug/10/fighting-for-breath-how-the-medical-oxygen-industry-is-failing-african-hospitals

systems) offer cost-effective opportunities to provide electricity and the possibility to run O_2-concentrators and other biomedical equipment even in remote settings.[42,43] WHO and other agencies advice on context-adapted options for reliable O_2-supply systems.[93,215,217a]

bCPAP treatment and adaptation to changing respiratory function

Persistent or worsening respiratory dysfunction

In case of limited improvement of WOB and/or oxygenation after starting bCPAP, only an escalation of CPAP-pressure up to 8 cm H_2O was recommended in order to avoid risks of complications (e.g., air leaks/pneumothorax, reduction of venous return). The objective was to provide pragmatic management protocols in a clinical setting with high work-load. Children not improving with this level of non-invasive respiratory support would potentially benefit from mechanical ventilation in high-resource settings.[98] SpO_2 targets were in general $\geq$ 94%. In children with SOF, $SpO_2 \geq$ 90-92% were accepted.[39]

Management of acute deterioration

In the study setting described in paper 1, clinical teams were trained to follow emergency procedures outlined in ETAT and other paediatric life support algorithms, in case of any acute clinical deterioration.[38,40] In addition, training associated with the introduction of bCPAP can follow similar principles as clinical crisis management in mechanical ventilation. A systematic approach to the assessment of patients and review of biomedical equipment in case of sudden respiratory deterioration is outlined in paediatric life support guidelines.[40] Vital organ functions of patients need to be stabilized immediately, followed by a structured management approach (e.g. using the acronym DOPE):

- D: Displacement of the interface
- O: Obstruction of airways, interfaces or air/oxygen tubing
- P: Problems associated with the patient (e.g., evaluation for pneumothorax, signs of shock)
- E: Problems associated with biomedical equipment; leaks in air/oxygen tubing etc.

If during evaluation of patient and equipment, problems are not immediately identified it is advised to rapidly switch to an alternative O_2-source, while a team member evaluates air/O_2-tubing as well as the bCPAP-machine for malfunction. Care-takers and non-clinical staff, working in clinical areas can be involved in pragmatic training and should be encouraged to immediately notify clinical teams in case of concerns regarding clinical conditions of patients and/or malfunctioning equipment.

Improving respiratory function: weaning of non-invasive respiratory support

In Paper 1, FiO_2 was reduced when SpO_2 in critically ill children was consistently $\geq$ 94%.[39] If signs of WOB and RR improved with SpO_2 remaining consistently $\geq$94% (with $FIO_2 \leq 0.5$) bCPAP pressures were reduced gradually. If the patient remained stable on a bCPAP level $\leq$ 5 cm H_2O (with FIO_2 <0.3-0.4), a trial "off bCPAP" was started and the child was placed on low-flow O_2 (1–2 liters O_2/min). In cases of clinical deterioration, bCPAP was restarted. The duration of the weaning process was guided by the child's clinical progress.

Non-invasive respiratory support: Alternatives to bCPAP

Non-invasive respiratory support: High-flow-nasal cannula humidified air oxygen/HFNC

HFNC is an important mode of non-invasive respiratory support in newborns and children, which can also be initiated in EDs.[97,99,161,218,219] Different HFNC-devices exist and have been compared in the care of premature newborns with respiratory dysfunction.[220] Trends in certain publications suggest that CPAP might be more efficient than HFNC in the treatment of acute respiratory dysfunction, particularly in young infants.[166,221-223] Some studies in newborns and children indicate that the use of HFNC is associated with a lower risk to cause nasal trauma, than the use of nasal CPAP,[107,223] highlighting the importance of good quality interfaces in the use of HFNC or nasal CPAP.

An important RCT conducted in a critical care unit Bangladesh showed that critically ill children with severe pneumonia and hypoxaemia treated with bCPAP had a significantly lower mortality rate (4%) compared with a group of patients treated with high-flow O_2 (mortality rate 13%) or low-flow O_2 (15% mortality rate).[166,222] However, it needs to be noted that in the high-flow O_2 treatment used in this study the maximum flow rate was 12 liters/min, which might have been relatively low to match peak inspiratory flow demands for children with a weight above 6-8 kg.[160-162]

A RCT evaluating benefits of HFNC and CPAP is currently being conducted on several PICUs in the UK ("First-ABC").[224,225] This RCT compares clinical outcomes of children (term newborns to 16 years) with an acute illness associated with respiratory dysfunction treated with HFNC or CPAP. Children requiring non-invasive respiratory support post extubation are also included in the study. Among the exclusion criteria are: immediate need for intubation and invasive ventilation (e.g. severe hypoxaemia, upper airway obstruction, MOF).[225] Results of this trial can help to guide future research options and clinical care.

Non-invasive respiratory support : Bi-level Positive Airway Pressure (BIPAP)

Different forms of non-invasive ventilation are used for treatment of children with respiratory dysfunction.[97,98] The role of non-invasive bi-level positive airway pressure (BIPAP)[j] in the care of critically ill children is summarized in the PEMVECC recommendation (2017).[98] According to PEMVECC increasing evidence exists, suggesting the value of non-invasive BIPAP modes in different clinical scenarios e.g.:

- Respiratory dysfunction in children associated with cardiac conditions and asthma.
- Non-invasive BIPAP can be considered in children with less severe PARDS.[104]
- BIPAP is among options for non-invasive respiratory support post-extubation.

In settings, where mechanical ventilation can be provided, clinicians need to ensure not to delay intubation and invasive ventilation in patients who can't be stabilized with non-invasive respiratory support. In this context vital organ functions and response to treatment needs to be monitored closely.[98] Additionally, PEMVECC identifies important knowledge gaps, regarding use of non-invasive BIPAP in high-resource contexts:[98]

- More evidence is needed to determine the role of different modes of non-invasive respiratory support in different clinical scenarios. Optimal timing of escalation of different modes of non-invasive and invasive respiratory support needs further evaluation.[98]
- Further research is needed, regarding the use of optimal interfaces for different modalities of non-invasive respiratory support in children (e.g. full face mask, oral-nasal masks or helmets). Alternating different interfaces in order to reduce risks of skin and mucosal lesions might be beneficial.[98]

In the care of premature newborns early initiation of nasal intermittent positive pressure ventilation (NIPPV) appears to be superior to nasal CPAP in the management of respiratory distress syndrome.[226]

Critical care in the context of the SARS-CoV2 pandemic highlights the importance to reduce risks of aerolisation and infection control measures (e.g. ventilation of clinical zones, personal protective equipment for health workers, adequate adaptation of medical devices and ventilation circuits) during the use of non-invasive respiratory support.[202,227,228]

[j] The term non-invasive BIPAP is used in this thesis as equivalent term to non-invasive positive pressure ventilation (NPPV).

Future research evaluating the role of non-invasive BIPAP in the management of children with acute respiratory failure with or without additional organ-dysfunction treated in resource-limited contexts will be of high value.

Paper 2: Mechanical ventilation of patients with acute respiratory failure following neurotoxic snakebites

Of the 174 patients snakebite victims admitted to ICU in Lacor hospital between January 2006 - November 2017, 60 (36.5%) patients presented with ARF, requiring mechanical ventilation. Most of these 60 patients suffered from ARF with minimal signs of additional organ dysfunction (SOF). ARF was mostly caused by transient muscle paralysis associated with neuro-toxic snake-bite envenomation. Respiratory dysfunction was not associated with severe primary lung injury. Therefore, these patients could be mechanically ventilated with relatively low ventilation pressures and FIO_2. The clinical team could anticipate that in this specific condition, mechanical ventilation needed to be maintained for a relatively short period of time, which is different to a clinical situation of patients who suffer from severe ARDS and MOF.

As diagnostic options were limited in the study context other causes of neurological dysfunction like intra-cranial bleeding could not be excluded. However, if there were no focal neurological signs suggesting an upper motor-neuron lesion, no signs of raised intra-cranial pressure and no external signs suggesting coagulopathy associated with snake-bite envenomation, intra-cranial haemorrhage was an unlikely diagnosis.

WHO management guidelines suggest that neuro-toxic snake bite envenomation in Northern Uganda can be caused by different snake species, including black Mambas.[121] The medium length of stay on the ICU of snake-bite victims, who required mechanical ventilation was 5 days, suggesting that the toxin of neurotoxic snakes in this region mostly has a transient effect.

The mortality of snakebite patients developing paralysis and ARF is likely to be high without mechanical ventilation.[229-232] As fatality rate of snakebite victims who required mechanical ventilation in the reported cohort was as low as 16.7%, it can be assumed that mechanical ventilation was a life-saving intervention for the majority of study patients with ARF.

The medium age of the 60 patients requiring ventilation was 28 years (interquartile ranges: 16-35 years), suggesting that mainly physically active, young people were affected by snake-bites. 17 of these patients were younger than 18 years. Mortality among children (N=17) was significantly higher

than among the 43 adult patients (35.3% *vs*. 9.3%; p=0.02). Two of the 17 children suffering from ARF following snake bite envenomation were younger than 5 years, both of whom died. Reported snakebite fatality rates are generally higher in children than in adults. Possibly the smaller volume of distribution and consequently higher toxin levels in children is one of the factors associated with this higher mortality risk.[121,233]

Due to challenges in the supply chain and financial constraints, only a small number of study patients (16.7%), who required mechanical ventilation received antivenom. The antivenom used during the study period is not among products currently recommended by international experts.[121,163] Findings from Sri Lanka showed that snakebite victims presenting with signs of severe neurotoxicity progressed to respiratory failure requiring mechanical ventilation even when antivenom had been given. These results suggest that antivenom alone is not sufficient to treat critically ill snakebite victims.[234] A study from India reported no fatalities in 51 patients with neurotoxic snake envenomation after they were treated with a combination of antivenom therapy and mechanical ventilation.[235] In the cohort of patients with ARF in Paper 2, it could not be determined whether early administration of adequate doses of appropriate antivenom combined with advanced airway management and mechanical ventilation could have improved survival rates or reduced the required duration of mechanical ventilation.

In the study described in paper 2, acetyl-cholinesterase inhibitors (ACHEIs; e.g. neostigmine) were not used in the management of patients with neurotoxic snakebite syndromes. ACHEIs might only be beneficial in patients exposed to snake-neurotoxins leading to a competitive effect at the post-synaptic part of the neuro-muscular junction.[121,232,236] Patients exposed to black Mamba bite envenomation can present with signs of muscle paralysis, including ARF associated with muscle fasciculation.[121,232,236] The presence of muscle fasciculations can indicate a neurotoxic effect of the snake venom, which is associated with a depolarizing effect at the neuro-muscular endplate. It is advised not to use ACHEIs in these clinical scenarios.[121,232,236] Further research regarding specific benefits of ACHEIs in the treatment of neuro-toxic snake-bite envenomation is needed.[232,236]

Snake venoms can present diverse mechanisms of action at the level of the neuro-muscular junction associated with considerable geographical, interspecies and intraspecies variations.[232,236] For critical care clinicians it can therefore be difficult to determine in emergency situations to which extent these neurotoxins have depolarizing effects at the neuro-muscular junction.[232,236] It may be good practice

to use non-depolarizing muscle relaxing agents during anaesthetic induction if intubation is needed and to avoid the use of suxamethonium (the author's consideration).

A strategy to reduce deaths and disability associated with snakebites in SSA needs attention to preventive measures. Strengthening of context-adapted treatment of critically ill patients, including snakebite victims, on different levels of referral pathways is important.[236] Provision of efficient antivenoms needs to be integrated in clinical care of snake-bite victims in peripheral health facilities.[236] Paper 2 indicates that under certain circumstances mechanical ventilation can be provided safely on ICUs in rural hospitals in SSA. Non-invasive respiratory support was not available in the study setting described in Paper 2. The role of non-invasive BIPAP modes in the treatment of snake-bite victims could be included in future research. Additionally, ICUs offering advanced respiratory support in resource-limited contexts need to be prepared for the care of critically ill children.

Mechanical ventilation: Quality and safety aspects

Set-up of an ICU in a regional hospital in northern Uganda – some considerations

The study setting in Lacor Hospital in northern Uganda is comparable to other rural healthcare regions in SSA which are characterized by single hospitals, who support a network of peripheral health facilities. In contrast to many other rural health facilities in SSA, Lacor Hospital runs an ICU which can provide intensive care interventions including mechanical ventilation.[141 237,238] To put this into perspective, a recent survey revealed that the density of ICU beds was one ICU bed for every one million inhabitants in Uganda.[239] In order to provide good quality ICU services sustained multi-disciplinary efforts are under-taken in Lacor Hospital, including:

- EECC services adapted to high workload and resource limitations on all levels of the hospital's patient circuit are strengthened.
- The hospital has strong non-clinical supporting services e.g.: biomedical and technical department, pharmacy/supplies, laboratory as well as blood bank.
- Members of the anaesthetic department lead clinical ICU-services and ensure good interaction with other clinical departments (e.g., paediatrics, surgery, maternity).
- Efforts are undertaken to provide good working conditions for health workers. Despite rotation of staff members, skill levels in the ICU-team are maintained. Clinicians and nurses working on the ICU benefit from continuous medical education.

Additionally, a formal clinical officer training program in anaesthesia was introduced in Lacor Hospital. The hospital also runs training programs in nursing and midwifery, besides other training modules.[240] Lacor Hospital also serves as a teaching hospital for medical students and internes.

In hospitals providing advanced respiratory support, indications for mechanical ventilation need to be carefully considered. Benefits and risks for patients as well as available resources need to be balanced.[241] In settings with considerable resource limitations the definition of levels of critical care (Table 1) can help health facility management teams to define realistic objectives for their institutions. The establishment of a "level 3 critical care unit" can be considered if essential levels of EECC are strengthened within a referral pathway and hospital patient circuit. A large number of patients can benefit from interventions provided on level 1 & 2 critical care units. Multi-disciplinary arrangements required to successfully establish good quality level 1 & 2 units are the foundation on which the potential set-up of level 3 units can be based on.

Biomedical devices for respiratory support – some important considerations

In Paper 2, ventilators capable to provide intermittent positive pressure ventilation (Glostavent; Diamedica, Bratton Fleming, UK) were used on the ICU in Lacor Hospital. The Glostavent ventilators can be used independent of pressurized medical gases and are compatible with different oxygen sources (e.g. O_2 concentrators, O_2-cylinders).

WHO suggests technical specifications for ventilators used for non-invasive and invasive respiratory support in the context of the SARS-CoV2 pandemic.[242] Some of the following elements need to be considered in the selection or development of context adapted devices, used for non-invasive and mechanical ventilation in resource-limited settings:

- Inbuilt battery with several hours of autonomy time, allowing use during transfer and power cuts.
- Inbuilt compressor to ensure independence of pressurized medical air. Ventilators need to be compatible with use of low-pressure O_2-sources (O_2-concentrators) as well as pressurized O_2 sources (O_2 cylinders and piped wall O_2).[93,242]
- Pressure or volume controlled ventilation modes need to be equipped with adequate alarm settings.
- In order to allow gradual weaning of respiratory support, ventilators need to allow un-restricted spontaneous ventilation. Ideally the ventilator is equipped with a triggered (flow or pressure trigger) support mode e.g.: Assist control, synchronised intermittent mandatory ventilation

(SIMV)/pressure support. Hybrid techniques like pressure regulated volume control or volume assured pressure support are interesting options,[243] but might not be an immediate priority (author's opinion).

- For non-invasive respiratory support the ventilator needs to have a CPAP/ pressure support mode with or without the possibility to set a back-up-rate.
- Ventilators need to be set-up for paediatric and adult use.

For all biomedical equipment energy consumption, maintenance, repair as well as availability and costs of spare parts as well as consumables needs to be considered. SOPs need to be put in place to guide IPC measures. Biomedical equipment used in low-resource settings, needs to under-go thorough biomedical testing. These procedures needs to follow standards for biomedical equipment defined by WHO.[244] Pragmatic training programs for clinical and biomedical teams need to accompany the introduction of biomedical equipment.

Paper 3: Management of haemodynamic instability

Paper 3 describes the re-analysis of data from a previous large RCT conducted in East Africa (FEAST-study).[131] Results of this analysis indicate that in the treatment of critically ill children with haemodynamic instability, fluid resuscitation with normal saline and HAS (5%) can be associated with respiratory and neurological dysfunction, hyperchloraemic acidosis as well as reduction in Hb levels. Fluid resuscitation with unbuffered electrolyte solutions can cause harm and therefore should be avoided. The effects of lower volumes of isotonic, electrolyte balanced resuscitation fluids needs to be evaluated further. Hb levels need to be monitored carefully in critically ill children receiving IV fluid boluses.

Paper 3: Pragmatic, clinical training associated with the preparation of the original study

During the preparation of the FEAST-study and during time of recruitment, a paediatric training team (page 12 of the original publication) invested considerable efforts to integrate study procedures in routine clinical activities of participating units.[131, k] Health workers recruited for the FEAST-study, participated in the care of critically ill patients. On-going capacity building in combination with the introduction of some biomedical equipment and consumables ensured that all children treated in participating units benefitted from improvements in essential elements of critical care.

[k] The author contributed substantially to clinical training at the four Ugandan study- sites of FEAST. Units in Uganda recruited the majority of patients for this RCT.

A protocol amendment was needed in June 2010 to increase the sample size from the initially anticipated 2800 to 3600 patients, because the mortality in the cohort of study patients was lower than anticipated (page 5 of the original publication).[131] Potentially this lower than expected risk of paediatric hospital mortality indicated the positive impact of the quality improvement measures in essential emergency and critical care associated with the FEAST-study. However, it is important to note that multiple factors could have contributed to this lower than expected mortality.

WHO definition of shock and circulatory impairment

In the revised WHO ETAT-guidelines (2016) important results of the FEAST-study were taken in consideration.[39] A WHO expert committee reviewed degrees of haemodynamic instability (see Table 14): ***Shock*** was defined as the presence of the following clinical signs: cold extremities, capillary refill time > 3 seconds, weak and fast pulse. The term ***"circulatory impairment"*** is used if only 1 or 2 of these clinical signs are detected. While the presence of circulatory impairment needs to be considered as a sign of critical illness, these children should not receive IV fluid bolus resuscitation.[39]

WHO also gives management recommendation of haemodynamic instability in the presence of specific clinical conditions e.g.: severe anaemia, severe dehydration, SAM. Of note, patients with severe dehydration as well as patients with SAM were not included in the FEAST-study nor in the Paper 3 analysis.[131] Further details, regarding the management of children with haemodynamic instability treated in resource-limited contexts are discussed in the following paragraphs.

Clinical phenotypes in children presenting with haemodynamic instability

In Paper 3, 1991 out of 3141 patients (stratum A) recruited in the FEAST study were classified in cluster 1. These patients had the least derangement in terms of respiratory, cardio-vascular and neurological function as well as Hb concentration and lactate levels, compared with other study participants. The mortality risk among patients classified in cluster 1 was low (around 1% mortality in the non-bolus group and 4% in the bolus-group). According to the revision of WHO Guidelines (2016) for the treatment of critically ill children, the circulatory status of most patients in cluster 1 could be classified as "impaired circulation". According to these guidelines it is not recommended to administer rapid IV fluid infusion in this clinical context (Appendix, Table 14).[39]

Paper 3 identified two further clusters of patients with certain clinical phenotypes who showed comparable response to clinical management and outcomes. Patients in these clusters had considerably higher mortality-risks than patients in cluster 1.

Cluster 2 (n=795) consisted of patients with severe anaemia (Hb levels <5 g/dL), high lactate-levels and high cardiovascular scores. The mortality in this group of patients was high (14% in the non-bolus group and 21% in the bolus group). An inverse relationship was observed in cluster 2 between low Hb levels and high lactate concentrations. Additionally, low bicarbonate levels and low base excess were documented. These results suggests that baseline hyperlactataemia and metabolic acidosis was largely caused by impaired O_2 carrying capacity and reduced O_2 delivery. In cluster 2, administration of fluid blouses was associated with worsening respiratory as well as neurological function. These important results of the FEAST-study were taken in consideration in revised WHO ETAT-guidelines (2016): Patients with severe anaemia and haemodynamic instability should not receive IV fluid boluses before transfusion. Maintenance fluids can be started during preparation of safe blood transfusions (Appendix, Table 14).

Cluster 3 (n=384) was characterised by extremely high respiratory and neurological scores, but better maintained Hb levels. Among the three clusters mortality was highest in cluster 3 (26% in the non-bolus group and 23% in the bolus group).

The results from Paper 3 indicate that context-adapted support of all vital organ-functions is needed in order to substantially improve clinical outcomes in critically ill children with haemodynamic instability treated in resource-limited contexts.

Respiratory support for children with haemodynamic instability

Paper 3 describes the impact of fluid resuscitation on vital organ functions. In IV bolus recipients cardio-vascular scores decreased transiently at 1 h after admission. However, during later measurements this effect on cardio-vascular function was not sustained. Importantly, respiratory and neurological scores, Hb levels as well as bicarbonate, chloride levels and base excess worsened in the early hours after fluid bolus administration (Paper 3, table 2).

The endpoint review committee in the FEAST study had only limited information to judge if fluid resuscitation contributed to increased "extra-vascular lung water" and associated deteriorating respiratory function. While SpO_2 was monitored, no SpO_2/FiO_2 ratios were documented.[87-89] No POC-lung-ultrasound or echocardiography was available in the FEAST-study.[131,164,165]

International guidelines suggest a pro-active approach in terms of respiratory support in the management of children with septic shock, who require fluid resuscitation.[85,98,104] As outlined above, mechanical ventilation should only be considered as a safe management option in hospitals with adequate resources and skill-levels (Paper 2). However, also supplemental O_2 and non-invasive

respiratory support have the potential to improve clinical outcome of critically ill patients with haemodynamic instability and signs of respiratory dysfunction treated in resource-limited settings. Further research is needed to optimize benefit of non-invasive respiratory support in children with multi-organ dysfunction.

Fluid resuscitation in shock: How much fluids to give?

WHO Guidelines 2016 (Appendix Table 14),[39] designed for resource-limited settings suggest to treat children with signs of shock with 10-20 ml/kg of isotonic fluids infused over 30-60 min. Should signs of shock persist a further 10 ml/kg of isotonic fluids should be given over 30 min. Children with SAM and signs of shock should receive 10-15 ml/kg over the first hour. In children with haemodynamic instability and severe anaemia no pre-transfusion bolus should be given. Maintenance fluids can be started for these patients, while rapidly preparing administration of safe RBC transfusions. [39] This is a far more cautious approach as the fluid resuscitation of septic shock suggested by the "SSC paediatric guidelines (2020)" for high-resource contexts: *"In healthcare systems with availability of intensive care, we suggest administering up to 40–60 mL/kg in bolus fluid (10–20 mL/kg per bolus) over the first hour, titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence)".* [85]
The SSC-paediatric guidelines (2020) suggest for healthcare systems with no availability of level 3 intensive care: *"In the absence of hypotension, we recommend against bolus fluid administration while starting maintenance fluids (strong recommendation, high quality of evidence). If hypotension is present, we suggest administering up to 40 mL/kg in bolus fluid (10–20 mL/kg per bolus) over the first hour with titration to clinical markers of cardiac output and discontinued if signs of fluid overload develop (weak recommendation, low quality of evidence)".* The SSC expert team recommends slightly higher fluid volumes over a potentially shorter period of time as suggested by WHO guidelines (2016).[39] Paper 3 provides arguments to follow the more cautious approach recommended by WHO (Appendix, Table 14).

In recommendations for hemodynamic monitoring for critically ill children by the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) a less aggressive approach to fluid resuscitation with smaller boluses (5-10 ml/kg) is suggested. Careful monitoring of haemodynamic parameters is recommended in order to assess fluid responsiveness.[154] Using small bolus volumes of not more than 5-10 ml/kg and review of clinical response (e.g., respiratory rate, SpO_2/FIO_2,

haemodynamic parameters, Hb levels, neurological function, urine output) may be an appropriate approach for the treatment of critically ill children with signs of shock in resource-limited settings.

Children who do not show all clinical signs of shock and are not hypotensive should not receive fluid boluses. Maintenance fluids should be started in these patients (WHO Guidelines 2016).[39,85,128]

Fluid resuscitation: Which IV fluids to use?

Paper 3 indicates that hyperchloraemic acidosis associated with administration of normal saline or HAS 5% (constituted in "un-buffered" electrolyte solutions) is an important factor contributing to adverse outcomes among critically ill children with haemodynamic instability treated in malaria-endemic low-resource contexts. Further studies conducted in high-resource settings suggest that the use of electrolyte balanced IV crystalloids as compared to unbuffered IV solutions in seriously ill adults and children is associated with improved clinical outcomes (e.g. in-hospital survival, level of vaso-pressor support, renal function).[245-248] Several studies evaluating critical care in adult and paediatric cohorts confirm that administration of normal saline is associated with increasing chloride-levels and reduction of bicarbonate concentrations as compared to the use of electrolyte balanced resuscitation fluids.[245,246,248,249] Additionally, SSC – paediatric guidelines (2020) advocate the use of electrolyte balanced crystalloids, rather than 0.9% saline, for resuscitation of children with septic shock or other sepsis-associated organ dysfunctions.[85] Of note, a study from Weiss et al, analysing data from multiple hospitals in north-America did not show differences in outcome among children with sepsis managed with Ringer's lactate as compared to the treatment with normal saline.[250]

Furthermore, Paper 3 and FEAST study results indicate that in resource-limited, malaria-endemic settings the use of HAS 5% does not contribute to improved clinical outcome of critically ill children with haemodynamic instability.[131] In a previous smaller clinical trial in Kenya, reduced mortality was reported in children with severe malaria treated with HAS 4.5% as compared to children treated with Gelofusin.[251] Supporting results of Paper 3, SSC-paediatric guidelines (2020) did not identify at this stage convincing evidence suggesting benefits of HAS versus crystalloids as resuscitation fluids in septic children with haemodynamic instability.[85]

Regarding other colloid IV fluids like starches and gelatines, no benefit in terms of clinical outcomes has been demonstrated in the treatment of critically ill patients.[85] In adult studies the use of hydroxyethyl-starch (HES) was even associated with increased clinical risks (e.g., coagulopathy, renal dysfunction).[85 252-254] The European Medicines Agency has recommended to suspend the use of

HES completely.[255] The SSC paediatric guidelines (2020) advice against the use of starches and gelatines in septic shock and other sepsis associated organ dysfunctions.[85]

Paper 3 as well as further studies imply that the use of unbuffered resuscitation fluids should be avoided. Future research can be directed to evaluate potential benefit of isotonic, electrolyte balanced fluids in the treatment of haemodynamic instability, using lower volume fluid boluses (e.g. 5-10 ml/kg).[154] In case clinical trials are considered to evaluate the use of HAS in certain clinical conditions, albumin solutions constituted in electrolyte balanced fluid should be preferred.[256]

Cumulative IV fluid administration in critically ill children

Paper 3 and the FEAST study focused on the administration of IV fluid resuscitation boluses in the treatment of critically ill children with haemodynamic instability. In the FEAST-study over the first 8 hours after recruitment, the median cumulative volume of fluid documented was 40.0 ml/kg (IQR, 30.0 to 50.0 ml/kg) in the albumin-bolus group, 40.0 ml/kg (IQR, 30.4 to 50.0) in the saline-bolus group, and in the control group 10.1 ml/kg (IQR, 10.0 to 25.9).[131] Additionally, 1408 out of 3141 recruited children (45%) received RBC transfusions (20 ml/kg of whole blood over 4 hours).[131]

In order to optimize quality of critical care and prevent complication, any fluid administration needs careful attention e.g.: Administration of blood products in case of severe anaemia or coagulation disorders, IV maintenance as well as enteral fluids. Additional sources of IV fluid administration can be underestimated:

- IV fluids used to administer vaso-active drugs or other medication[l] can considerably contribute to total IV fluid volume as well as sodium and chloride load in critically ill patients (so called "fluid creep").[257-259]
- While at this stage international guidelines recommend boluses of 2 ml/kg of dextrose 10% for the correction of hypoglycaemia,[40] current WHO ETAT guidelines still suggest 5 ml/kg of dextrose 10% (commonly administered without any additional electrolytes).[38] Especially in children with recurrent hypoglycaemic episodes, hypoglycemia corrections can substantially contribute to total daily IV fluid administration.[m]

Maintenance fluids need to be monitored carefully and "fluid creep" needs to be included in fluid balances.[257-259] The "4-2-1" rule suggested by Segar & Holliday (1957) is commonly used to calculate

[l] In FEAST, quinine was still used in most study sites for treatment of severe malaria. IV quinine was administered according to national guidelines. In some settings dextrose 5% without additional electrolytes was used for this purpose.
[m] If feasible, IV fluids given for hypoglycaemia correction should be given as an isotonic, electrolyte-balanced, dextrose 10% containing solution (remark of the author).

daily fluid requirements.[260] However, in critically ill children this "4-2-1" rule can contribute to an over-estimation of fluid requirements.[261,262] Different mechanisms (e.g., increased secretion of anti-diuretic hormone) can result in reduced free-water clearance in patients with respiratory failure, severe neurological conditions (e.g., meningitis, cerebral malaria) or other critical conditions.

Besides potentially decreased free water clearance, critically ill children (e.g., septic children) may develop increased capillary permeability, renal dysfunction, hypoalbuminemia. In conjunction with these factors, inadequately high maintenance fluids can contribute to further complications (e.g., respiratory failure).[261] It can therefore be advised to reduce daily IV maintenance fluids in critically ill children with certain clinical complications (e.g. respiratory or neurological dysfunction) to 50-70% of the "4-2-1" calculations in order to prevent fluid overload and electrolyte abnormalities.[261,262] Importantly, clinical fluid status and fluid balances need to be monitored regularly. In certain clinical conditions fluid administration needs specific adaptation e.g.: acute kidney injury, diabetic keto-acidosis, burns.[262]

Isotonic IV maintenance fluids need to be used to prevent iatrogenic hyponatremia, which can be associated with life-threatening complications (e.g. cerebral oedema).[263,264] Paper 3 suggests the use of electrolyte balanced resuscitation fluid, which is supported by the SSC paediatric guidelines (2020).[85] As maintenance fluids contribute considerably to total fluid administration in critically ill children, the use of isotonic, electrolyte balanced IV maintenance fluids is likely to be beneficial. Pre-mixed, isotonic, electrolyte balanced, dextrose containing maintenance fluids exist. Fluid losses (e.g., gastric tube drainage, diarrhea) need to be replaced,[262] ideally with electrolyte balanced fluids. Once critically ill children are stabilized, enteral fluids and enteral nutrition can be introduced gradually.[265] The "ESICM global intensive care" working group suggest a similar approach regarding enteral nutrition for critically adult patients treated in low- resource settings.[130]

Management of haemodynamic instability and severe anaemia

Severe anaemia is a frequent complication among critically ill children, treated in malaria endemic regions. In the FEAST-study, 32% of patients had Hb levels of less than 5 g/dl and 45% of participants required RBC transfusions. Only 23% of patients had Hb levels above 10 g/dl.[131] Among patients with severe anaemia who received RBC transfusion during the first 48 hours, transfusion were started earlier in the control group (non-bolus group). However, by 2 hours the number of children who received RBC transfusions as well as volumes of blood administered were similar in all study groups (appendix of the FEAST-study).[131]

In Paper 3, cluster 2 consists of patients with low Hb levels, signs of haemodynamic instability and high lactate levels. Overall mortality in cluster-2 was high and administration of IV fluid boluses was associated with increased mortality (21% in the bolus group; 14% in the non-bolus group). Paper 3 suggests that potential transient benefit of improving intra-vascular volume, was outweight by dilutional effects on Hb levels, leading to reduction of O_2-carrying capacity and O_2-delivery. These patho-mechanisms were associated with increased lactate concentrations (high anion-gap acidosis). Additionally, fluid bolus administration potentially had an impact on respiratory function. Furthermore, administration of NaCl 0.9% or HAS 5% was associated with the development of an hyperchloraemic acidosis (normal anion gap-acidosis), which was super-imposed on an already existing metabolic acidosis. In the most critically ill patients, the combination of adverse effects might then have overwhelmed compensatory mechanisms (figure 5, Paper 3).

Results of the FEAST-study contributed to a review of WHO guidelines (2016) regarding management of critically ill children with haemodynamic instability and severe anaemia: no IV fluid bolus should be administered to severely ill children with severe anaemia before the start of RBC transfusion (Table 14).[39] Maintenance fluids can be started before RBC transfusions are available. According to WHO guidelines, RBC transfusion (20ml/kg of whole blood or 10ml/kg of RBC concentrates) needs to be administered over 3-4 hours. Faster administration is needed in acute haemorrhage. WHO guidelines suggest lower volume of RBC transfusion for children with SAM and severe anaemia: 10 ml whole blood/kg over at least 3 hours.[38,39]

In the revised WHO guidelines (2016), RBC transfusion threshold of Hb 5 g/dl (or 6 g/dl for critically ill children according to the WHO pocketbook: hospital care for children) was not adapted.[38,39] RBC transfusion threshold and transfusion volumes suggested by WHO are debated.[266]

Haemoglobin transfusion thresholds in critically ill children

According to SSC – paediatric guidelines (2020), there is insufficient evidence to define a Hb cut-off range for RBC transfusion for critically ill children with unstable septic shock during the resuscitation phase.[85,128] Regarding critically ill children with stable circulation SSC paediatric-guidelines (2020) follow the view of the "Paediatric Critical Care Transfusion and Anaemia Expertise Initiative (TAXI)" from 2018,[267] which is based on results of a multi-center study from Lacroix et al (TRIPICU).[268] TRIPICU study results indicate that in critically ill children managed in PICU settings with stabilized organ functions (e.g., on mechanical ventilation, stable doses of inotropes) target levels of Hb of $\geq$ 7 g/d or Hb $\geq$ 9.5 g/dl are associated with similar clinical outcomes.[267] The latest adult

SSC-guidelines suggest RBC transfusion in critically ill adults with Hb levels less than 7 g/dl (in the absence of specific circumstances like myocardial ischaemia, severe hypoxaemia, acute haemorrhage).[86] "Roger´s textbook of paediatric intensive care" suggests to maintain Hb > 8-10 g/dl in critically ill septic children with unstable haemodynamics.[243]

In low-resource settings risks and benefits associated with RBC transfusions as well as availability of blood products need to be balanced. In a review of WHO ETAT guidelines (2016) a transfusion threshold of Hb 5 g/dl is recommended.[39] The WHO pocket-book (2nd edition, 2013) suggests to transfuse in the following clinical scenarios:[38] All children with an Hb of ≤ 4 g/dl and children with Hb 4–6 g/dl with any of the following clinical features:

- Deep, laboured breathing
- Clinically detectable dehydration or shock; signs of heart failure
- Impaired consciousness
- Very high malaria parasitaemia (> 10% of red cells with parasites).

Outcomes of a large prospective, observational study conducted in six tertiary hospitals in The Gambia, Malawi, Gabon, Kenya, and Ghana indicate that among children with severe malaria and reduced level of consciousness or high lactate levels, RBC transfusion was associated with improved survival at Hb levels above the transfusion thresholds currently suggested by WHO.[266] Additionally, "real-life" clinical situations need to be taken into account. As highlighted in Paper 3, Hb levels in critically ill patients can deteriorate considerably during the first hours of critical care treatment, while important delays can be associated with the preparation of RBC transfusions in many low-resource settings. In this context it is crucial to anticipate preparation of RBC transfusions early.

RBC transfusions volumes for anaemic children treated in low-resource settings

In a large RCT conducted in Uganda and Malawi: "Transfusion and Treatment of Severe Anaemia in African Children Trial (TRACT)", investigators evaluated different interventions in children with severe anaemia (Hb < 6 g/dl).[269,270] In an essential part of the TRACT study, children with severe anaemia and further signs of diseases severity or additional risk factors (e.g. reduced level of consciousness, respiratory distress, sickle cell anaemia) were transfused if Hb levels were less than 6 g/dl. Critically ill children with severe anaemia were assigned to RBC transfusion volumes of 20 or 30 ml whole blood/kg over 3-4 hours. If packed red blood cells were used, lower volumes were transfused over 2-3 hours.[269] Overall 28-day mortality did not differ between the two transfusion strategies. However, there were differences between subgroups of children presenting with or without

fever at time of recruitment. Children presenting with severe anaemia and fever (39% of patients) had higher 28-day mortality rates, when receiving 30 ml whole blood/kg as compared to 20 ml/kg currently recommended by WHO. Among afebrile children, higher transfusion volume of 30 ml whole blood/kg was associated with higher survival rates and lower rates of re-transfusion.[269] Further research can help to better understand differences in mortality among subgroups described in the "TRACT-study".

WHO currently recommends lower volumes for RBC transfusions for critically ill children with SAM and severe anaemia (10 ml/kg – over a period of 3 hours). In many cases these volumes of blood might not be sufficient to correct severe anaemia. In the TRACT study only 4% of the patients had SAM.[269] Results of the TRACT study therefore do not answer the question if higher transfusion volumes in severely anaemic critically ill children with SAM are safe. Two echocardiography studies conducted in East Africa did not demonstrate significant differences in cardiac function among severely malnourished and non-malnourished hospitalised children.[271,272] Results of these studies indicate that RBC transfusion volumes (20 ml whole blood/kg, transfused over 3-4 hours) suggested by WHO for non-malnourished children could be evaluated in children with SAM in future research projects. POC lung ultrasound and echocardiography can play an important role in this context.

A further important research topic is to review the benefit of higher Hb transfusion thresholds (compared to current WHO guidelines) for critically ill children treated in malaria endemic regions (e.g., children with haemodynamic instability, neurological complications).[266] Paper 3 highlights the importance of sequential POC tests of Hb levels during the critical care phase.

Neurological function and haemodynamic instability

Neurological complications are common in critically ill children hospitalised in malaria endemic contexts. Hospital mortality as well as post-discharge mortality risk is high among these children.[273-275] In the FEAST-study 15% of recruited patients presented with coma, while in 37% of patients seizures were reported during the course of the presenting acute illness.[131] More than 50% of patients evaluated in the FEAST-study had positive malaria tests and many of these patients had signs of cerebral malaria.[131] Studies from Malawi show that certain children with severe malaria are at risk to develop cerebral oedema, which is associated with a high mortality risk.[16,146] Children with neurological insults surviving critical illness in these contexts carry a considerable risk to suffer from neurological sequalae following discharge (e.g. epilepsy).[15,276]

According to international paediatric critical care guidelines, the outcome of children presenting with signs of severe non-traumatic neurological insults (e.g., coma, prolonged seizures), in terms of neuro-disability-free survival is determined by multiple factors e.g.:[40,243,262,277]

- Respiratory function and oxygenation as well as cardio-vascular stability.
- Time to termination of seizure activities. Anti-seizure medication should allow easy administration in emergency situations and should be associated with minimal cardio-respiratory adverse effects.
- Cause and severity of the primary neurological insult as well as time to initiation of adequate treatment (e.g., bacterial infections, malaria, opportunistic infections in HIV-infected patients).
- SCD needs to be considered as a potential co-morbidity in many settings in SSA.[77,78]

Paper 3 highlights the need to optimize a comprehensive approach to context-adapted neuro-critical care, including stabilization of respiratory and circulatory function, careful fluid management using electrolyte-balanced IV fluids as well as maintenance of adequate Hb levels. Preservation of sufficient O_2-content and O_2-delivery needs particular attention in children with neurological complications.[210]

In certain settings more advanced respiratory support and administration of vaso-active medication can be considered in order to maintain adequate cerebral perfusion and O_2-delivery. Improved neuro-protective measures have the potential to reduce mortality risk of children with acute neurological insults, but also the risk of long-term neurological complications.[15,16,276]

Renal function and treatment of critically ill children

Acute kidney injury (AKI) is a frequent complication of critical illness in children and is associated with an increased risk of poor clinical outcomes.[278,279] Among children with severe malaria AKI is a common complication and is associated with an increased risk of mortality and long-term morbidity.[273,280,281] In an additional analysis of the FEAST-study, increased blood urea nitrogen (BUN) levels were identified as a risk factor for mortality among critically ill children.[147] However, monitoring of renal function in the FEAST study was limited: no creatinine levels were measured and no urine output measurements were documented. Therefore, commonly used "Kidney Disease: Improving Global Outcomes (KDIGO) criteria" could not be determined to define severity of AKI in the FEAST-study population.[131,282-284]

Management of treatable causes of AKI among critically ill children and context adapted management of AKI needs particular attention in future research projects conducted in resource-limited settings. WHO guidelines, suggested for "optimized supportive care of Ebola viral disease"

offer a pragmatic management approach in settings, where renal replacement therapy is not a feasible option.[56]. Additionally, pragmatic experience exists in the use of peritoneal dialysis in resource constraint contexts.[59-61]

Critically ill children with haemodynamic instability – further important topics

Several important topics regarding critically ill children with haemodynamic instability managed in resource-limited settings, could not be addressed in Paper 3. For example, children children with severe dehydration and/or SAM were not included in the FEAST-study nor in Paper 3.[131]

Critically ill children without SAM: severe dehydration

Acute gastro-enteritis and associated dehydration is one of the major causes of death among children under the age of five years.[285,286] In young children, severe diarrheal diseases are among common causes of sepsis (see global burden of sepsis estimates).[9] Several studies identified severe dehydration among hospitalized children treated in resource-limited settings as an important risk factor for mortality. Children with severe dehydration and associated HIV-infection or malnutrition are particularly vulnerable.[170,171,287] Data from Kenya describe a high post-discharge mortality risk among children needing hospital treatment for severe diarrheal diseases.[171] Severe diarrheal disease is frequently associated with further organ dysfunctions (e.g. respiratory dysfunction).[81 287,288] Children with severe dehydration associated haemodynamic instability carry a particularly high mortality risk.[289,290]

Regarding fluid management for non-malnourished children with severe dehydration WHO recommends to administrate a total of 100 ml/kg of Ringer's lactate (or if not available normal saline) over a period of 3 – 6 hours depending on the age of the child (Plan C; Appendix, Table 14).[38,39] This suggested fluid volume reflects replacement of an estimated fluid loss of 10% body weight. Plan C consists of 2 steps of fluid administration: Step 1: 30 ml/kg over 30 min (for children < 1 year over 60 min); Step 2: 70 ml/kg over 2.5 hours (for children < 1 year over 5 hours). Additionally, in case of shock associated with severe dehydration WHO Plan C suggests to administer rapid fluid boluses of 20 ml/kg of normal saline (up to 3 boluses) followed by step 2 of Plan C (further 70 ml/kg).[38] WHO guidelines suggest to regularly re-evaluate children during the administration of these large volumes of IV fluids. However, as clinical assessment of the degree of dehydration is difficult, risks of fluid overload exist. So far there is limited evidence regarding safety and effectiveness of this Plan C suggested by WHO.[291] A multi-centre open-label phase II RCT focused on the evaluation of two rehydration strategies in 122 Ugandan and Kenyan children (aged 60 days to 12 years) with severe

dehydration (median lactate-level: 1,3 mmol/litre; 3 of 122 children fulfilled WHO criteria of shock). Participants were either treated according to Plan C or with a more careful fluid management plan administering 100 ml/kg of Ringer's lactate over 8 hours. In terms of serious adverse events, there were no significant differences in the two groups (mortality 3.3%).[292]

As recommended in international guidelines, critically ill child with severe dehydration and haemodynamic instability will benefit from a context-adapted approach to the support of all vital organ functions (e.g. respiratory support, treatment of neurological complications).[85] Paper 3 advocates the use of isotonic, electrolyte balanced resuscitation fluids in the management of haemodynamic instability, which is supported by SSC paediatric guidelines (2020).[85] This is of particular importance in the treatment of severe dehydration, which often requires administration of relatively high volumes of IV fluids. Evaluation of safety and effectiveness of slower rates of IV rehydration as currently suggested by WHO needs to be evaluated in further studies. Particularly, the approach to patients presenting with anaemia and severe dehydration needs to be reviewed.

Critically ill children with severe acute malnutrition (SAM) and haemodynamic instability

Children with SAM and acute clinical complications face a particularly high in-patient and post-discharge mortality risk.[170,171,287,293,294] This particularly vulnerable group of children was not included in the FEAST-study and the review described in Paper 3.[131]

WHO guidelines suggest a particularly careful approach to IV fluid management in children with SAM presenting with haemodynamic instability, including severe dehydration.[38,39] These guidelines are based on the assumption that children with SAM (particularly children with kwashiorkor) would more frequently present with cardiac dysfunction as compared to non-malnourished patients. The evidence for this assumption is limited[295] and is not confirmed by echocardiography studies conducted in East Africa among hospitalized children with SAM.[271,272] In view of the high mortality risk in critically ill children with SAM and haemodynamic instability, improvements of a comprehensive "critical care package" are needed e.g.:

- Monitoring of respiratory function (e.g., SpO_2/FIO_2), reliable O_2 supply and if feasible, non-invasive respiratory support can be of benefit.
- The use of isotonic, electrolyte-balanced IV fluids in the treatment of haemodynamic instability needs to be considered in children with SAM (see paper 3). Rates and volumes of IV fluid administration need further evaluation with attention to all vital organ functions.

- WHO suggests relatively low RBC transfusion volumes for children with SAM. In a RCT conducted in Uganda and Malawi (TRACT-study), assessing different transfusion volumes, mainly non-malnourished children with severe anaemia were evaluated.[269] Hb target levels, volume and rate of transfusions need further evaluation in critically ill children with SAM.

Further important knowledge gaps exist in the care of critically ill malnourished children: Children recovering from severe dehydration and/or shock might not tolerate enteral fluids or nutrition for a period of time. Administration of enteral therapeutic feeds in a child with SAM just recovering from shock can potentially be associated with serious complications (e.g., regurgitation of gastric contents). Careful administration of IV maintenance can be beneficial, while enteral fluids and enteral nutrition is introduced gradually, as suggested for critically ill patients in high-resource settings.[265] On-going fluid losses need to be compensated. Nutritional rehabilitation according to WHO – guidelines[38] can be initiated after the "critical care phase", when vital organ functions have been stabilized.

WHO guidelines suggest to use ReSoMal (an oral rehydration solution/ORS for the treatment of malnourished children), which has lower sodium (45 mmol/l) and higher potassium content (40 mmol/l), than ORS suggested by WHO for use in non-malnourished children. Some studies describe a considerable risk of hyponatraemia associated with the use of ReSoMal.[296] The composition of oral rehydration fluids used in children with SAM needs to be reviewed in future research.[296] To potentially harmonize electrolyte-composition of ORS used in children with and without SAM would facilitate pragmatic clinical care.

Critically ill children with haemodynamic instability: use of vaso-active medication

The care package provided in units participating in the FEAST-trial was guided by WHO guidelines (pocket book: hospital care for children, ETAT), which do not include the use of vaso-active medication.[38,39,131] If haemodynamic instability persists, despite optimization of intra-vascular fluid status, further fluid bolus administration can be associated with serious adverse effects (e.g., respiratory, neurological dysfunction).[85,297,298]

The SSC paediatric guidelines (2020) suggest adrenaline or noradrenaline as first-line vasoactive medication for treatment of fluid-refractory septic shock.[85] Panel members of these guidelines prefer to use adrenaline in case of presence of myocardial dysfunction and low cardiac output and noradrenaline in case of signs of decreased systemic vascular resistance.[85] Dopamine can be used as vaso-active infusion if adrenaline or noradrenaline are not available.[85]

In case of fluid refractory shock, the use of continuous infusions of vaso-active medication can be considered in resource-limited settings as part of an improved critical care package if adequate equipment and clinical competencies are available (Table 15). Low-dose, diluted adrenaline or noradrenaline infusions can initially be administered via well monitored peripheral lines.[85] This approach was practiced on treatment units during the Ebola outbreak in the eastern Democratic Republic Congo, guided by pragmatic WHO guidelines.[56, n] The "European Society of Intensive Care Medicine (ESICM) Global Intensive Care" working group suggests to use a similar approach for the management of adult patients with septic shock.[299]

Future research projects, can help to evaluate safety and clinical benefit of low-dose infusions of vaso-active medication in the context of an "improved care package" for the treatment of children with fluid refractory shock, treated in resource-limited contexts. POC-lung ultrasound and echocardiography can help to improve haemodynamic monitoring.[154,164]

Monitoring of vital organ functions

Papers presented in this thesis describe treatment of respiratory and haemodynamic instability among critically children. These efforts need to be accompanied by pragmatic monitoring of vital organ functions in routine clinical practice and clinical research. 87% of deaths in the FEAST-study occurred in the first 24 hours.[131] Paper 3 highlights that in order to describe physiological mechanisms, impact of critical care interventions and interaction of different co-variates a more complete data-set is beneficial. This is particularly important in the first 24-48 hours of critical care management, when there is a high risk of clinical deterioration. Modern, affordable essential monitoring tools (e.g., SpO_2 & HR-monitors; POC-Hb & biochemistry-tests, POCUS) are valuable in this context.

Monitoring of respiratory function

Routine assessment includes: Respiratory rate; assessment of respiratory effort and work of breathing and further clinical examination.

SpO_2/FIO_2 ratio is a pragmatic parameter to define severity of respiratory dysfunction.[87-89] FIO_2 can be estimated in children treated with nasal prongs or face masks.[94,300] Biomedical devices providing non-invasive respiratory support need to allow adaptation of FIO_2. SpO_2/FIO_2 ratios were not determined in the FEAST-study and were therefore not available in the data-set of Paper 3.[131] Also in

[n] The author intermittently worked in Ebola centers in DR- Congo & Guinea supported by ALIMA in 2019, 2020, 2021.

Paper 2 and 3 SpO_2/FIO_2 ratios were not documented. However, sequential evaluation of SpO_2/FIO_2 ratios needs to be considered as a crucial parameter in essential critical care and future research.

Capnography (end-tidal CO_2 monitoring) is needed in units providing advanced airway management and mechanical ventilation and contributes to improved quality and safety of care.[143,301]

Monitoring of Circulation and Hb levels

Routine assessment : WHO suggests to assess circulatory function in children with the following clinical parameters: palpation of central and peripheral pulses, CRT and assessment of temperature gradient (Table 14). Evaluation of additional parameters are needed to guide clinical care according to WHO guidelines: signs of dehydration, pallor and screening of nutritional status (e.g., MUAC).[38,39] While physical examination of cardio-vascular function has its limitations,[154,302] sequential assessment of response to interventions (e.g., small volume fluid boluses) is important. Clinical evaluation needs to include the impact of circulatory function on other vital organs (e.g., level of consciousness, Hb levels, urine output).[40,85,154]

Non-invasive blood pressure (NIBP): FEAST-study results highlight that hypotension is a late sign of circulatory decompensation in critically ill children. Children classified in Stratum B, presenting with hypotension had a high mortality risk (18 from 26 children in this group died).[131] In the FEAST-study systolic BP levels below the 5th centile were chosen to define hypotension: <50 mm Hg in children younger than 12 months of age, <60 mm Hg in children 1 to 5 years of age and <70 mm Hg in children older than 5 years of age. "Moderate hypotension" was defined in this study as systolic BP values around the 5th centile of normal levels for different age ranges.[131,262] This level of moderate hypotension was detected in 6% of patients at the time of recruitment.

Adult international recommendations suggest to target a mean arterial blood pressure (MAP) above 65 mm Hg (5th percentile) in adults and children above the age of 12 years with septic shock.[86,154] The expert panel of the SSC-paediatric guidelines (2020) did not identify clear evidence regarding age-adapted MAP targets in the management of children with septic shock and associated organ dysfunction.[85] However, recognized practice is to target MAP levels between the 5th and 50th percentile or greater than 50th percentile for age.[85]

According to WHO guidelines, basic clinical assessment remains the priority in the assessment of cardio-vascular function.[38,39] However, if low-dose infusions of vaso-active medication are used, automated NIBP at short intervals needs to be included in the routine monitoring (Appendix, Table 15).[56] In order to provide reliable NIBP measurements correct equipment needs to be available (e.g.

age-adapted BP-cuff sizes). If measurements of MAP are not feasible, monitoring of systolic BP is an acceptable alternative.[85]

Safe use of invasive BP measurements needs specific clinical skills, equipment and supplies.[154] Potential complications need to be considered. Therefore, introduction of invasive BP monitoring is not among priority interventions in essential paediatric critical care (authors comments; Table 1).

Further non-invasive monitoring of cardio-vascular function can be considered, depending on clinical settings or in the context of research projects e.g.:[154] POC lung ultrasound, echocardiography and suprasternal doppler. Other forms of cardiac-output monitoring, near infrared spectroscopy (NIRS) and micro-circulation assessment may be used in research contexts.[154]

Haemoglobin levels: Sequential point of care Hb measurements are important to guide clinical management of patients with haemodynamic instability, particularly in malaria-endemic regions (Paper 3). The need for potential RBC transfusions in case of low Hb levels on admission or worsening Hb level during the course of critical care management needs to be anticipated.

The role of POCUS- monitoring of respiratory and cardio-vascular function

In the preparation period of the FEAST-study a small POC echocardiography study among 30 children with severe malaria was conducted in a paediatric unit in coastal Kenya.[303o] Two further echo-cardiography studies, conducted in East Africa evaluated cardiac function among children with SAM.[271,272] The inclusion of POC-lung ultrasound could have added further important value to these three studies.[154] However, these examples demonstrate that it is feasible to conduct echocardiography and supra-sternal doppler assessments at the bed-side of critically ill children in low-resource contexts. Experience from pragmatic POCUS training programs indicate that clinician can acquire important ultrasound skills in challenging resource-limited settings.[304]

Panels of echocardiography assessments need to be pragmatic. Qualitative and semi-quantitative assessments allow critical care clinician to perform echocardiography evaluations rapidly at the bed-side.[154,164] Supra-sternal doppler examination adds further value to the haemodynamic evaluation (in association with Hb & SpO_2 measurements O_2-delivery can be estimated and monitored).[154,303,305] Lung ultrasound gives the opportunity to evaluate signs of extravascular lung-water.[164,165] Additionally, lung ultrasound and can support clinicians to recognize pleural space pathologies (e.g., pleural effusions, pneumothorax) as well as lung consolidation.[164]

[o] The author of this thesis largely contributed to this study.

POCUS findings need to be interpreted in conjunction with vital signs and clinical assessment. Sequential evaluation of clinical signs and POCUS findings allows dynamic monitoring of clinical progress and response to critical care interventions (e.g., fluid boluses, transfusions, vaso-active medications).[154] Additionally, POCUS can contribute to safety and quality of clinical interventions (e.g., thoracocentesis, peri-cardiocentesis, chest drain placement, central line insertion).[164]

Monitoring of lactate levels

Elevated lactate levels (> 3 mmol/l) and especially persistently high or increasing lactate levels are associated with increased mortality risk among critically ill children.[85,154] 39% of patients (1159 out of 2981 cases with available results) in the FEAST-study had lactate levels $\geq$ 5 mmol/l at the time of recruitment, describing severity of illness among these study participants.[131]

The SSC paediatric guidelines (2020) and other international recommendations highlight that blood lactate levels in septic children can be affected by multiple mechanisms besides tissue hypoxia. Therefore, blood lactate results need to be interpreted in conjunction with further clinical parameters assessing systemic perfusion. High and especially persistent elevation in lactate levels need to prompt thorough clinical evaluation of patients.[85 154] Different factors associated with critical illness need to be considered in this context:[306]

High lactate levels can be associated with tissue hypoxia and anaerobic metabolism. Tissue hypoxia is associated with reduced O_2-delivery, which is determined mainly by cardiac output, respiratory function (oxygenation) as well as Hb levels/O_2-carrying capacity. Complex mechanisms affecting micro-circulation can further affect tissue perfusion in septic patients.[306-308] Paper 3 describes the inverse association of low Hb and high lactate levels in critically ill children treated in malaria-endemic settings.

Decreased lactate clearance in patients with hepatic dysfunction and/or decreased hepatic blood flow (associated with shock) can contribute to elevation of blood lactate.[306]

Severe acute lung injury associated with inflammatory processes (e.g., sepsis) can be associated with considerable regional lactate production.[306]

Inflammatory processes can accelerate aerobic glycolysis, without the initial presence of anaerobic conditions associated with tissue hypoxia. In the context of inflammatory processes, wight blood cell metabolism as well, can contribute to increased lactate production, which is not necessarily associated with haemodynamic instability.[306]

Pyruvate-dehydrogenase function on mitochondrial level can be altered by complex mechanism associated with inflammatory processes.[306] In this context, thiamine deficiency can be considered as a contributing factor in some settings (e.g. critically ill children with severe acute malnutrition).[309] In clinical practice and future research evaluating paediatric critical care in low-resource settings, sequential lactate levels can contribute to describe disease severity and monitor response to treatment.

Monitoring of neurological function

Mental status, level of consciousness (e.g., AVPU-scale) and a basic neurological assessment needs to be monitored. This assessment includes evaluation of patient comfort and pain-control. Additional techniques (e.g., electro-encephalogram/EEG, transcranial dopplers) can be considered in specific projects and research contexts.[310,311]

Renal function, fluid balance and electrolyte abnormalities

AKI is a common complication of critical illness in children and is associated with an increased mortality risk and long-term morbidity.[273,278-281] International consensus definitions of AKI by the "Kidney Disease Improving Global Outcomes (KDIGO) working group" are based on creatinine levels, changes of creatinine-levels from baseline and urine output measurements.[283,312] "KDIGO-criteria" highlight the importance of basic urine output monitoring to determine renal function.[282,284] In order to prevent nosocomial infections and avoid urethral injuries, non-invasive methods of UO-monitoring are beneficial (e.g., use of urine bags, weighing of nappies).[p] Despite limitations of serum creatinine measurements to detect early stages of renal dysfunction, sequential measurements allow to describe renal function during the course of critical illness.[283] Monitoring of renal function and classification according to KDIGO-criteria needs to be considered in future research projects evaluating treatment of critically ill children in resource-limited settings.

Administration of all IV and enteral fluids needs to be monitored. Fluid balances need to be completed by estimation of fluid losses. Body weight needs to be documented regularly.

Testing of creatinine, electrolyte or blood gases might not be an initial priority in the set-up of essential paediatric emergency and critical services, but can be considered in more advanced settings (Table 1). Introduction of monitoring and correction of electrolyte abnormalities adds considerable complexity to essential critical care, and if not done correctly can be associated with additional clinical risks. The following aspects can be considered in this context e.g.:

[p] Non-invasive UO-measurements: good quality weighing scales are needed.

- Pragmatic management guidelines are provided by WHO (WHO guidelines: "optimised supportive are for Ebola Virus Disease").[56] Adequate training is needed in this context.
- POC-testing is important as results need to be available as soon as possible after correct blood sampling in order to be of optimal clinical value.

Further laboratory tests, including liver function, full blood count, coagulation, microbiological investigations, inflammatory biomarkers are of value in certain contexts (Table 1), but are not the focus of this thesis.

Methodological considerations, strengths and limitations

Methodological considerations: Paper 1 Bubble CPAP

Study design

Interpretation of results is limited by the basic observational set-up of the study. The small sample size limited more detailed subgroup analyses.

Quality of data collection

Data quality (e.g., frequency of vital signs monitoring) was affected by limited human resources, limited monitoring equipment (e.g., SpO_2-monitors) as well as very high workload. Sequential documentation of SpO_2/FiO_2 ratios in association with CPAP-pressure documentation could have improved description of severity of respiratory dysfunction and response to treatment.[87,88]

Human resource gaps contributed to the fact that most, but not all, children who were managed with bCPAP during the study period were included in the analysis. Only isolated, CPAP-runs of short duration (less than 12 hours) might have been missed during week-ends. Of these isolated cases, all children survived as all files of children, who died on the unit were screened specifically.

Limitations of the study

During the study, the clinical team faced considerable resource-limitations and high workload. The following measures could have improved quality of non-invasive respiratory support e.g.:

- Improved nurse to patient ratio can improve quality of care (e.g., monitoring of respiratory support, fluid management, progressive introduction of enteral feeds).
- Better supply of essential equipment is important (e.g., adequate number of dedicated bCPAP set-ups, SpO_2-monitors).
- Strengthening of blood transfusion service can contribute to improved clinical outcomes of critically ill children with severe anaemia and haemodynamic instability.

Anthropometric measurements were suboptimal in our survey. Length measurements were not done in a large number of patients. We therefore used weight/age as a marker of nutritional status.

Methodological considerations: Paper 2 Mechanical ventilation

Study design

A cohort study, designed as a retrospective analysis of a prospectively collected database. The non-randomized study design limits conclusions on the true outcome effects of intensive care interventions, including mechanical ventilation in snakebite victims with acute respiratory failure.

Data collection

Unfortunately, the hospital information system of Lacor-hospital did not provide data on the number of patients referred from peripheral facilities or hospitalized patients with snakebites, who did not need ICU admission. A better epidemiological assessment of snake-bites in the region could help to improve organisation of preventive measures as well as referral pathways and improvement of pre-referral management of snake-bite victims and other critically ill patients.

The analysis was designed retrospectively which explains why the presenting clinical symptoms of snakebite victims could be determined in only 23% of study patients. Paper 2 can, therefore, give only limited insight into the differences in management and outcome of patients presenting with different snakebite-associated clinical syndromes. Among 60 patients requiring mechanical ventilation, clinical symptoms were documented in more detail in only 16 cases. Neurotoxicity leading to ARF was the most commonly documented indication for advanced respiratory support (87.5%). It can be emphasized that in the absence of any other documented complication patients with ARF requiring mechanical ventilation most likely had a neurotoxic snakebite syndrome.

Limitation of resources and impact on quality of care

Monitoring of patients could have been improved by the availability of capnography. Capnography needs to be considered as an essential monitoring devices in units offering advanced airway management and mechanical ventilation.[143,301]

In Paper 2 only a small number of patients with ARF, who required mechanical ventilation received anti-venom (10 out of 60 ventilated patients). The anti-venom used during the study period is not among the products currently recommended by international specialist.[121,163] It can therefore not be determined if in patients with ARF early administration of adequate doses of good quality anti-venom in combination with advanced airway management and mechanical ventilation could have improved survival or reduced the required duration of mechanical ventilation.

Methodological considerations: Paper 3 Fluid management of shock

Initial FEAST study: Study design, study procedures, data collection and analysis

The initial FEAST study was a RCT conducted in 6 different paediatric departments in three East African countries. Different aspects of essential paediatric emergency and critical care were improved in the participating units prior to the start of recruitment of study patients. In this context study procedures were integrated in routine clinical processes.[131]

Monitoring of study procedures and data collection was conducted at all participating sites on a regular basis.[131] The statistical analysis was done by experienced statisticians and the study oversight was in-line with international standards.[131]

An endpoint review committee, reviewed all deaths, adverse events and neurologic sequelae. However, diagnostic means were limited at the study sites.[131] It was therefore difficult to clearly define causes of death in a considerable number of patients.

The FEAST-study demonstrates that it is feasible to conduct good-quality clinical trials in emergency and critical care in low-resource settings. Future research projects evaluating critical care in comparable contexts, need to conduct a careful needs assessment in order to strengthen essential emergency and critical care standards in participating units.

Paper 3: Identified limitations

In Paper 3 some limitations were identified which can lead to future research opportunities:

In the care of critically ill children with haemodynamic instability associated with respiratory dysfunction, treated in a low-resource setting, the role of non-invasive respiratory support needs further evaluation.

The respiratory organ function score, presented in Paper 3 can be strengthened by sequential documentation of SpO_2/FIO_2 ratios. This approach is in-line with international standards to define severity of PARDS.[88] Also in resource-limited settings, where access to blood gases and imaging is difficult SpO_2/FIO_2 ratios can be monitored.[89,91,300]

Critically ill children with signs of severe dehydration as well as children with SAM were not included in the FEAST-study. Paper 3 could therefore not address questions related to these particularly vulnerable patient populations.

Low-dose infusions of vaso-active medication have not been used in the FEAST-study. This is a further element in context-adapted paediatric critical care, which can be considered in future practice and pragmatic research.

AKI is a common complication of critical illness in children and is associated with an increased risk of poor clinical outcomes.[278,279] AKI is also described as a complication in children with severe malaria.[273,280,281] Blood urea nitrogen levels (BUN) were measured at different time points during the FEAST-study.[131] However, no urine output and creatinine levels were documented. Therefore, "KDIGO criteria" could not be used to describe renal function in the study population.[131,283,284]

POCUS was not used in the FEAST study. However, POC lung ultrasound, supra-sternal doppler and a pragmatic application of bed-side echocardiography have the potential to contribute to improvements of quality of care and diagnostic processes.[154,164,303]

Paper 3 highlights the importance that research projects evaluating paediatric critical care in resource-limited settings need to ensure frequent, sequential vital sign documentation as well as review of the most important blood results (e.g., electrolytes, acid-base, Lactate, Hb), particularly in the first 24-48 hours of critical care, when patients have a high risk of clinical deterioration.

Methodological considerations: Context adapted severity of illness (SOI) scores

A detailed discussion on outcome measures in critical care is beyond the scope of this thesis. However, papers 1, 2 and 3 describe clinical care of critically ill children in low-resource settings with a high mortality risk. In Paper 1 and 2 no SOI scores were used, which limits the possibility to compare clinical outcomes described in other publications.

SOI scores allow description and comparison of cohorts of critically ill patients. [243,262] Scores like Paediatric Index of Mortality 2 & 3 (PIM)/Pediatric Risk of Mortality Score III (PRISM) used in PICUs in high-resource settings are based on parameters describing the degree of acute organ-dysfunctions and chronic health variables.[243,262] Sequential assessment of SOI-scores like paediatric logistic organ function-score (PELOD) allows to analyse trends regarding clinical progress of patients and response to treatment.[243,313-315] Different clinical severity scores have been evaluated in low-resource settings in paediatric and adult populations. [147,316,317] Organ function scores described in Paper 3 used basic clinical parameters to describe severity of acute organ dysfunction. These assessments can be strengthened, examples:

- SpO_2/FIO_2 ratio is a pragmatic and important marker to assess respiratory function.[87-89]
- Assessment of organ-function can be adapted to different contexts and can be strengthened by POC- laboratory parameters (e.g., blood gases, Lactate, Hb, renal function).[154,283,284]
- POCUS and supra-sternal doppler can contribute to description of respiratory and cardio-vascular dysfunction in some contexts.[154,164]

Chronic health variables influence clinical outcomes of critically ill children and need to be included in the description of SOI of patient cohorts.[243,262] Nutritional status and HIV-status are important factors in this context.[135,170,171] Sickle cell disease is a further important co-morbidity in critically ill children, particularly in SSA.[77] Other chronic health variables (e.g., cardiac or renal conditions, malignancies, neuro-disability) need to be considered.[190,243,262] SOI-scores do not replace triage systems. WHO and partners recommend a pragmatic interagency triage tool.[45]

Outcome measures: economic, clinical and humanistic outcomes[243]

Sequential assessment of SOI-scores (e.g., context-adapted PELOD) can facilitate estimation of required resource allocation in health facilities and patient transfer systems, considering seasonal variation of activities as well as disease outbreak preparedness. Additional information can contribute to a further needs assessment associated with efforts to improve comprehensive EECC services e.g.:

- Post-discharge mortality and morbidity as well as quality of life of critical care survivors can be assessed, which allows to plan future support strategies.
- Perception of patients and families regarding critical care can be evaluated.

Ethical considerations: Advanced critical care in low-resource settings

Advanced critical care in resource-limited settings – example: mechanical ventilation

Setting-up a level 3 critical care unit in resource-limited contexts with the ability to provide mechanical ventilation needs a sustained multi-disciplinary effort, requiring considerable resources and clinical capacity. Critical reflection on resource allocation and ethical decision making is required.[241] Additionally, mechanical ventilation can be associated with considerable risks e.g.:[243,262]

- Haemodynamic instability during the intubation process; failed intubations.
- Complications associated with mechanical ventilation e.g.: dislocation and obstruction of endo-tracheal tubes as well as problems with ventilation circuits, equipment failure, ventilation associated lung injury (VALI), pneumothoraxes, ventilation associated pneumonia (VAP).

Patients with ARF and a potential to recover relatively quickly with adequate critical care support might benefit most from advanced airway management and mechanical ventilation in low- resource contexts e.g.: upper airway obstruction, post-operative care, prolonged seizures or ARF due to transient muscle paralysis caused by neurotoxic snake bite envenomation (Paper 2 & Table 13).

Therefore, benefits, clinical risks for patients as well as available resources need to be balanced. Exposed to these challenges, considerable ethical dilemmas arise for critical care teams. A PICU-team from Cape Town describes from a South African perspective the development of policies to

guide "fair and equitable" utilization of limited critical care resources.[241] Institutional guidelines should be introduced to guide rational decision-making processes in stressful emergency situations. These arrangements can help to identify patients, who are most likely to benefit from mechanical ventilation, while considering available resources.[241,318]

Palliative care for critically ill patients not responding to intensive care measures needs to be included in these guidelines and support structures can be developed in this context.[319]

Guideline development processes need to be transparent. Clinical decision-making and outcomes of critically ill patients needs to be audited, while encouraging trust-full discussions among health workers. Patients, parents and community representatives can be invited to participate in this process.

Ethical considerations: research in critical care in low-resource settings

The role of observational studies

Paper 1 and 2 are observational studies. Observational studies are considered as "low-level evidence" in the pyramid, grading the level of evidence provided by clinical research.[320] However, observational studies can be conducted at comparably low-costs and can be set-up relatively quickly, as compared to RCTs. Paper 1 and 2 are examples on how pragmatic studies can be integrated in routine clinical processes. In this context observational studies can contribute to quality of care improvement in participating units.

Essential principles of clinical research need to be respected in the set-up and conduction of observational studies as well as documentation, analysis of data and interpretation of results. Frameworks provided by international experts can guide this process (e.g. Enhancing the QUAlity and Transparency Of health Research Equator Network).[321-323] While observational studies can't be used to the same extend as RCTs to state facts regarding efficacy of interventions, these studies can still describe feasibility to introduce certain clinical interventions (e.g., bCPAP) in "real-life clinical contexts".[322] Additionally, results described in observational studies are useful to identify pragmatic future research opportunities and quality improvement measures. Well-conducted observational studies, therefore have the potential to contribute to agility and flexibility of clinical research in "real-life contexts". Especially in resource-limited settings this form of pragmatic research has the potential to serve as a tool in implementation research.[324]

Informed consent & clinical research in critical care in low-resource settings

The FEAST-study evaluated elements of EECC among children with signs of haemodynamic instability. An informed consent process assures voluntary participation of patients in clinical research. This process reflects respect of patient´s rights and contributes to adequate ethical conduct of clinical research. International guidelines exist to protect patients recruited in emergency and critical care research.[156,157]

Implementation of good quality consent processes in paediatric critical care research conducted in resource-limited settings needs careful planning.[158,159] During the FEAST trial a system of deferred consent was adopted during the recruitment process.[131] Trained staff was allocated to conduct a verbal assent conversation with care-takers at the time of recruitment, while deferring complete informed consent. The process of "verbal assent", did not delay or interfere with clinical emergency care. During the process of verbal assent care-takers were assured that quality of care for their children was independent of their decision to participate in the research.

Once emergency procedures were initiated and a degree of clinical stability was achieved the consent process was continued. Health workers conducting the "clinical consent conversation" had the same cultural and linguistic background as the child´s care-takers. To maintain voluntariness among care takers in the process of verbal assent and consent is particularly challenging in clinical trials evaluating care of critically ill children in resource limited settings.[159] This reflection highlights the importance to ensure adequate context-adapted standards of care for all children admitted to participating paediatric units.

Despite considerable challenges associated with verbal assent and consent in the FEAST-study, important lessons were learned and reviewed. This review included perceptions among guardians and health workers.[159] Consent processes need to be adapted to particular studies, clinical conditions of patients as well as cultural contexts.[159] In this process staff members, parent and community representatives need to be consulted.[159] Opinions of children and parents with experience of their children requiring emergency treatment can provide valuable input to optimize conduct of research and consent processes in paediatric emergency and critical care.[325,326]

Conclusion

The high survival rates among HIV-negative children with acute respiratory dysfunction and no other severe organ dysfunctions in Paper 1, indicate that bCPAP can be used efficiently in resource-limited but well-supervised paediatric units in malaria-endemic regions. The role of bCPAP and other

forms of non-invasive respiratory support as part of a care package for critically ill children with multi-organ dysfunction (e.g., haemodynamic instability) needs further evaluation. Children with malnutrition or HIV infection need particular attention in this context.

Paper 2 suggests that provision of basic intensive care, including advanced airway management and mechanical ventilation, is a feasible treatment option for critically ill snakebite victims presenting with acute respiratory failure in a rural hospital in sub-Saharan Africa. Most of these patients showed signs of a neuro-toxic snake-bite envenomation, which led to acute respiratory failure without severe acute lung injury and no other associated severe organ-dysfunctions. The set-up of an intensive care unit, able to provide this level of advanced respiratory support requires a sustained multi-disciplinary effort.

Paper 3 highlights that critically ill children with signs of circulatory impairment, who do not fulfill WHO definition of shock should not receive fluid boluses. Additionally, children with signs of shock and severe anaemia should not receive pre-transfusion IV fluid boluses, while blood transfusions need to be initiated as soon as possible. Fluid resuscitation of critically ill children with normal saline and HAS (5%) can be associated with severe adverse events like respiratory and neurological dysfunction, hyperchloraemic acidosis as well as reduction of Hb levels. These findings suggest that fluid resuscitation with un-balanced electrolyte solutions may cause harm and should be avoided. A more cautious approach to fluid resuscitation using smaller volumes of electrolyte balanced IV fluids needs to be evaluated. Future pragmatic research needs to be directed to optimize a comprehensive approach to paediatric emergency and critical care adapted to resource-limited contexts, with attention to all vital organ-functions.

Implications and future perspectives

Implications for policy: context-adapted paediatric critical care

Access to EECC on different levels of referral pathways in resource-limited settings

Access for populations living in resource-limited settings to essential paediatric emergency and critical care needs to be strengthened on different levels of referral pathways. Populations exposed to acute humanitarian crisis need particular attention. Population-based research on epidemiology of severe infections (e.g., sepsis) can describe disease burden and facilitate evaluation of needs associated with prevention and treatment of critically illness.[327] However, particular efforts need to be undertaken to sustainably implement efficient interventions in this context.[324]

Oxygen supply, non-invasive respiratory support and quality control of medical devices

Sustainable O_2-provision is an integral part of EECC. Multi-disciplinary efforts are required in low-income countries to strengthen health systems to effectively and safely provide medical O_2 on different levels of referral pathways.

Non-invasive respiratory support has the potential to improve quality of critical care for children with acute respiratory dysfunction. Biomedical equipment used for respiratory support, needs to be adapted to resource-limited contexts and needs to undergo thorough biomedical testing. Strengthening of biomedical engineering services, able to test, maintain and repair medical devices is an important element in efforts to improve quality of EECC in low-income countries.

Safe administration of IV fluids, blood products and monitoring

Safe administration of IV fluids is a major challenge in resource-limited settings. International guidelines can only be implemented if adequate supplies and materials are available (e.g. paediatric giving sets, infusion/syringe pumps). Safe and efficient blood transfusion services need to be strengthened.

Availability of context-adapted modern clinical monitoring devices as well as good quality point of care tests needs to be assured in order improve quality of EPECC.

Essential biomedical equipment and need for sustainable energy solutions

O_2 concentrators and other medical devices (e.g., for non-invasive respiratory support, essential monitoring) need reliable and affordable electricity supply. Development of sustainable energy solutions (e.g., solar systems) are needed to improve access of populations to EPECC in low-resource settings.

Implications for future research – context adapted paediatric critical care

In the discussion of this thesis, important knowledge gaps were described in relation to improvements of a comprehensive approach to EPECC provided in low-resource settings. Several research questions can be related to elements highlighted in international recommendations and "translated to clinical realities" in resource limited settings (table 10) e.g.:

- International guidelines for the management of sepsis-associated organ dysfunction in children (e.g., SSC-paediatric guidelines (2020), recommendations for mechanical ventilation of

critically ill children from the "Paediatric Mechanical Ventilation Consensus Conference (PEMVECC 2017)", recommendations of the WHO sepsis expert technical group.[85,98,327]

- Recommendations summarized by working groups of the European society of paediatric neonatal and intensive care (ESPNIC) e.g.: hemodynamic monitoring for critically ill children and international guidelines on POCUS for critically ill neonates and children [154,164] as well as recommendations for nutritional support for children during critical illness.[265]

Table 10. Implications for future research.
Suggestions for future research topics in essential paediatric emergency and critical care in low-resource settings.

Organ function and support	Specific topic and suggested research questions
Non-invasive respiratory support	**bCPAP**. Evaluation of the following aspects can lead to improvements of respiratory support : Optimized warmed humidification of air/oxygen flow Flow and pressure characteristics of bCPAP systems in different age groups Improvement of interfaces e.g.: affordable; simple and secure fixation; minimal flow resistance Improvement of energy efficiency of bCPAP devices and O_2-concentrators
	bCPAP versus HFNC. Further evidence is needed to determine the role of these modes of respiratory support in different "clinical scenarios" and different age groups
	Non-invasive BIPAP. Benefits of non-invasive BIPAP can be evaluated in different clinical conditions e.g.: patients with respiratory dysfunction with or without haemodynamic instability
	CPAP-air entrainment devices. Characteristics of these devices needs to be evaluated e.g.: Pressure/flow characteristic in the respiratory cycle using low-pressure O_2-sources
Mechanical ventilation	A comprehensive approach is required to determine benefits of mechanical ventilation in resource-limited settings, including: - Biomedical and logistic considerations - Indication for mechanical ventilation and ethical considerations
Circulation: haemodynamic instability, severe dehydration, anaemia	**Use of isotonic, electrolyte balanced IV fluids** in different clinical scenarios e.g.: Shock and/or dehydration in children with and without SAM Use of small volume fluid boluses and adaptation to clinical response
	Severe anaemia & haemodynamic instability. Different questions can be evaluated: Transfusion thresholds as well as transfusion volumes in severely ill children (e.g. haemodynamic instability, neurological complications) Treatment of children with severe anaemia and severe dehydration Benefits of packed red cell versus whole blood transfusions
	Use of low-dose infusions of vaso-active medication in more advanced settings. Evaluation of children with different "clinical phenotypes" with and without SAM: Fluid refractory shock +/- severe anaemia ; care of children with neurological complications
Monitoring of respiratory and haemodynamic functions	**Integration of POCUS in the care of children with respiratory and haemodynamic instability**: POC-lung ultrasound & POC echocardiography Supra-sternal doppler (in association with Hb & SpO_2 monitoring O_2- delivery can be monitored)
	Sequential or continuous monitoring of vital organ functions: Vital signs, including SpO_2/FIO_2-ratios, NIBP, urine output; sequential HB measurements Further tests can be considered in some settings e.g., renal function/electrolytes & blood gases/lactate; biomarkers, microbiology
Context adapted neuro-critical care	**Neuro-protective care** - research topics to consider e.g.: Use of anti-seizure medication (ASM) in the treatment of status epilepticus (SE) associated with better respiratory and circulatory side-effect profile (e.g. Levetiracetam). Control of SE refractory to 2nd line ASM in settings where advanced airway management and mechanical ventilation is rarely an option (e.g., the role of Ketamine can be explored). Use of vaso-active agents may contribute to better cerebral perfusion in case of haemodynamic instability.
Renal function and electrolyte abnormalities	**Different aspects of context-adapted management of AKI can be evaluated e.g.** Prevention of AKI and management of treatable causes (e.g., haemodynamic stabilisation) Fluid management and treatment of complication (e.g., hyperkalaemia) Renal-replacement therapy may be feasible in some contexts (e.g., peritoneal dialysis)
Enteral nutrition	**Guidelines for enteral nutrition** of critically ill children need to be developed for resource limited settings
Training	**Multi-disciplinary, pragmatic training programs** need further development to provide competencies required for provision of EPECC in different contexts and available levels of critical care

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Appendix

Referral pathways and patient circuits

Table 11. Referral pathways/"clinical networks" and patient circuits.
Strengthening of referral pathways is important in order to improve access of populations in urban and rural contexts to EECC. These elements are also relevant for disease outbreak management (e.g. Ebola, SARS-CoV2).[27,28,31] Community engagement is crucial on all levels of a referral pathway.[33]

Referral pathway	Interventions
Community based care, peripheral health facilities and transfer	
Workers (CHW)[32]	CHWs participate in disease prevention and disease surveillance. Essential paediatric care provided by CHWs is guided by WHO algorithms: "integrated community case management of common childhood illnesses (iCCM)".[328] ICCM includes the following elements: - Treatment of common non-severe conditions : respiratory infections, malaria, diarrhea without dehydration - Screening of nutritional status - Early recognition of "danger signs" and referral to health facilities
Peripheral health centres	For health centers WHO algorithms "integrated management of childhood illnesses (IMCI)" include guidelines on: Treatment of common childhood illnesses, essential newborn care as well as ambulatory nutritional care, disease prevention (e.g., immunizations).[34-36] Health centers need to be set-up for pre-referral management and clinical observation. Reliable O_2- supply should be available. WHO algorithms for essential adult & adolescent clinical care exist e.g.: Integrated Management of Adolescent & Adult Illness (IMAI)[329] Integrated Management Of Pregnancy & Childbirth [330]
Referral health centres	WHO guidelines "Pocketbook: Hospital care for children" are useful at this level of referral pathways. These guidelines include ETAT algorithms.[38,39] Health centers need to be set-up to provide pre-referral treatment of critically ill children e.g.: - Basic management of respiratory complications. Reliable O_2-supply needs to be available on this level of the referral pathway.[43,93] - Initiation of treatment of shock, severe dehydration. RBC transfusions may be possible in some centres. - Control of hypoglycaemia and seizures; start of anti-microbial treatment and infectious source control.
Transfer of patients	Set-up of referral systems between peripheral health facilities & hospitals need a multi-disciplinary approach, including: - Establishment of communication lines between referring and receiving facility; means of communication in ambulances - Preparation of "transfer kit": essential medical supplies & equipment, including portable O_2-sources - Ambulances need to be maintained and need safe and pragmatic set-up for patient transfer - Training of health workers and ambulance drivers Accessibility of peripheral facilities: Seasonal changes need to be considered (e.g., rainy seasons) as well as security aspects. Community involvement can facilitate innovative forms of transfer in resource limited contexts.

Hospital based care: Patient circuit & levels of critical care (table 1) **A multi-disciplinary team is needed to maintain quality of care** e.g.: Biomedical equipment , logistic set-up (e.g., O_2-supply, electricity, supplies), laboratory & blood bank, human resource management, support of health workers, pragmatic training programs	
Triage	Triage: A new inter-agency triage tool is recommended by WHO.[45] Vulnerable patient populations need particular attention e.g.: pregnant women, children and new-borns, the elderly
Emergency department (ED)	Adequate space needs to be dedicated for the ED. EDs need to be prepared for a variety of situations: - Seasonal variation of clinical activities needs to be anticipated (e.g., rise of activities during the malaria season) - EDs need to be prepared for surges of activities (e.g., mass casualties); outbreak management (e.g., Ebola, Lassa, SARI, Measles) EDs need to be set-up for specific patient populations e.g.: - Designated clinical zones need to be prepared for paediatric and newborn care - Preparation for obstetric emergencies, surgical emergencies and trauma In many district hospitals it is useful to maintain one ED for adults and children. Large hospitals might benefit from separate paediatric and adult EDs.
Short-stay unit, linked to the ED	Short stay units serve for observation of patients with non-critical conditions, but with the potential for clinical deterioration (e.g., non-severe pneumonia, non-severe malaria, diarrhea). These units have the following benefits:[19] - Observation periods of several hours allows to evaluate clinical progress and response to treatment (e.g. oral rehydration, initial drug administration). This process can contribute to a reduction of hospital admissions among children, who improve after initiation of treatment. - Identification of clinical deterioration of patients, initially classified as "non-urgent", who subsequently need hospital admission.
Critical Care unit	Dedicated units are needed to provide further critical care for adults and children after initial stabilization in the ED: - Context-adapted support of vital organ functions, monitoring and initiation of definitive treatment of the underlying disease processes.
Step-Down units	Step-down units are needed to provide further, less intensive clinical monitoring and treatment for patients recovering from critical illness, who are not ready to move to standard ward care. The set-up of "step-down units/zones" is crucial in order to guarantee adequate patient flow.
Unit for young infants	After stabilisation of vital organ functions, these clinical zones can function as "step-down units" for young infants (< 6-12 months), while providing better adapted care and protection for this vulnerable group (e.g., re-establishing breast-feeding, prevention of hypothermia).
Standard Ward Care	Patients can be transferred to "standard ward care" if vital organ functions are stabilized and risk of clinical deterioration is minimal. Early warning systems help to rapidly identify clinical deterioration. Care-takers need to be integrated in these processes.
Newborn care	Patient circuits need to be set-up for the care of newborns (e.g., triage, EDs, operating theatres, delivery rooms, patient transfer). Dedicated context-adapted neonatal units in district and regional hospitals contribute to improved quality of care.[50]
Planning for hospital discharge, follow-up and rehabilitation in the community, outpatient departments or peripheral health facilities is essential in order to prevent clinical deterioration after discharge. Parents and close care-takers need to be integrated in the care of their children.	
Preparedness for outbreak management on all levels of a referral pathway. Multi-disciplinary "early outbreak response teams" can support local health facilities. "Isolation pathways" need to be prepared for identification & treatment of patients with suspected or confirmed highly contagious diseases (e.g. Ebola, Lassa, SARI):[27,28,31,57] - Early recognition of patients with potentially highly contagious diseases on community level; notification of a coordinating outbreak response team. - Emergency and critical care of patients with highly contagious disease follow standard principles of critical care, while respecting strict IPC measures.	

Patient circuit in health facilities

An efficient patient circuit and support of essential paediatric emergency and critical care can substantially reduce preventable paediatric hospital mortality.[19,49] Important elements of a patient circuit are described in figure 9.

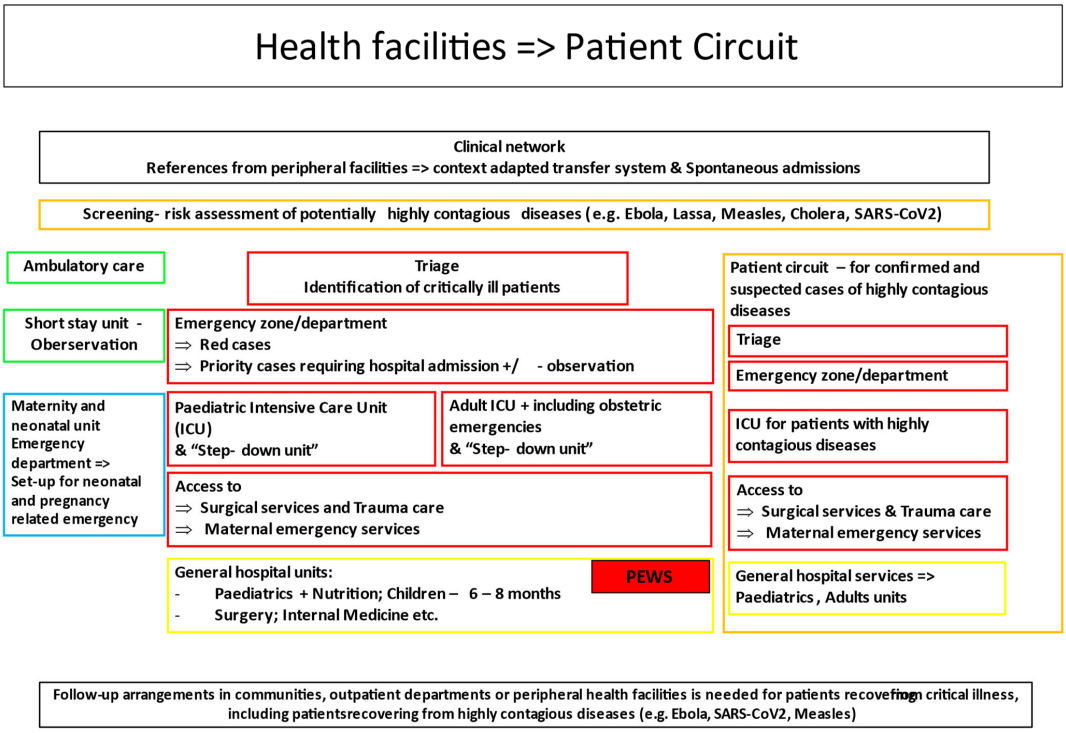

Figure 9. Patient circuits in health facilities.
A simplified description of important elements of a patient circuit within a health facility, focusing on triage, emergency and critical care. Outbreak preparedness is important in this context (e.g., SARI (SARS-CoV2), Ebola, Lassa, measles).[29,31,57]

Statistical analysis in Paper 3: summary of main results

Table 12. Paper 3: summary of results – stepwise approach.
Outline of main steps of statistical analysis (Figure 1; Paper 3) and summary of results. Important, in the FEAST-study 87% of deaths occurred before 24 hrs.[131] FEAST-study data were collected at the following time-points: Vital signs: baseline, 1h, 4h, 8h, 24h, 48h; organ-function-scores in Paper 3 were calculated at the same time points; documentation of Hb &Lactate: baseline, 8h, 24h; biochemistry (e.g. base-excess (BE), chloride & bicarbonate): baseline, 24h.

Statistical analysis	Key results
Development of "Organ-function/physiological scores" & Comparison of scores between FEAST & 4 additional patient cohorts	
Organ-function scores were used to describe SOI of the FEAST-cohort & four additional cohorts at baseline (Paper 3 Annex 1, pp 9, 22).	**Respiratory scores** at baseline of the FEAST-cohort were significantly higher than in other cohorts. **CVS-scores** in FEAST were similar to the meningococcal-sepsis cohort from the UK.[145] Among FEAST-patients, CVS scores were significantly higher in fatal cases than in survivors at baseline, but not significantly different at 1 h after administration of initial fluid bolus (if received). However, after 4 h CVS-scores were significantly higher in those dying than in survivors. **Neurological scores** were highest in the Malawian cerebral malaria cohort.[146] Patients who subsequently died had significantly higher respiratory & neurological scores than survivors at all timepoints up to 24 h. In FEAST, ten unit increase in baseline score was associated for all three organ function scores with an increased risk of mortality. In the four additional cohorts ten-unit increase in baseline scores was at least associated with a trend towards increased risk of adverse outcomes. **These results indicate that suggested scores are valuable tools to describe SOI at baseline & in FEAST in sequential assessments over 48 h.**
Pre-planned analysis in the FEAST-cohort	
Effect of fluid boluses on sequential organ-function scores (first 48 hours). HB & acid-base, biochemistry are included in the analysis (paper 3; table 2 & Paper 3 Annex 1; p 23).	**Respiratory scores** were significantly higher among bolus recipients at 1 h, 4 h. No significant difference was documented at later time points. **Neurological scores** were significantly higher in bolus recipients at 1 h. At later time points no significant difference were documented. **CVS-scores:** fluid bolus decreased mean CVS score at 1 h. No significant difference in CVS-scores between bolus & no-bolus groups at 4 h, 12 h. Overall, after 4 h, there were no significant differences in organ-function scores in the bolus and non-bolus group. **N-Saline versus HAS:** With the exception of respiratory score at 8 h, which increased more in HAS recipients than in normal saline recipients, there were no significant differences between participants who received normal saline or HAS. **Hb levels:** IV fluid bolus administration was associated with a significant decrease in Hb levels at 8 h. **Lactate:** IV fluid bolus administration was not associated with change in lactate at 8 h and 24 h. **Bicarbonate & BE:** Fluid bolus was associated with significant decrease in mean bicarbonate and BE in patients surviving up to 24 h. **Chloride:** Fluid bolus was associated with a significant increase in chloride in patients surviving to 24 h.
Identification of patients with larger changes in organ	**Organ-function scores:** IV fluid bolus recipients had an increased risk of a large or very large increase in respiratory & neurological scores at 1 h and of a large or very large decrease in CVS-score at 1 h. Bolus associated changes in respiratory score persisted at 4 h.

function-scores & blood parameters (figure 7[g]; Paper 3 Annex 1, pp 10-12)	When absolute values of scores at 1 h and 4 h were considered, rather than change from baseline, a greater proportion of the bolus group had high respiratory and neurological scores than in the no bolus group, whereas a smaller proportion had high CVS-scores. **Hb levels:** A greater proportion of bolus recipients had very low Hb concentration (<7·5 g/dL and <5 g/dL) at 8 h. **Biochemistry:** Larger decreases from baseline in BE and bicarbonate, and larger increases in chloride were observed in bolus recipients.
Impact of bolus-volume on organ-function scores & blood parameters (Paper 3 Annex 1; pp 13, 14).	Effect of IV fluids bolus volume (< 30ml/kg or >30ml/kg) on organ-function, Hb & biochemical parameters was assessed in a further analyses. **Organ-function scores:** At 4 h first vital sign observation after high-volume bolus are documented, there were higher respiratory/neurological scores in patients who received high volume bolus (≥30 mL/kg). Distribution of cardiovascular scores at 4 h was similar in low and high-volume recipients. **Hb levels:** At 8 h there were lower Hb levels (but only in non-transfused participants) in high-volume bolus recipients. **Biochemistry:** At 24 h there were higher chloride and lower BE as well as bicarbonate levels, in the high-volume bolus recipients.
Identification of clusters of comparable "clinical phenotypes" (figure 8[h] & Paper 3 Annex 1; pp 17, 24–27).	Three clusters of patients with comparable "clinical phenotypes" were identified on the basis of their baseline characteristics. **Cluster-1** (n=1991) had the least derangement in organ function scores, Hb, lactate. **Mortality in cluster-1**: non-bolus group - 1%; bolus group - 4%. **Cluster-2** (n=795) included patients with severe anaemia (Hb <5 g/dL), high lactate, high CVS scores. Cluster-2 also had increased BE, lower bicarbonate and high chloride concentrations. **Mortality in cluster-2**: 14% in non-bolus group; 21% in bolus group. **Cluster-3** (n=384) was characterised by extremely high respiratory and neurological scores, but better maintained Hb levels. **Mortality was highest in cluster-3**: 26% in non-bolus group; 23% in bolus group. Considering all participants, there was a negative correlation between Hb and lactate (figure 3C). Associations between bolus and respiratory/neurological score, Hb, biochemistry in clusters-1 and cluster-2 were consistent with those seen in FEAST overall.
Post-hoc analysis to evaluate physiological changes associated with fluid bolus administration in the early hours of critical care management.	
Multivariant analysis of effects of fluid boluses on clinical outcomes (Paper 3, figure 4; Paper 3 Annex; pp 6, 7, 8 & table 8; pp 28-31) *Only samples with complete measures for all covariates were used for this analysis (N=1901).*	A covariate-analysis assessed: organ-function scores, Hb , chloride, bicarbonate, BE. Two approaches were chosen to estimate Hb & biochemical levels at 1 h in order to compensate for the gap of available data at this important time point: 1) Hb and biochemical values at 1 h were estimated based on measured values measured at 8 h (Hb) and 24 h (biochemistry) respectively. These estimates potentially underestimate derangement of Hb & biochemical levels, as patients who died in the first hours after recruitment are likely to have had the most severe derangements. 2) An additional estimation of biochemical values at 1h was conducted, using baseline values & data derived from the literature. Principal component analysis using organ-function scores & predicted values of blood parameters at 1 h was conducted. This analysis showed that distribution of fatal cases was distinct from survivors, while risk of mortality and derangements of covariates were related to effects of IV fluid bolus. When 1-h post-bolus values were used to predict mortality, using both methods of biochemical value estimations induced by fluid bolus, no longer a significant difference in terms of mortality between bolus and non-bolus group could be determined. Overall, results of the post-hoc analysis demonstrates that after fluid bolus administration respiratory/ neurological score and BE were major determinants of increased mortality risk. Specifically, SpO_2, AVPU score and BE were important parameters in this context. Potential interactions of different physiological mechanisms associated with "un-buffered" fluid administration are summarized in figure 5 (Paper 3).

Respiratory support

Mechanical ventilation in resource limited contexts - important considerations

Table 13 gives an overview of suggested aspects, which need to be considered if a unit introduces advanced airway management and mechanical ventilation. As outlined previously risks and benefits of mechanical ventilation need to be balanced, while considering resource limitations. Guidelines can support rational decision-making processes in stressful emergency situations.[241]

Table 13. Introduction of mechanical ventilation – important elements to consider.

A multi-disciplinary approach is required to set-up and maintain a "level 3 critical care unit (Table 1)".
Patients with following causes of ARF can benefit from short periods of invasive ventilation e.g.: - Upper airway obstruction (e.g. epiglottitis, tracheitis) - Refractory status epilepticus (e.g. cerebral Malaria) - Post-operative care; certain trauma contexts - Pleural space abnormalities (e.g. pleural effusion/empyema) - Neuro-toxic snake-bite envenomation Patients with severe ARDS and MOF may need invasive ventilations for longer periods and are likely to have a higher mortality risk. Associated co-morbidities need to be considered in the risk assessment (e.g. nutritional status, HIV status, haemato-oncological diseases as well as chronic respiratory, cardiac, neurological and renal conditions).
Advanced airway management **Preparation and direction of the intubation – a "check list" of intubation is required:[331]** - An experienced clinical team needs to be present - Suitable equipment for different age groups needs to be prepared - Close monitoring of vital functions; End-Tidal-CO_2/capnography is an essential parameter.[262,332] - "Intubation and emergency medication" Algorithms preparing for difficult airway / intubation scenarios:[331] - "Can ventilate, but cannot intubate"; "Cannot ventilate & cannot intubate"
Advanced airway management – preparation of frequent challenging clinical scenarios: Stabilize vital organ function prior to the start of the intubation process and administration of intubation drugs: - Airway management and respiration + oxygenation - Cardiovascular instability (e.g. septic shock, severe anaemia): o Consider careful fluid resuscitation or transfusion if indicated o Start of IV/IO adrenaline/noradrenaline infusion if indicated Rapid sequence induction or modified rapid sequence induction (e.g. Ketamine + fast acting neuromuscular blocking agent (e.g. Rocuronium)[332]
"Pit falls and troubleshooting" – Emergency response to respiratory complications of a ventilated child **CALL FOR HELP – "DOPE" approach[40]** Disconnect the patient from the ventilator => ventilate with another circuit / Ambu-bag + O_2 + stabilization of vital organ functions ("ABCDE") **Rapid and systematic problem analysis and management – DOPE** - **D**isplacement of the Endo-tracheal tube (ETT) or **O**bstruction - "**P**atient associated complications" o Pneumothorax / pleural effusion / empyema

○ Bronchospasm and secretions; reduced lung compliance ○ Patient-ventilator asynchrony ○ Cardiovascular instability - **E**quipment: ○ Technical issues: problems with ventilator circuit, ventilator, ventilator settings ○ Electricity, medical gas supply
Ventilation strategies for common clinical scenarios e.g.:[85,98,243,262] - Upper airway obstruction - Increased lower airway resistance/bronchospasm (e.g. asthma) - Decreased lung compliance (e.g. ARDS) - Infectious and non-infectious causes of encephalopathies & neuroprotection **Strategies for protective ventilation of the lungs:**[85,86,98,202,333] - Low tidal volume (< 10ml/ kg; 4-8ml/kg in adults) + adequate PEEP - Permissive hypercapnia can be considered in the absence of contraindications (e.g. encephalopathy, traumatic brain injury) - Prone position to consider; caution – complications. - Bundles for the prevention of ventilator-associated pneumonia - "Weaning" of mechanical ventilation and safe extubation (e.g. transition to NIV non-invasive ventilation)
Training : Regular skills and clinical simulation training in the working environment can be of important value to improve team-work and optimization of the working environment.
The "ESICM global intensive care" working group published recommendation regarding ventilatory support of adult patients with sepsis or septic shock in resource-limited settings.[333]

Circulation

WHO ETAT-update from 2016: A summary of definition of shock and management recommendations

Definition of shock and "impaired circulation" were reviewed by an WHO expert panel in 2016. Management recommendations were described considering the nutritional status of critically ill patients. Important elements of Hb transfusion thresholds or management of severe dehydration were not specifically revised.[39] The recommendations are designed for settings corresponding to a "level 1 critical care unit", described in Table 1.

Table 14. Shock: definition and management recommendations for children by WHO (2016)[38,39]
Management recommendations of shock and circulatory impairment according to a review by a WHO expert panel in 2016. These recommendations are defined for settings without high resource intensive care facilities. The right column contains some comments as well as management options for a "level 2 critical care unit" (Table 1).

Children with signs of haemodynamic instability need immediate evaluation & treatment, following WHO ETAT guidelines:[38] "ABCDE" **WHO definitions: Shock** – all three of the following signs: Cold extremities, CRT > 3 seconds, weak & fast pulse; Circulatory impairment – 1 or 2 of these signs		
Children with haemodynamic instability: No dehydration and no severe anaemia		
Clinical scenarios	**Management according to WHO guidelines**	**Comments and considerations, including management options on a "level-2 intensive care unit (see Table 1)**
Shock in non-malnourished children	Fluid management: 10–20 mL/kg, isotonic crystalloid fluids, 30–60 min. Regular clinical re-evaluation. If signs of shock persist, consider further fluid bolus: 10 ml/kg, 30 min. If shock has resolved, provide fluids to maintain normal hydration status. If, at any time, there are signs of fluid overload, cardiac failure or neurological deterioration, IV fluid infusion needs to be stopped	Respiratory function needs to be monitored (e.g. RR, SpO_2/FIO_2).[88,91] Supplemental O_2 needs to be available. SpO_2 should be maintained $\geq$ 94%.[39,210] Non- invasive respiratory is an option: in case of severe respiratory distress and/or $SpO_2 \leq 94$ despite supplemental O_2. Increasing evidence suggest the use of electrolyte balanced, isotonic solutions for fluid resuscitation (Paper 3; SSC- paediatric guidelines (2020).[85] Fluid refractory shock: low-dose inotrope infusion is an option in settings with adequate skill-level (Table 15; WHO – optimized supportive care of Ebola).[56] POCUS can support evaluation of cardiac function /fluid responsiveness.[154,164,303] Further research is needed to evaluate cardiac function and fluid responsiveness of children with SAM and haemodynamic instability.[271] Critically ill children with SAM might not immediately tolerate enteral fluids after stabilisation of vital organ functions. In these situations also children
Shock in children with SAM	IV fluids: 10–15 mL/kg of IV fluids over 30-60min; Consider to repeat (maximum volume: 30ml/kg).[38] Children with SAM, who do not improve after 1 hr need to receive a blood transfusion (10ml/kg, over 3 hrs). Children, who improve after the initial infusion need to receive, according to WHO, maintenance fluids via gastric tubes.	
Circulatory impairment	No IV fluid bolus. Appropriate maintenance fluids need to be started. According to WHO IV fluids in malnourished children should be avoided.	

		with SAM can benefit from careful administration of IV maintenances fluids (see below).
In the absence of shock or severe dehydration, rapid IV infusion of fluids may be particularly harmful for critically ill children with the following conditions e.g.: severe pneumonia, acquired or congenital heart disease, severe anaemia, neurological complications (e.g.; severe malaria, meningitis). Particular care needs to be taken in children with severe anaemia and/or SAM. In specific conditions fluid management needs to be adapted e.g.: Acute and chronic kidney injury, diabetic ketoacidosis.		

Children with severe anaemia, with and without SAM
In a review of WHO ETAT guidelines (2016) a transfusion thresholds of Hb levels: 5g/dl is recommended.[39] The WHO pocket-book (2nd edition, 2013) suggests to transfuse in the following clinical scenarios:[38]
- All children with an Hb of ≤ 4 g/dl
- Children with Hb, 4–6 g/dl with any of the following clinical features:
  ○ Deep, laboured breathing
  ○ Clinically detectable dehydration or shock; signs of heart failure
  ○ Impaired consciousness
  ○ Very high malaria parasitaemia (> 10% of red cells with parasites).		

Haemodynamic instability	**Management according to WHO guidelines**	**Comments and considerations, including management options on a "level-2 intensive care unit (Table 1)"**
Severe anaemia and signs of shock or "circulatory impairment"	No pre-transfusion fluid bolus should be given. RBC transfusion needs to be started as early as possible. While waiting for transfusions IV maintenance fluids can be started. RBC transfusion volumes and rates according to WHO: - Patients with no SAM: 15-20ml/kg over 3-4 hrs of packed red blood-cells or whole blood respectively - Patients with SAM 10ml/kg, RBC transfusion over 3 hrs	Some evidence suggests that a Hb threshold for transfusion of 5g/dl may be too low for critically ill children with signs of respiratory, circulatory and/or neurological dysfunction. There is some evidence that these critically ill children may benefit from earlier RBC transfusions (see also Paper 3).[85,266] Echocardiography studies suggest that hospitalized children with SAM may not have a higher risk to present with cardiac dysfunction as compared to children with no SAM. [271] A degree of harmonization of WHO-transfusion and resuscitation guidelines for children with and without SAM would facilitate "real life" practice.
Children with severe dehydration		
Haemodynamic instability	**Management according to WHO guidelines[38]**	**Comments and considerations, including management options on a "level-2 intensive care unit (Table 1)"**
Severe dehydration in non-malnourished children	Start IV fluid immediately. Give 100 ml/kg Ringer's lactate solution (or, if not available, normal saline), divided as follows: Age > 12 months: - Step 1: First give 30 ml/kg in 30minutes	Plan C needs to be used with caution. Level of dehydration is often difficult to evaluate. Patients need to be reviewed frequently in order to prevent fluid overload.

<table>
<tr><td></td><td>- Step 2: Then give 70 ml/kg in 2,5 hours
Infants (< 12 months):
- Step 1: First give 30 ml/kg in 60 minutes
- Step 2: Then give 70 ml/kg in 5 hours
Step 1: Repeat once if radial pulse is still weak or not detectable
Reassess every 15–30 min. If hydration status is not improving, give the IV drip more rapidly.
Avoid overhydration. Give ORS (about 5 ml/kg per h) as soon as the child can drink.</td><td rowspan="2">Paper 3 suggests the use isotonic, electrolyte balanced fluids. This is particularly relevant in the treatment of severe dehydration as potentially large volumes of IV fluids are administered.
In general, a more careful approach to rehydration in children with severe dehydration might be beneficial.[292]
POCUS can be of benefit to guide fluid management in this context.[154,164]
Hb levels need to be monitored in children requiring fluid resuscitation (Paper 3). Children presenting with severe dehydration and severe or moderate anaemia need particular attention. RBC transfusion might be needed at an early state in the treatment of these children.
WHO does not clearly specify fluid management in children with severe anaemia and severe dehydration while waiting to prepare RBC transfusions. If pre-transfusions IV fluids are given in this particular context, only small volumes should be administered (e.g., 5-10 ml/kg IV fluids- suggestion of the author).</td></tr>
<tr><td>Severe dehydration & severe anaemia</td><td>According to the the WHO pocket-book (2nd edition, 2013) WHO, with Hb, 4–6 g/dl with clinically detectable dehydration should be transfused.</td></tr>
<tr><td>Signs of severe dehydration in children with SAM</td><td>Children with SAM, severe dehydration and no signs of shock should receive according to WHO, the following treatment:
“ReSoMal rehydration fluid orally or by nasogastric tube:
– Give 5 ml/kg every 30 min for the first 2 hr.
– Then give 5–10 ml/kg per hr for the next 4–10 hrs on alternate hours, with F-75 formula. The exact amount depends on how much the child wants, the volume of stool loss and whether the child is vomiting.”</td><td>ReSoMal (an oral rehydration solution (ORS) for the treatment of malnourished children), has lower sodium (45mmols/l) and higher potassium content (40mmols/l), than ORS suggested for treatment of non-malnourished children. Some studies describe a considerable risk of hyponatraemia associated with the use of ReSoMal.[296] The composition of oral rehydration fluids used in malnourished children needs to be reviewed in future research.[296]</td></tr>
<tr><td colspan="3">Critically ill children with haemodynamic instability with and without SAM have a considerable mortality risk and need to be monitored closely. Monitoring and treatment on a critical care unit is needed:
- Further stabilisation of vital organ function depending on available level of care.
- Treatment of severe infections and infectious source control needs to be initiated as soon as possible.[85]
- Renal function (urine output)[284] and fluid balanced needs to be monitored carefully in critically ill children.
- After stabilisation of vital organ functions in many children with and without SAM enteral ORS/RESOMAL or enteral nutrition is not tolerated immediately. IV maintenance fluids may be needed for a period of time. Electrolyte balanced, isotonic solutions containing Dextrose 5% or 10% should be used. Careful surveillance and adaptation of maintenance fluids in different clinical scenarios is needed.
- International guidelines and practice suggests to introduce enteral nutrition progressively in children recovering from haemodynamic instability.[265] These principles should also be practiced and evaluated in malnourished and non-malnourished children treated in resource-limited settings.</td></tr>
<tr><td colspan="3">For the management of dengue toxic shock syndrome – see specific WHO guidelines.[39]</td></tr>
</table>

Introduction of low-dose infusions of vaso-active medication – important considerations

Table 15. Infusion of vaso-active medication – aspects to consider.
Units using infusions of vaso-active medication as part of care package of critically ill children need adequate set-up and skilled clinical teams (Table 1, level of critical care).

Clinical aspects	Details
Respiratory support	Provision of supplemental O_2 and/or non-invasive respiratory support.
Fluid management and transfusions	Careful optimization of intra-vascular fluid volumes. POCUS can play an important role in this context. Optimization of Hb levels; safe blood transfusion services need to be available.
Monitoring	Regular clinical re-evaluation, vital signs : SpO_2/FIO_2, RR, HR, automated non-invasive blood pressure measurements, clinical neurological assessment, urine-output (non-invasive methods are preferred). Hb and blood sugar levels need to be reviewed regularly. Electrolytes (e.g., ionized Calcium levels) and blood gases/Lactate can be reviewed in some settings.
Infusion of vaso-active medication	Pragmatic clinical management guidelines and working aids (e.g., Adrenaline & Noradrenaline infusion charts) need to be available.[56,299] IV-lines need to be inserted and fixed with care. Infusion sites need to be monitored closely. "Midlines" and peripherally inserted central lines can be considered in some settings. Central lines, if available are recommended for the use of vaso-active medication in adult patients [299]. Central lines in children can only be considered if adequate skill-levels to safely insert and maintain central venous access are available. IPC measures need to be respected during line insertion as well as during preparation of infusions. Medical teams need to be trained in the use of intra-osseous access.[38,40] Syringe pumps should be used for administration of vaso-active medication.[56,299]
Further aspects	Pragmatic training programs are needed including clinical training as well as the correct use and maintenance of biomedical equipment.

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BMJ Open Respiratory Research

Use of bubble continuous positive airway pressure (bCPAP) in the management of critically ill children in a Malawian paediatric unit: an observational study

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ABSTRACT

Introduction In low-resource countries, respiratory failure is associated with a high mortality risk among critically ill children. We evaluated the role of bubble continuous positive airway pressure (bCPAP) in the routine care of critically ill children in Lilongwe, Malawi.

Methods We conducted an observational study between 26 February and 15 April 2014, in an urban paediatric unit with approximately 20 000 admissions/year (in-hospital mortality <5% approximately during this time period). Modified oxygen concentrators or oxygen cylinders provided humidified bCPAP air/oxygen flow. Children up to the age of 59 months with signs of severe respiratory dysfunction were recruited. Survival was defined as survival during the bCPAP-treatment and during a period of 48 hours following the end of the bCPAP-weaning process.

Results 117 children with signs of respiratory failure were included in this study and treated with bCPAP. Median age: 7 months. Malaria rapid diagnostic tests were positive in 25 (21%) cases, 15 (13%) had severe anaemia (Hb < 7.0 g/dL); 55 (47%) children had multiorgan failure (MOF); 22 (19%) children were HIV-infected/exposed. 28 (24%) were severely malnourished. Overall survival was 79/117 (68%); survival was 54/62 (87%) in children with very severe pneumonia (VSPNA) but without MOF. Among the 19 children with VSPNA (single-organ failure (SOF)) and negative HIV tests, all children survived. Survival rates were lower in children with MOF (including shock) (45%) as well as in children with severe malnutrition (36%) and proven HIV infection or exposure (45%).

Conclusion Despite the limitations of this study, the good outcome of children with signs of severe respiratory dysfunction (SOF) suggests that it is feasible to use bCPAP in the hospital management of critically ill children in resource-limited settings. The role of bCPAP and other forms of non-invasive ventilatory support as a part of an improved care package for critically ill children with MOF at tertiary and district hospital level in low-resource countries needs further evaluation. Critically ill children with nutritional deficiencies and/or HIV infection/exposure need further study to determine bCPAP efficacy.

Key messages

- The high survival rates among children with very severe pneumonia and no other severe organ dysfunctions, documented in this study, indicate that bCPAP can be used safely and efficiently in resource-limited but well-supervised paediatric units in SSA.
- Multiorgan failure, malnutrition and HIV infection/exposure were associated with an increased mortality risk. The role of bCPAP and other forms of NIV as a part of an improved care package for malnourished and non-malnourished critically ill children (including shock ± anaemia) needs further evaluation.
- The study highlights the importance of a multidisciplinary approach in the implementation process of basic paediatric critical care measures like bCPAP, e.g.: efficient logistic set-up of patient circuits, reliable oxygen systems including reliable electricity supply, cost-effective, good quality medical equipment, biomedical input, support of health workers and training.

INTRODUCTION

In 2015, 5.9 million children died before the age of 5 years with approximately 50% of these deaths occurring in sub-Saharan Africa (SSA).[1] Very severe pneumonia (VSPNA) based on the WHO classification remains a leading cause of child mortality.[1] Although there has been a considerable decline in mortality in hospitalised Malawian children between 2000 and 2012, mortality remained high in 2012 in critical subgroups including those with VSPNA (12%), severe undernutrition (15%) and severe acute malnutrition (35%).[2] Despite the introduction of *Haemophilus influenzae* B and pneumococcal conjugate vaccines, severe respiratory infections (bacterial and viral) are likely to remain a major cause of morbidity and mortality in

SSA. Paediatric emergency and critical care, adapted to available resources, is therefore essential in order to achieve further reductions in child mortality. Improvements of non-invasive respiratory support can play an important role in this context.

Respiratory failure is also a common feature of critically ill children with severe sepsis.[3] Severe infections can lead to a complex systemic inflammatory response, and a variety of conditions such as pneumonia, bacteraemia and malaria can coexist.[4 5] Without early, efficient management, these infections can progress to significant organ dysfunction, including acute respiratory distress syndrome and respiratory failure.[3] Respiratory support is therefore an essential element in the management of critically ill, septic children.[6–8]

Improved paediatric emergency care in health facilities and streamlined referral pathways can have a significant impact on child survival. Improvement of oxygen delivery and respiratory support plays an important role in this context. A recent study conducted in Malawi showed that the use of pulse oximetry in peripheral outpatient health facilities and village clinics can help clinicians and community health workers to identify children with severe pneumonia and hypoxaemia.[9] A study in Papua New Guinea demonstrated that the reliable supply of low flow oxygen can reduce mortality among children with signs of severe pneumonia.[10] Oxygen concentrators in conjunction with reliable electricity systems associated with 'uninterruptable power supply' are cost-effective and provide a reliable method of oxygen supply in low-resource settings.[11 12] Installation and maintenance of these 'oxygen systems', however, remain a challenge in many health facilities in African countries.[13] The combination of solar-powered energy systems and the use of oxygen concentrators can be an option to improve oxygen supply in health facilities in remote settings.[14]

Non-invasive respiratory support has the potential to improve the outcome of critically ill children managed in low-resource settings, and notably, the role of non-invasive ventilatory (NIV) support in the management of septic children with 'less severe Acute Respiratory Distress Syndrome (ARDS)' is also under evaluation in high-resource settings.[15]

Different forms of NIV exist: continuous positive airway pressure (CPAP), high-flow of warmed and humidified air/oxygen via nasal cannula, bilevel positive airway pressure and neuronally adjusted ventilatory assist.[16 17]

CPAP has been used efficiently for the treatment of children with respiratory dysfunction in high-resource settings (eg, viral bronchiolitis).[18–20] It has been shown that bubble CPAP (bCPAP) administered through nasal prongs offers a good quality, relatively low-cost alternative to ventilator-delivered CPAP on neonatal units.[21] Feasibility and safety of bCPAP use on neonatal units in middle-income and low-income countries have also been evaluated.[22]

A recent randomised controlled trial (RCT) conducted in Bangladesh showed that children with VSPNA treated with bCPAP had a significantly lower mortality rate (4%) compared with a group treated with low-flow O_2 (15%).[23] A further study conducted in Ghana demonstrated that CPAP can be used efficiently in the management of children with respiratory distress in SSA.[24]

A smaller study described the use of an improvised bCPAP set-up (mostly non-humidified flow) on an extremely busy paediatric unit in Malawi for children (29 days to 59 months) with VSPNA and children presenting with signs of respiratory dysfunction in the context of critical illness (eg, severe malaria) including shock and severe anaemia.[25] Several months later, the authors had the opportunity to introduce a better adapted bCPAP set-up in the same clinical environment. Its use with a larger and better-described cohort, and its success or failure dependent on patient risk characteristics and their association with death while on bCPAP, is reported here.

METHODS

Study population and setting

We conducted an observational study of all children 0–15 years treated with bCPAP between 26 February and 15 April 2014 in the paediatric department at Kamuzu Central Hospital in Lilongwe, Malawi. In 2014, this department had approximately 20 000 paediatric admissions of infants and children ages 0–15 years. This observational study was conducted during the peak of the malaria season in 2014, with >3000 admissions/month in March and April 2014 and a mortality rate of approximately 4%.[26] Most newborns were treated on a dedicated neonatal unit. A small number of newborns born outside Kamuzu Central Hospital, received respiratory support with bCPAP on the paediatric unit. Only these newborns were included in the study.

Patients were initially screened in a triage/admission zone. Critically ill children with emergency signs[27] were managed in a 'resuscitation zone (4 beds for 4, sometimes up to 16 patients)'. This area was directly connected to a 'critical care/emergency zone' (approximately 16–18 beds—for up to 30–60 patients), where further basic critical care, according to WHO guidelines[27] (including management of airway and breathing, intravenous or intraosseous fluids, blood transfusion, nutritional support, oral and intravenous medications), was provided. Approximately eight oxygen concentrators, backed up with oxygen cylinders, were available. The oxygen flow provided by each of these devices can be split to deliver low-flow O_2 to up to five patients.

This centralisation of basic critical care enabled a limited number of staff to provide the best possible management (including vital signs approximately 2–3 times per day and more frequent monitoring in very sick patients) to a large number of critically ill children (nurse to patient ratio: 1:15–30, doctors/clinical officers: 2–4 (day) and 1–2 (night); supervision by at least one consultant on site for 12 hours per day). In a six-bed 'high

dependency unit (HDU)', closer observation of selected critically ill children could be provided (spot-checks of vital signs approximately 2–4 hourly). The number of HDU beds was insufficient for the management of the large number of critically ill children.

Survival was defined as survival during the bCPAP treatment and during a period of 48 hours following the end of the bCPAP-weaning process.

The unit's policy was to offer HIV testing and counselling to every hospitalised child. However, because of the high workload and limited numbers of HIV counsellors not all admitted children were tested prior to death or discharge.

Basic 'point of care tests' were usually available, including malaria rapid diagnostics tests (MRDT), haemoglobin tests and blood sugar analysis. Further laboratory tests like blood gases, electrolytes, renal and liver function, and full blood counts were not available. The blood bank was able to provide urgent whole blood transfusions generally within 2–4 hours but at times there was more of a delay.

Basic bedside ultrasound and echocardiography helped to define thoracic and abdominal pathologies, cardiac function and congenital heart diseases. Access to chest X-rays was inconsistent.

Definitions and comorbidities

VSPNA was diagnosed by the presence of cough or difficulty breathing with either SpO_2 <90%, central cyanosis, severe respiratory distress (very severe chest indrawing), danger signs such as inability to drink or breast feed, lethargy, and reduced level of consciousness. Multiorgan failure (MOF) was defined as having respiratory dysfunction with either cardiovascular dysfunction (including severe anaemia) or central nervous system dysfunction at the time of bCPAP initiation. Severe anaemia was defined as an Hb <7 g/dL or clinically when rapid point-of-care testing was not available. Central nervous system dysfunction was defined as a Blantyre Coma Scale ≤3 or status epilepticus.

HIV status was defined as 'infected' if a child <2 years had a positive DNA PCR test or a child ≥2 years had a positive rapid test. A child was considered to be HIV 'exposed' if there was a positive rapid test for a child <2 years or a documented maternal positive test, but no DNA PCR had yet been performed.

Malaria was diagnosed by MRDT, and all children with malaria receiving bCPAP would have been found to have severe malaria by virtue of their respiratory distress, shock or neurological dysfunction.

Nutritional status was described as either normal, moderate acute malnutrition or severe acute malnutrition by WHO guidelines when data—usually mid-upper arm circumference (MUAC)—were available.

Other comorbidities included congenital heart defects diagnosed by bedside echocardiography, cerebral palsy, spina-bifida, hydrocephalus, neuromuscular disorders and other forms of neurodisability, sickle cell disease, malignancy or clinically suspected tuberculosis.

Inclusion criteria and initiation of bCPAP

Critically ill children of any age were initiated on bCPAP if, after initial resuscitation, they were found to have severe respiratory distress with or without further organ dysfunctions like shock, severe anaemia or neurological dysfunction. bCPAP could be initiated in the emergency zone or HDU depending on bed availability.

Fluid resuscitation

Children with signs of shock and no signs of dehydration received only careful fluid resuscitation (10 mL/kg isotonic crystalloid solution). After re-evaluation, one further fluid bolus was administered in some children (a third bolus was only given very rarely). Malnourished children with signs of shock and no dehydration received only one fluid bolus. If possible, haemoglobin (Hb) was rechecked after each fluid bolus.

Children with severe anaemia did not receive a pre-transfusion bolus. In case of severe anaemia, 20 mL/kg whole blood was transfused over 3–4 hours if HBs were <5–6 g/dL. This practice is in line with the latest WHO recommendations from 2016.[28]

In case of severe dehydration, WHO guidelines for the management of malnourished and non-malnourished children were followed as well.[28]

bCPAP device (see figure 1)

The low-cost bCPAP devices used in this study were modified oxygen concentrators with a maximum air/oxygen flow of 16 litres per min (LPM) (maximum oxygen flow: 8 LPM, maximum air flow: 8 LPM; http://go.gomango.co.uk/diamedica.co.uk/english/product_details_diamedica.cfm?id=1562). The FiO_2 could be determined by adjusting the ratio of oxygen/air flow. The blended flow was humidified and in some devices could be warmed using the heat produced by the compressor of the oxygen concentrator. The pressure was determined by the distance of the distal part of the expiratory limb of the ventilation circuit below the water surface of a water bottle ('resistor').

In case not enough 'bCPAP set-ups' were available, oxygen cylinders were used to provide O_2 flow required to provide bCPAP. With this 'suboptimal set-up', the FiO_2 could not be adapted but oxygen flow could still be humidified. Patients were switched to the described 'modified oxygen concentrator' whenever such a device was available.

Basic further care of critically ill children managed with bCPAP

Additional aspects of care for patients on bCPAP included head-up positioning, nasogastric tube (NGT) insertion for initial gastric decompression and drainage, intravenous maintenance fluids initially at 2/3 of the

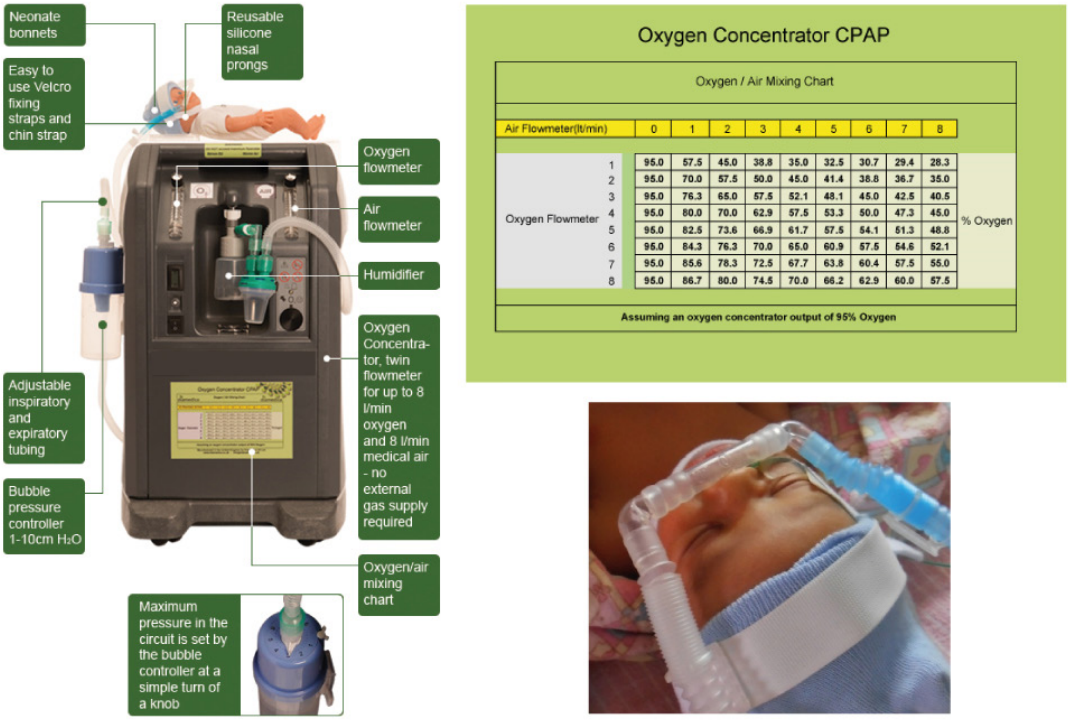

Figure 1 Bubble continuous positive airway pressure (bCPAP) set-up. (With permission of Diamedica: http://go.gomango.co.uk/diamedica.co.uk/english/product_details_diamedica.cfm?id=1562)

'4-2-1 rule'[29] were administered. Isotonic electrolyte solutions (Ringers lactate and dextrose)[30] were used as maintenance fluids. Once vital organ functions were stabilised, 3-hourly NGT feeds were introduced gradually with expressed breast milk for infants, F-75 for children>6 months with SAM. Regarding enteral nutrition of critically ill children without severe acute malnutrition (SAM): Not enough therapeutic nutrition (F75 or F100) was available for the nutrition of critically ill children without SAM. No other specific enteral nutrition was available for this purpose. Therefore ordinary milk products or porridge were used for gastric tube feeding of these critically ill children. In many cases, tolerance of enteral feeds was initially tested with the administration of oral rehydration fluids via NGTs. The maximum volume of enteral feeds administered during this 'critical care phase' for malnourished and non-malnourished children was 100% according to the '4-2-1 rule'[29].

National and WHO guidelines were applied to treat tuberculosis, HIV, malnutrition and common conditions like severe malaria, respiratory infections, diarrheal diseases, meningitis and bacterial sepsis.[27]

Monitoring and vital signs

Rapid clinical screening was done to triage patients requiring non-invasive respiratory support. Basic vital signs (heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2), temperature) were monitored usually 2–3 times per day by vital signs assistants[31] or qualified nurses.

CPAP settings

bCPAP pressure was commenced at 6–7 cm H_2O.[19] The initial FiO_2 was set at approximately 0.6%. Pressure and FiO_2 were adjusted depending on signs of work of breathing and peripheral oxygen saturation measurement by pulse oximetry (SpO_2). The aim was to maintain SpO_2 >94%. bCPAP pressure was usually kept ≤8 cm H_2O and only in rare cases increased to 10 cm H_2O. Humidified air/oxygen flow was used for all children.

bCPAP weaning protocol

When using the modified oxygen concentrator set-up, FiO_2 was reduced when SpO_2 was consistently >94% (FIO_2 could not be adapted if O_2 cylinders were used as

flow generator). If work of breathing and RR improved with SpO_2 remaining consistently >94% (with an FIO_2 ≤0.5%) bCPAP pressures were reduced gradually. If the patient remained stable and the bCPAP level was ≤5 cm H_2O (with an FIO_2 <0.3-0.4), then a trial 'off bCPAP' was started and the child was placed on low-flow oxygen (1–2 LPM). In cases of clinical deterioration, bCPAP was restarted. This clinical scenario was not considered as a 'treatment failure'. In the data analysis, this additional phase of 'bCPAP management' was considered as part of the 'bCPAP weaning process' and the initial treatment. The duration of the weaning process was depending on the child's clinical progress. In the data analysis, the end of the weaning process was documented as the end of the bCPAP treatment.

Data collection and analysis

A case record form, an observation chart and a patient register were used for data collection. Data were entered into an Excel database. We describe the proportion of bCPAP cases who survived by risk group, sex, age, complications, HIV status and treatment methods. We conducted univariable logistic regression to determine if the odds of bCPCP survival were higher in particular subgroups. The small number of cases precluded multivariable analysis. We also present a breakdown of survival and death (failure) by HIV status and comorbidities including shock, malaria, anaemia, MOF and severe malnutrition, and describe the reasons for complications of treatment. This study was done in a routine setting without dedicated funding and did not have a target sample size. The sample includes most bCPAP cases seen between 26 February and 15 April 2014. All analyses were done in Stata V.14.2 for Mac.

RESULTS

A total of 117 patients were included and 79 (68%) survived (table 1). Survival was similar among males and females, and did not differ statistically by age group, though there were small sample sizes in each group. Survival was lower in those with MOF (45%) than those with single-organ failure (SOF) and no comorbidities (86%; p<0.0001, table 1). Survival was also significantly lower in those with severe acute malnutrition (36%) than with no severe or moderate malnutrition (81%; table 1), and in those with confirmed HIV infection or exposure (45%) than those who were HIV negative (81%) or with an unknown HIV status (68%; table 1). There were no statistically significant differences in survival by bCPAP delivery device or treatment initiation location (table 1).

All 19 children with VSPNA who were HIV negative and had no comorbidities and no other organ dysfunctions survived (five children in this group had suspected TB). Also, 40/42 (95%; 95% CI 84% to 99%) of children with VSPNA (unknown or negative HIV status) and no comorbidities and no other organ dysfunction survived. Children with VSPNA and HIV infection/exposure and/or malnutrition had significantly increased mortality risk (see table 2). Respiratory failure with additional organ dysfunctions (shock, anaemia) was associated with lower survival rates.

In total, 14/15 (93%) children with severe anaemia were transfused. Four out of seven with severe anaemia and shock survived. Also, 6 out of 14 children with anaemia who were transfused died. The one patient with severe anaemia who was not transfused survived. And, 11 out of 15 children with severe anaemia had positive malaria tests. Also, 7 of these 11 children survived.

Among the 31 children with severe malaria, 24 had multiorgan dysfunction. In total, 14 of these 24 children survived. Of children with positive malaria tests, 11/31 (35%) had signs of shock. Also, 5 of these 11 children survived.

Technical issues and complications

The average flow set was 9.1 LPM (SD 2.0, range 5–16). The average starting pressure was 6.7 cm H_2O (SD 1.0, range 4–9).

In total, 13/117 patients experienced equipment-related complications, including blocked nostrils (2) or nasal prongs (2), interruption of oxygen supply from depleted cylinder (2), nasal septum lesions (7) and aspiration of feeds (1). One parent refused the continuation of bCPAP. Some patients had more than one complication. The total number of treatment failures among those experiencing complications was 3/13 patients.

DISCUSSION

This basic observational study was conducted on a very busy paediatric unit in Malawi during peak malaria season.

We describe a group of children with a high mortality risk. Because of resource limitations, we took the approach of offering bCPAP to those children having the most severe clinical presentations.

In high-resource settings, a considerable number of the 62 children with respiratory dysfunction and the 55 children with MOF potentially would have been mechanically ventilated and would have received further critical care interventions in a paediatric intensive care unit (PICU).[7]

Context-adapted disease severity scores (comparable to Paediatric Index of Mortality (PIM)[32]/Pediatric Risk of Mortality Score (PRISM)[33] -scores used in PICUs) based on parameters describing acute physiological status and underlying conditions (eg, HIV infection, nutritional status) can help to describe and compare cohorts of critically ill children and adults managed in low-resource settings. Further research in this context is needed.[34–37]

In the study setting, only some children could benefit from intubation and ventilation. Surveys highlight the challenges associated with the set-up of intensive care units providing mechanical ventilation of children. Significant resources will be directed to only a small

Table 1 Demographics and outcomes

	Patients (n)	n=survived bCPAP (%)*	n=bCPAP death (%)*	OR of death (95% CI)
Total	117	79 (68%)	38 (32%)	
Demographics				
Male†	58	40 (69%)	18 (31%)	1.00
Female†	51	34 (67%)	17 (33%)	1.11 (0.50 to 2.49)
Median (IQR) age in months	7 (2– 15)	6 (2–15)	7 (4–14)	
Age (months)†				
<1	6	3 (50%)	3 (50%)	1.00
1–12	76	53 (70%)	23 (30%)	0.43 (0.81 to 2.31)
13–24	23	17 (74%)	6 (26%)	0.35 (0.06 to 2.25)
25–48	10	5 (50%)	5 (50%)	1.00 (0.13 to 7.57)
Organ failure				
VSPNA	62	54 (87%)	8 (13%)	
VSPNA no comorbidities‡; including children<1 month	59	51 (86%)	8 (14%)	1.00
VSPNA with comorbidities‡	3	3 (100%)	0 (0%)	
VSPNA no comorbidities; no HIV exposure/infection, no malaria, no suspected TB‡	14	14 (100%)	0 (0%)	
VSPNA; no comorbidities; no HIV exposure/infection, no malaria; including suspected TB	19	19 (100%)	0 (0%)	
MOF >1 organ dysfunction‡: respiratory dysfunction and at least one further organ dysfunction	55	25 (45%)	30 (55%)	vs VSPNA: 8.10 (3.25 to 20.18)¶
MOF >2 organ dysfunctions‡: (respiratory dysfunction and at least two other organ dysfunctions)	21	9 (43%)	12 (57%)	
Malnutrition†				
SAM	28	10 (36%)	18 (64%)	7.59 (2.88 to 19.97)§
MAM	13	8 (62%)	5 (38%)	2.63 (0.75 to 9.29)
No MAM or SAM	73	59 (81%)	14 (19%)	1.00
HIV status				
Infected or exposed	22	10 (45%)	12 (55%)	4.97 (1.53 to 16.13)¶
Negative	36	29 (81%)	7 (19%)	1.00
Unknown	59	40 (68%)	19 (32%)	1.97 (0.73 to 5.29)
bCPAP delivery device				
Cylinder	50	35 (70%)	15 (30%)	1.00
Concentrator	48	30 (62%)	18 (38%)	1.40 (0.60 to 3.25)
Unrecorded	17	12 (71%)	5 (29%)	0.97 (0.29 to 3.25)
Treatment initiation location				
High dependency unit	29	17 (59%)	12 (41%)	1.55 (0.65 to 3.70)
Emergency zone	83	57 (69%)	26 (31%)	1.00
Intubation**				
No	100	77 (77%)	23 (23%)	1.00
Yes	15	2 (13%)	13 (87%)	21.8 (4.6 to 103.5)††

Continued

Table 1 Continued

	Patients (n)	n=survived bCPAP (%)*	n=bCPAP death (%)*	OR of death (95% CI)
Median (IQR) treatment duration (hours)	24 (24–60)	24 (24–60)	24 (24–48)	

Comorbidities: congenital heart diseases (4 (children with congenital heart diseases: AVSD: 2 (1 with trisomy 21), VSD: 1; PDA: 1 (and trisomy 21))), neurodisability (cerebral palsy (1), hydrocephalus (1), neuromuscular disorder (1), severe thorax wall infection/defect (1). bCPAP,bubble continuous positive airway pressure; HB, haemoglobin; MAM, moderate acutemalnutrition; MOF, multiorgan failure; SAM, severe acute malnutrition; TB,tuberculosis; VSPNA, very severe pneumonia. AVSD, Atrio-ventricular Septum Defect; VSD, Ventricular Septum Defect; PDA, Persistent Ductus Arteriosus

*The percentages given in column 3 and 4 describe the ratios to the subtotals documented in column 2.
†Information on sex (male/female) was not recorded for eight patients. Information on age was not recorded for two patients. Information on malnutrition (MAM or SAM) was not recorded for three patients.
‡Organ dysfunction: respiratory failure (signs of very severe pneumonia[50], signs of shock or 'impaired circulation'[28], severe anaemia (HB< 7 g/dl), coma/prolonged convulsions, clinical signs of liver/renal failure.
§p<0.0001.
¶p=0.008.
**In 2 of the 117 patients the information on potential intubation and ventilation was not documented.
††p<0.000.
bCPAP, bubble continuous positive airway pressure; HB, haemoglobin; MAM, moderate acutemalnutrition; MOF, multiorgan failure; SAM, severe acute malnutrition; TB, tuberculosis; VSPNA, very severe pneumonia.

number of critically ill patients and specific skill levels are required.[38–40] Routine mechanical ventilation of critically ill children is therefore not yet a feasible option for a large number of paediatric units in SSA.

A survey conducted on the same unit in 2012 using an improvised bCPAP set-up showed the following survival rates: overall survival—41/77 (53%), survival among children with VSPNA—19/26 (73%) and VSPNA in HIV-negative children—14/17 (82%).[25]

Several factors could explain the improved outcome of patients with respiratory failure managed with bCPAP described in this publication. The disease severity of the cohorts described in this publication and the study from 2012 are difficult to compare. Furthermore, in the 2-year interval between the studies training, senior supervision and paediatric emergency care was improved on the unit in Lilongwe. Introduction of conjugated pneumococcal vaccine in the routine vaccination schedule in Malawi in the time period between 2012 and 2014 could have had an impact on the spectrum of pathogens causing severe respiratory infections and other severe bacterial infections in young children. However, the improved bCPAP set-up including the use of humidified air/oxygen might have contributed to improved outcomes as well. There is considerable evidence indicating that the relatively high air/oxygen flow used in NIV should be 'conditioned (warmed and humidified)'.[41 42]

The outcome of HIV-negative children with severe respiratory dysfunction (SOF) managed with bCPAP in this study (mortality rate in this subgroup: 0%) is comparable to outcomes of children with respiratory failure managed with bCPAP in the context of an RCT recently conducted in Bangladesh (mortality rate: 4%).[23] Outcomes of this subgroup indicate that the use of bCPAP as a form of NIV is feasible on a busy paediatric critical care department in SSA.

In high-resource settings, proactive respiratory support is standard care in the management of multiorgan dysfunction.[8] In this context, the role of NIV in less severe ARDS requires further evaluation.[15] In low-resource settings, NIV has the potential to improve respiratory care for critically ill children, where options for safe mechanical ventilation are extremely limited.

An increased mortality risk among children with respiratory dysfunction associated with severe malnutrition and/or HIV infection/exposure is suggested by this survey, as demonstrated in other studies.[43] In total, 17 out of 28 children with SAM treated in this study had more than one organ dysfunction (eg, shock).

An RCT is currently being conducted in Malawi comparing the use of bubble CPAP and low-flow oxygen in children with respiratory failure with and without further organ dysfunctions, including children with HIV and malnutrition.[44]

Children who had their treatment initiated in the emergency zone had a higher survival rate than children treated in the HDU. This difference was not statistically significant. This 'trend' is likely to be explained by a significant selection bias with much sicker patients being treated in the HDU. The six-bedded HDU was certainly too small for a paediatric unit with around 20 000 admissions per year. Following rapid identification further 'context adapted' critical care management in a 'HDU- setting' is very likely to improve survival chances of critically ill children.

One child in this study suffered an episode of aspiration. A recent study conducted in Australia showed that children requiring CPAP did not have an increased risk

Table 2 Survival by HIV status and presence of a positive MRDT, signs of shock ±anaemia, MOF and malnutrition

Diagnostic categories (N)	Survival	VSPNA, no comorbidity*, N=58 (% who survived or died; 95% CI)	Suspected TB, N=20 (% who survived or died; 95% CI)	Signs of shock†; N=22 (% who survived or died; 95% CI)	MRDT positive; N=31 (% who survived or died; 95% CI)	Anaemia N=15 (% who survived or died; 95% CI)	MOF‡ >1 organ failure; N=54 (% who survived or died; 95% CI)	SAM (61% had MOF) § N=28 (% who survived or died; 95% CI)
HIV non-exp. or non-reactive (n=36)	Survived	19 (100%; 82% to 100%)	7 (78%; 40% to 97%)	3 (43%; 10% to 82%)	6 (60%; 26% to 88%)	2 (67%; 9% to 99%)	9 (56%; 30% to 80%)	4 (50%; 16% to 82%)
	Died	0 (0%; 0% to 17%)	2 (22%; 3% to 60%)	4 (57%; 18% to 90%)	4 (40%; 12% to 74%)	1 (33%; 1% to 91%)	7 (44%; 20% to 70%)	4 (50%; 16% to 82%)
HIV exposed or reactive (n=22)	Survived	8 (57%; 29% to 82%)	2 (22%; 3% to 60%)	1 (100%; 2.5% to 100%)	2 (50%; 7% to 93%)	1 (33%; 1% to 91%)	1 (14%; 0% to 58%)	2 (17%; 2% to 48%)
	Died	6 (43%; 18% to 71%)	7 (78%; 40% to 97%)	0 (0%, 0% to 97.5%)	2 (50%; 7% to 93%)	2 (67%; 9% to 99%)	6 (86%; 42% to 100%)	10 (83%; 52% to 98%)
HIV status unknown (n=59)	Survived	21 (91%; 72% to 99%)	1 (50%; 13% to 99%)	6 (43%; 18% to 71%)	12 (71%; 44% to 90%)	6 (67%; 30% to 93%)	15 (47%; 29% to 65%)	4 (50%; 16% to 82%)
	Died	2 (9%; 1% to 28%)	1 (50%; 13% to 99%)	8 (57%; 29% to 82%)	5 (29%; 10% to 56%)	3 (33%; 7% to 70%)	17 (53%; 35% to 71%)	4 (50%; 16% to 82%)
Total (n=117)	Survived	48 (86%; 74% to 94%)	10 (50%; 27% to 73%)	10 (45%; 24% to 68%)	20 (65%; 45% to 81%)	9 (60%; 32% to 84%)	25 (45%; 32% to 59%)	10 (36%; 19% to 56%)
	Died	8 (14%; 6% to 26%)	10 (50%; 27% to 73%)	12 (55%; 32% to 76%)	11 (35%; 19% to 55%)	6 (40%; 16% to 68%)	30 (55%; 41% to 68%)	18 (64%; 44% to 81%)

*For explanation of comorbidity and organ failure, see table 2. Please note that 5 of these 19 patients had 'suspected TB'
†Signs of shock—all three positive signs: weak peripheral and/or central pulses, temperature gradient, delayed capillary refill time.[28]
‡Organ failure, for example, respiratory failure, shock/impaired circulation, severe anaemia, coma/prolonged convulsion.
§Z-score weight/height<3; MUAC <115 mm; if not height/weight or MUAC available: weight/age z-score < –3.
¶(61%) children with SAM had MOF.
MOF, multiorgan failure; MRDT, malaria rapid diagnostic tests; SAM, severeacute malnutrition; TB, tuberculosis; VSPNA, very severe pneumonia.

of aspiration, apnoeas/hypoxic events when managed via NGT feeding compared with intravenous maintenance fluids.[45] Because of limited monitoring options, we could not determine if some of the children had episodes of desaturation associated with NGT feeds. Careful monitoring of maintenance fluids and feeding practices are important elements to consider in the care of critically ill children in low-resource settings. We suggest that introduction of enteral feeds in critically ill malnourished and non-malnourished children managed in low-resource settings should follow basic principles used in paediatric intensive care. Enteral feeds for malnourished and non-malnourished children can be introduced gradually after stabilisation of vital organ functions (eg, stabilisation of respiratory function on O_2 or bCPAP, correction of shock, anaemia and dehydration as well as a phase of stability of the child's neurological function, even if still comatosed) and the absence of contraindications (eg, abdominal pathologies, large gastric aspirates).

In total, 11/117 children developed nasal prong-associated problems such as obstruction of the nostrils/nasal prongs (4) or injury of the nasal septum (7). Improved interfaces can help in this context. Good nursing care and adequate nurse to patient ratios in a HDU setting are essential in order to reduce complication rates and achieve good outcomes in critically ill children treated with bCPAP. Efficient and sustained training programmes need to accompany the introduction of bCPAP. Caretakers should be integrated in the care and should be encouraged to notify any concern regarding the condition of their child or any malfunctioning equipment.

Devices used for bCPAP and other forms of NIV in low resources need to be of good quality and should undergo independent biomedical review procedures.[46] Biomedical repair and maintenance arrangements need to be put in place. Infection prevention and control measures need to be established.

Limitations

Interpretation of results is limited by the basic observational set-up of the study. The small sample size limited more detailed subgroup analyses. Data quality (eg, frequency of vital signs monitoring) was affected by limited human resources and equipment as well as the extremely high workload. Limited human resources also contributed to the fact that most, but not all, children who were managed with bubble CPAP during the study period were included in the analysis. Some 'CPAP-runs' of short duration might have been missed during weekends. However, we do not think that this contributed to a selection bias, which affected the outcome of the study.

Monitoring of essential elements of critical care management (eg, fluid management) was also affected by low health worker to patient ratio. Adequate numbers of well-trained health workers and basic equipment (eg, SpO_2 monitors) can improve care packages and the potential positive impact of bCPAP on the outcome of critically ill patients with respiratory dysfunction. Laboratory tests allowing more detailed evaluation of renal and/or hepatic dysfunction were not available. This might have contributed to an underestimation of the number of children presenting with MOF. Renal dysfunction is an important parameter determining mortality risk among critically ill children, including children with severe Malaria.[47–49]

Anthropometric measurements were suboptimal in our survey. In many children, we therefore used weight/age as a marker of nutritional status.

Conclusion

Despite the limitations of this study, the good outcome of children with signs of VSPNA suggests that it is feasible to use bCPAP in the hospital management of critically ill children in low-resource settings.

BCPAP and other forms of NIV can potentially play an important role in the improvement of care for critically ill children with respiratory failure and further organ dysfunction (eg, shock, severe anaemia) managed in low-resource settings. Further research is required in this context. Children with malnutrition and HIV infection or exposure need particular attention. Different disease processes like malaria, bacterial sepsis and dengue fever need to be considered.

The impact on patient outcome of different forms of NIV should be evaluated. Adapted, good quality equipment with associated maintenance systems is required as well as adequate numbers of health workers and efficient, sustained training activities.

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Contributors SM: with the support of H-JL she set-up the 'survey structure', including data collection (case record forms, documentation of vital signs and management, etc). She was also involved in the clinical management of patients and clinical training of nurses, clinicians and students. Together with H-JL she wrote the initial draft of the manuscript and finalised the publication. PDPD contributed to the nursing care of patients, documentation of patient information, vital signs and management. PD contributed also to practical training of nurses regarding general patient care and specifically on the use of bCPAP. She was of

great value in the communication with parents and caretakers. MA and CS gave advice on the 'set-up of the survey'. They contributed to the care of patients, training of nurses and clinicians. They also made very important suggestions on the manuscript of the publication. RM advised on the 'set-up' of the survey. She made vital contributions to the introduction to bCPAP on the department's neonatal unit. She was involved in patient care, training of clinicians, nurses and students. RM made important comments on the manuscript of the publication. AP advised on the 'set-up' of the survey. He contributed to patient care and training of health workers and students. AP made important comments on the manuscript of the publication. TC contributed to 'set-up' of the survey regarding rational data collection under the given circumstances. He was responsible for data analysis and contributed to the write-up of the manuscript. EDM contributed to the introduction of bCPAP in Malawi (Lilongwe) and advised on the 'set-up' of the survey. He supported the write-up of the manuscript and interpretation of results. CM advised on the 'set-up' of the survey and supported the survey on administrative level. He made valuable contributions to the manuscript. PK advised on the 'set-up' of the survey and supported the survey on administrative level. He made valuable contributions to the manuscript. He also gave advice on the case management of critically ill children. H-JL contributed to the introduction of bCPAP in Malawi (Blantyre and Lilongwe) and initiated this and a previous survey conducted on the same unit. He contributed to logistic improvements of the department´s paediatric emergency unit and the management of critically ill children. He was involved in the training of clinicians, nurses and students. Together with SM he wrote the initial draft of the manuscript and finalised the publication. H-JL might include this publication in a portfolio required for an academic degree.

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II

Intensive-care management of snakebite victims in rural sub-Saharan Africa: An experience from Uganda

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Background. Antivenom is rarely available for the management of snakebites in rural sub-Saharan Africa(sSA).
Objective. To report clinical management and outcomes of 174 snakebite victims treated with basic intensive-care interventions in a rural sSA hospital.
Methods. This cohort study was designed as a retrospective analysis of a database of patients admitted to the intensive care unit (ICU) of St. Mary's Hospital Lacor in Gulu, Uganda (January 2006 - November 2017). No exclusion criteria were applied.
Results. Of the 174 patients admitted to the ICU for snakebite envenomation, 60 (36.5%) developed respiratory failure requiring mechanical ventilation (16.7% mortality). Results suggest that neurotoxic envenomation was likely the most common cause of respiratory failure among patients requiring mechanical ventilation. Antivenom (at probably inadequate doses) was administered to 22 of the 174 patients (12.6%). The median (and associated interquartile range) length of ICU stay was 3 (2 - 5) days, with an overall mortality rate of 8%. Of the total number of patients, 67 (38.5%) were younger than 18 years.
Conclusion. Results suggest that basic intensive care, including mechanical ventilation, is a feasible management option for snakebite victims presenting with respiratory failure in a rural sSA hospital, resulting in a low mortality rate, even without adequate antivenom being available. International strategies which include preventive measures as well as the strengthening of context-adapted treatment of critically ill patients at different levels of referral pathways, in order to reduce deaths and disability associated with snakebites in sSA are needed. Provision of efficient antivenoms should be integrated in clinical care of snakebite victims in peripheral healthcare facilities. Snakebite management protocols and preventive measures need to consider specific requirements of children.
Keywords. Africa, essential emergency and critical care, ICU management, mechanical ventilation, snakebite.

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Contribution of study
It is estimated that up to 138 000 people die each year following snakebites. Currently, reliable provision of efficient snake-bite antivenom is challenging in many rural health facilities in sub- Saharan Africa (sSA). Our results suggest that basic intensive-care interventions, including mechanical ventilation, is a feasible management option for critically ill snakebite victims in a rural sSA hospital, resulting in a low mortality rate, even without adequate antivenom doses being available.

Approximately 5.4 million people are bitten by snakes annually, with up to half of these victims experiencing signs of envenomation. This results in an estimated 138 000 deaths per year.[1] Only limited data exist on the long-term morbidity of snakebites, but one study suggested that between 5 900 and 14 600 amputations per year may be attributed to snakebites in sub-Saharan Africa (sSA) alone.[2] However, accuracy of epidemiological data is limited owing to under-reporting, patients' poor access to healthcare facilities and many victims attending traditional healers rather than health centres or hospitals.[1-3]

The burden of snakebites is unevenly distributed across the globe, with 95% of cases encountered in low- and middle-income countries in Africa and Asia.[4,5] Even in those areas, the health effects of snakebites are disproportional, with the poorest of the poor generally experiencing poor outcomes.[6,7] Rural sSA is specifically vulnerable owing to limited availability of healthcare services. In 2017, the World Health Organization (WHO) recognised snakebite envenoming as a neglected tropical disease.[7] Accordingly, snakebite antivenoms are included in the WHO's list of essential medicines.[8]

Common acute medical conditions arising from snakebites depend on the species, but include neurotoxicity, coagulation failure accompanied by shock or organ dysfunction, and local tissue destruction.[9] Multiple factors, including delayed presentation to healthcare facilities, adversely affect the management and outcome of snakebite victims.[2] Inadequate regulatory frameworks that result in ineffective or unsafe antivenom products being available, restricted access and high costs are crucial challenges limiting the use of antivenoms, particularly in sSA.[10,11] Supportive measures are often the only therapeutic options for patients presenting with snakebite envenoming in sSA.

In this study, we report the intensive care unit (ICU) management and outcomes of 174 snakebite victims who were treated mainly with basic intensive-care interventions (e.g. mechanical ventilation) in a rural sSA hospital where adequate doses of antivenom were not available.

Methods

This cohort study was designed as a retrospective analysis of a prospectively collected database of patients admitted to the ICU of St. Mary's Hospital Lacor in Gulu, Uganda, between 1 January 2006 and 30 November 2017. All patients from this database admitted to the ICU because of snakebite envenomation were included in the analysis. No exclusion criteria were applied. The analysis of the ICU data was approved by the institutional review board of the hospital. Owing to the retrospective design of the study, written and oral consent was waived. Selected data of 139 patients were included in a previous analysis reporting on admission diagnoses, use of mechanical ventilation and outcomes of critically ill patients treated at this ICU.[12]

Study setting

St. Mary's Hospital Lacor is a private, non-profit (former mission) hospital located in the north of Uganda, serving ~700 000 inhabitants in a poor, post-conflict area. It has 476 beds and six operating rooms, with ~5 000 surgeries being performed per annum. Using subsidised external funding, the hospital's objective is to provide barrier-free access to healthcare, particularly to the poorest of the community. The hospital also runs an eight-bed ICU where critically ill patients are admitted. The unit has eight trained nurses and four assistant nurses (with one nurse attending to between four and eight patients per shift). The medical responsibility for an ICU patient is shared by one anaesthetic officer and a physician. This team was assisted by a senior anaesthetist from 2002 to 2016. Table 1 outlines the operational features of the unit, as described previously.[12]

Patient management

Patients with snakebite envenoming account for 2 - 3% of the ICU population at this centre.[12] General principles of critical care were applied to stabilise vital organ functions. Specific treatment of snakebites was provided with available resources according to WHO guidelines.[9] All snakebite victims were continually monitored using non-invasive measurements (e.g. electrocardiogram, respiratory rate, peripheral oxygen saturation, non-invasive blood pressure and temperature). Respiratory support included the provision of supplemental oxygen and advanced airway management, as well as invasive mechanical ventilation for airway protection or in the case of respiratory failure. Mechanical ventilation was initiated when the attending anaesthetist judged patient survival to be at risk within an hour of assessment.

Adequate antivenom doses could not be provided in the majority of cases because of limited availability of appropriate antivenom. Safety and efficacy of the antivenom available at the ICU during the study period (VINS Bioproducts, India) has not yet been confirmed for use in Africa by the WHO validation processes. Experts from the WHO, the Global Snakebite Initiative and Médecins sans Frontières (MSF) recommend using products with better neutralisation capacity, such as the South African Institute for Medical Research (SAIMR) polyvalent antivenom;[9,13] however, this is more expensive than the VINS antivenom. The MSF Operational Centre in Geneva recently recommended a new algorithm for the management of snakebite victims in South Sudan, namely the use of Echitab-Plus for cytotoxic and haemotoxic envenoming (vipers and spitting cobras) and the SAIMR polyvalent antivenom for neurotoxic envenoming (cobras and mambas).[13]

When antivenom was available for the treatment of critically ill snakebite victims described in this study, usually only one vial could be administered; in special cases, two vials could be administered if indicated. WHO and MSF guidelines indicate that in persisting snakebite syndromes, several vials of antivenom are needed to achieve adequate neutralisation of snake toxins and clinical stabilisation.[9,13] In view of the limited availability of effective antivenom, advanced airway management and mechanical ventilation were prioritised over antivenom therapy in critically ill patients with signs of neurotoxic snakebite envenoming (e.g. fasciculation, paralysis and respiratory failure).

The snake could rarely be identified by patients or relatives. No DNA sequencing techniques from swabs of bite sites could be performed for identification purposes.[14]

Data analysis

The following data were collected from all patients included in this analysis: gender, age, therapeutic interventions (continuous monitoring; endotracheal intubation and mechanical ventilation; tracheostomy; antivenom therapy), complications, length of ICU stay, and mortality. Clinical symptoms of patients documented in the database were categorised as fasciculation/paralysis (due to neurotoxicity), coagulopathy/shock/haemolysis, or extensive tissue damage.

All statistical analyses were performed using the PASW statistical software package (version 20.0) (IBM Corp., Austria). We compared the occurrence of and variables related to different envenoming symptoms (fasciculation/paralysis, coagulopathy/shock/haemolysis or extensive tissue damage) between survivors and non-survivors using chi-squared, Mann-Whitney *U*-rank sum and Fisher's exact tests, as appropriate. Data are presented as absolute values with percentages in parentheses, or median values along with interquartile ranges (IQRs). A significance level $p<0.05$ was used.

Results

Of the 6 976 patients admitted to the ICU during the study period, 174 were treated for snakebite envenomation (2.5%). More than a third of the patients were younger than 18 years ($n=67$; 38.5%) (Fig. 1). As shown in Table 2, non-survivors more frequently presented with coagulopathy, shock or haemolysis than survivors. Invasive mechanical ventilation was used more often for treating non-survivors than survivors. Complications were documented for more non-survivors than survivors. Antivenom (at low and probably inadequate doses[9,13]) was administered to 12.6% of patients ($n=22$). The median (IQR) length of ICU stay was 3 (2 - 5) days and overall mortality was recorded as 8% ($n=14$).

Information on clinical symptoms at presentation could be extracted from the database for 40 patients (23%) (Table 3). The need for invasive mechanical ventilation and subsequent ICU mortality differed among snakebite victims who presented with clinical symptoms.

Table 4 summarises the characteristics of patients who required mechanical ventilation ($n=60$; 34.5%). Among these, clinical symptoms were documented in more detail in only 16 cases. Neurotoxicity (fasciculation/paralysis) was the most commonly documented indication for advanced respiratory support (87.5%). However, it should be noted that in the absence of any other documented complication, it can be assumed that patients with respiratory failure requiring mechanical ventilation experienced neurotoxic snakebite syndrome. Antivenom could be administered only to 10 (16.7%) of the 60 patients who required mechanical ventilation; three of these patients died (33.3%). Of the 50 ventilated patients who did not receive antivenom treatment, seven died (14%). There was no statistical difference in mortality between mechanically ventilated patients with or without antivenom therapy ($p=0.35$; Fisher's exact test).

Table 1. Operational characteristics of the intensive care unit at St. Mary's Lacor Hospital, Uganda[12]

Characteristic	Description
Admission criteria	Patients with life-threatening conditions requiring immediate intervention Patients with abnormal vital signs or other clinical concerns requiring close observation and treatment Postoperative care in case intensive care or close observation is required. These criteria were also applied to snakebite victims.
Beds	8 permanent beds; additional beds can be added if needed.
Nurse:patient ratio	1 nurse for every 4 - 8 patients
Doctors/clinical officers	One anaesthetic officer and the admitting physician share the medical responsibility for the ICU patients. A senior anaesthetist dedicated full clinical responsibility to the ICU (full-time consultant from 2002 to 2008; part-time consultant from 2009 to 2016).
Monitoring	Pulse oximeters: 2 Non-invasive blood pressure machines: 3 Multiparameter monitors: 1 12-lead electrocardiograph: 1 Capnography: not available (end-tidal CO_2 monitoring should be considered as an essential element during intubation and surveillance of mechanically-ventilated patients)
Equipment – examples	Basic resuscitation equipment Equipment for advanced airway management Ventilators capable of providing intermittent positive pressure ventilation (Glostavent; Diamedica, UK): 3 Oxygen concentrators (10 l/min): 3 Oxygen cylinders: limited supply Equipment for chest drain insertion Single-lumen central lines (as well as peripheral venous and intraosseous access)
Management options	Routine resuscitation measures Respiratory care Basic and advanced airway management Insertion of chest drains (e.g. for management of empyema, pneumothoraces) and aspiration of pleural effusions Low-flow O_2 and O_2 supplementation via face mask Advanced airway management and mechanical ventilation; non-invasive respiratory support was not available during the study period. Circulation Fluid management and blood transfusions Peripheral and central line insertion; no arterial lines used. Occasional adrenaline or dopamine infusions
Management of neurological emergencies	Management of comatose patients and status epilepticus No intracranial pressure monitoring Medication Enteral and intravenous medications (based on national guidelines and the WHO list of essential medications[8]) Essential antibiotics, including ceftriaxone, ciprofloxacin (no carbapenems, amikacin or vancomycin) Nutrition Enteral nutritional support; parenteral nutrition not routinely used. Renal replacement therapy Peritoneal dialysis could be performed by the end of the study period, on rare occasions; not used in the patients described in this study.
Laboratory	Point-of-care tests: malaria rapid diagnostic tests (available later during the study period); blood glucose, urine analysis Blood films (e.g. for detection of malaria parasites), haemoglobin and full blood count Analysis of CSF Rapid tests: HIV, hepatitis B and C, syphilis Sputum: tuberculosis smears (no Gen-Xpert was available during the study period) Not routinely available: electrolyte analysis, blood gas analysis, renal or liver function tests, clotting tests, no blood or CSF cultures.
Blood bank	Blood bank: rapid and safe blood transfusion services Not available: Tranexamic acid, fresh-frozen plasma, platelet concentrates
Imaging	Portable X-ray Ultrasound by a radiologist (no routine availability of point-of-care ultrasound)
Protocols	General principles of anaesthetics and critical care were followed. WHO management guidelines were followed for children. WHO protocols for snakebites[9]were followed with available resources (e.g. antivenom was administered only in a minority of patients).
Training	The clinical staff consist of nurses, anaesthetic officers who receive regular on-the-job training and coaching by an experienced senior anaesthesist, and visiting critical care doctors. The hospital invested in the training of nurses and anaesthetic clinical officers for several years. These training programmes are recognised by the Ugandan Minstry of Health.
Logistics, pharmacy and biomedical support	The hospital has a strong logistics and pharmacy team. Cleaners and ICU staff ensure infection prevention and control measures. Reliable maintenance and repair services are provided by a skilled and supportive biomedical department.
Electricity	The hospital has a reliable electricity system.

CSF = cerebrospinal fluid; ICU = intensive care unit; WHO = World Health Organization.

Table 2. Characteristics of the study population (*N*=174)

Characteristic	All (*N*=174), *n* (%)*	Survivors (*N*=160), *n* (%)*	Non-survivors (*N*=14), *n* (%)*	*p*-value†
Demographics				
Male	90 (51.7)	82 (51.3)	8 (57.1)	0.78
Age (years), median (IQR)	24 (12 - 34)	24 (12 - 35)	19 (8 - 29)	0.92
<5	12 (6.9)	9 (5.6)	3 (21.4)	0.06
5 - 10	25 (14.4)	24 (15)	1 (7.1)	0.7
11 - 18	30 (17.2)	27 (16.9)	3 (21.4)	0.71
>18	107 (61.5)	100 (62.5)	7 (50)	0.4
Clinical presentation (*N*=40)				
Fasciculation/paralysis, *n/N* (%)	23/40 (57.5)	19/32 (59.4)	4/8 (50)	0.7
Coagulopathy/shock/haemolysis, *n/N* (%)	5/40 (12.5)	2/32 (6.3)	3/8 (37.5)	0.046‡
Extensive tissue damage, *n/N* (%)	12/40 (30)	11/32 (34.4)	1/8 (12.5)	0.4
ICU care				
Invasive mechanical ventilation	60 (34.5)	50 (31.3)	10 (71.4)	0.006
Tracheostomy	1 (0.6)	0	1 (7.1)	0.08
Antivenom therapy	22 (12.6)	18 (11.3)	4 (28.6)	0.08
Outcome				
Any complication‡	6 (3.4)	3 (1.9)	3 (21.4)	0.007
Length of ICU stay (days), median (IQR)	3 (2 - 5)	3 (2 - 5)	3 (2 - 5)	0.99
ICU mortality				
<18 years, *n/N* (%)	7/67 (10.4)	n/a	n/a	n/a
>18 years *n/N* (%)	7/105 (6.5)	n/a	n/a	n/a

IQR = interquartile range; ICU = intensive care unit.
*Unless otherwise specified.
†Based on comparison between survivors and non-survivors; $p<0.05$ considered statistically significant.
‡Complications included acute lung injury (*n*=1), induced labour (*n*=1), acute renal failure (*n*=1), bed sore (*n*=1), ascites (*n*=1) and aspiration pneumonia (*n*=1).

The ICU mortality of patients requiring mechanical ventilation was 16.7%. Of the 60 patients who required mechanical ventilation, 17 (28.3%) were younger than 18 years; six with respiratory failure died (35.3% mortality). Among these 17 patients were two children younger than 5 years, both of whom died. Of the 43 patients older than 18 years who required mechanical ventilation, four died (9.3% mortality). The difference in mortality rates between children and adults requiring mechanical ventilation was statistically significant (p=0.02; Fisher's exact test).

Length of ICU stay (Fig. 2A) and mortality (Fig. 2B) were significantly higher in patients requiring mechanical ventilation than in those who did not need advanced respiratory support.

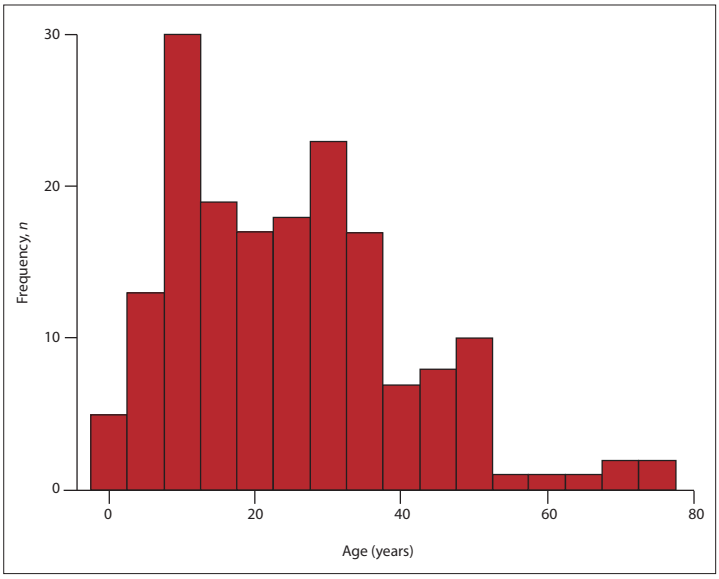

Fig. 1. Age distribution of snakebite victims treated at the intensive care unit at St. Mary's Lacor Hospital, Uganda (N=174).

Discussion

This analysis reports the ICU management and outcomes of 174 snakebite victims, of whom approximately a third were younger than 18 years, in a rural hospital in northern Uganda. The study setting appears comparable to other rural healthcare regions in sSA, which are characterised by single hospitals that serve large catchment areas and support a number of peripheral healthcare facilities. In contrast with many other facilities in sSA,[15,16] our centre runs an ICU that can provide basic intensive-care interventions, including mechanical ventilation.[12] To put this into perspective, a recent survey revealed that one ICU bed is available per 1 000 000 inhabitants in Uganda.[17]

Snakebite envenoming accounted for 2.5% of all ICU admissions at our centre. Clinical symptoms, which could retrospectively be determined for approximately a quarter of the study population, suggest that neurotoxic symptoms were encountered most frequently. We observed an overall mortality rate of 8%.

The cohort of 174 patients described in this study reflects the most severe cases of hospitalised snakebite victims. Unfortunately,

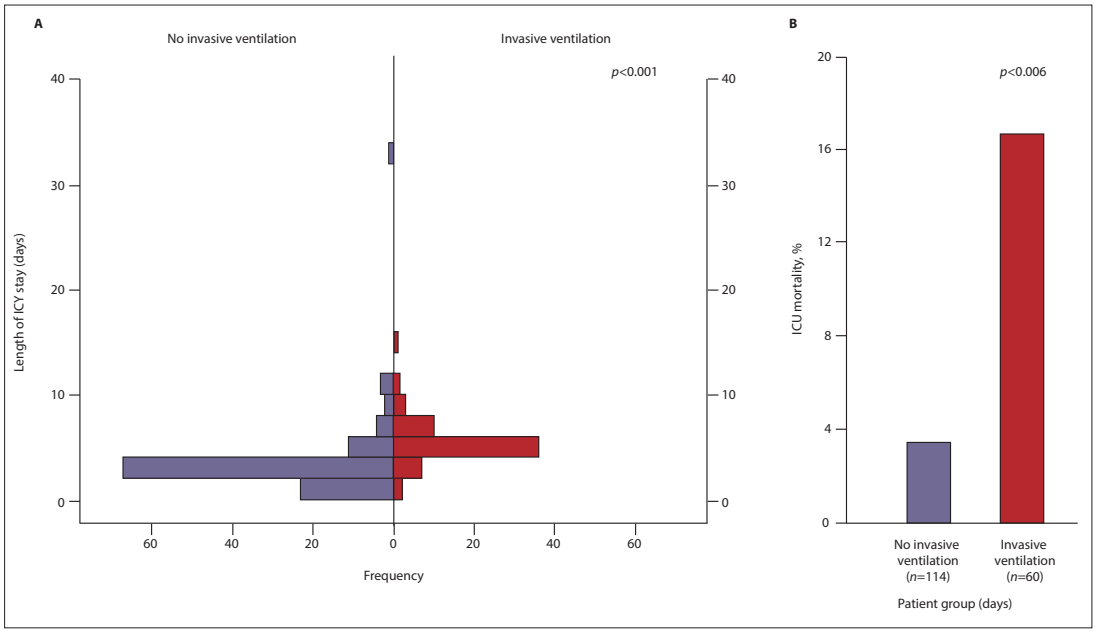

Fig. 2. (A) Length of stay in the intensive care unit for patients requiring invasive ventilation (n=60) compared with patients not requiring invasive ventilation (n=114). (B) Mortality of snakebite victims for patients requiring invasive ventilation (n=60) compared with patients without severe respiratory failure (n=114).

Table 3. Characteristics of patients according to clinical presentation (*N*=40)

Characteristic	Fasciculation/paralysis (*N*=23), *n* (%)*	Coagulopathy/shock/ haemolysis (*N*=5), *n* (%)*	Extensive tissue damage (*N*=12), *n* (%)*	*p*-value
Demographics				
Male	14 (60.9)	2 (40.0)	7 (58.3)	0.7
Age (years), median (IQR)	28 (12 - 34)	9 (5 - 30)	11 (4 - 35)	0.07
ICU care				
Monitoring	23 (100)	5 (100)	12 (100)	1
Mechanical ventilation	14 (60.9)	1 (20)	1 (8.3)	0.007†
Tracheostomy	0	0	0	1
Antivenom therapy	4 (17.4)	2 (40.0)	3 (25.0)	0.53
Outcome				
Any complication‡	3 (13.0)	1 (20.0)	0	0.35
Length of ICU stay (days), median (IQR)	4 (2 - 6)	8 (6 - 11)	4 (3 - 6)	0.16
ICU mortality	4 (17.4)	3 (60.0)	1 (8.3)	0.047†
ICU mortality of ventilated patients, *n*/*N* (%)	4/14 (28.6)	1/1 (100)	1/1 (100)	0.15

IQR = interquartile range; ICU = intensive care unit.
*Unless otherwise specified.
†Statistically significant difference between groups ($p<0.05$).
‡Complications included acute lung injury ($n=1$), acute renal failure ($n=1$), bed sore ($n=1$) and aspiration pneumonia ($n=1$).

the hospital information system does not provide data on the number of patients referred from peripheral facilities or hospitalised snakebite patients who did not need ICU admission during the study period. Although reliable regional epidemiological data regarding snakebites are scarce,[2,5] Uganda is considered to have a relatively high incidence of snakebite envenomation and faces considerable challenges in providing adequate access to basic emergency care for snakebites, especially in rural areas.[5]

All patients included in the study received continuous monitoring in the ICU. Approximately a third of the patients required advanced interventions, such as invasive mechanical ventilation. As this was a non-randomised cohort study, it is not possible to determine the true treatment effect of mechanical ventilation on mortality in our study population. However, the higher mortality rate and longer ICU stays reported for patients who required invasive mechanical ventilation compared with those who did not need ventilatory support likely reflect the high disease severity and risk of death in patients in whom mechanical ventilation was instituted. The authors are not aware of existing systematic data in peer- reviewed literature describing the clinical outcomes of neurotoxic snakebite victims with respiratory failure, treated in healthcare facilities without the facilities providing mechanical ventilation.

The risk of mortality among patients who develop paralysis and acute respiratory insufficiency following a snakebite is likely to be very high without mechanical ventilation.[18-21] As the fatality rate among snakebite

Table 4. Characteristics of snakebite victims requiring invasive mechanical ventilation (*N*=60)*

Characteristic	*n* (%)
Demographics	
Male	40 (66.7)
Age (years), median (IQR)	28 (16 - 35)
Clinical presentation (*N*=16)	
Fasciculation/paralysis	14 (87.5)
Coagulopathy/shock/haemolysis	1 (6.3)
Extensive tissue damage	1 (6.3)
ICU carew	
Monitoring	60 (100)
Tracheostomy	1 (1.7)
Antivenom therapy	10 (16.7)
Outcome	
Any complication†	5 (8.3)
Length of ICU stay	5 (4 - 6)
ICU mortality	10 (16.7)

IQR = interquartile range; ICU = intensive care unit.
*Further clinical symptoms were documented in 16 cases.
†Complications included acute lung injury (*n*=1), acute renal failure (*n*=1), bed sore (*n*=1), ascites (*n*=1) and aspiration pneumonia (*n*=1).

victims who received mechanical ventilation in our cohort was low (16.7%), mechanical ventilation can be considered to have been a life-saving intervention for the majority of patients with acute respiratory failure, particularly those presenting with neurotoxic symptoms.

Slightly more than one-third of patients in this cohort were younger than 18 years, with 7% younger than 5 years (Fig. 1, Table 2). In 2017, 48% of the Ugandan population was younger than 14 years;[22] this age group is slightly under-represented in our cohort. Children older than 5 years may be exposed to a higher risk of snakebite than younger children owing to the activities they are involved in (e.g. exposure during play, on their way to school, assisting the family with agricultural work). Adolescents and adults involved in manual labour (e.g. in the agricultural sector) seem to carry the highest risk for exposure to venemous snakes.[1,9]

Fatality rates associated with snakebite in children are generally higher than in adults, possibly due to the smaller volume of distribution and consequently higher toxin levels in children.[9,23,24] Although insignificant (p=0.4) in the analysis of the cohort of all 174 patients, mortality in children was higher compared with adult patients (10.4% v. 6.5%). In the analysis of 60 patients with respiratory failure requiring mechanical ventilation, mortality among children >18 years (N=17) was significantly higher than among adult patients (35.3% v. 9.3%; p= 0.02). These findings highlight that interventions to prevent snakebites as well as management strategies for snakebite victims need to address particular needs of children and adolescents.[25]

Most of the snakebite victims in our cohort did not receive what would be regarded as adequate antivenom doses by international standards,[9,13] owing to difficulties in the supply chain, poor local economic conditions and limited donor capacity. This finding reflects and highlights the challenges of provision and use of antivenom in rural sSA.[10,11,26] Considering findings from Sri Lanka, which showed that snakebite victims presenting with signs of severe neurotoxicity progressed to respiratory failure requiring mechanical ventilation even when antivenom had been given,[27] it is unlikely that antivenom alone is sufficient to treat critically ill snakebite patients. A study from India reported no fatalities in 51 patients with neurotoxic snake envenomation after they were treated with a combination of antivenom therapy and mechanical ventilation.[28] In our study only a small number of patients (16.7%) with respiratory failure and who required mechanical ventilation received antivenom. The antivenom used during the study period is not among the products currently recommended by international specialists in this field.[9,13] It could therefore not be determined whether early administration of adequate doses of appropriate antivenom combined with advanced airway management and mechanical ventilation could have improved survival rates or reduced the required duration of mechanical ventilation.

In this study, acetyl-cholinesterase inhibitors (ACHEIs) were not routinely used in the management of patients with neurotoxic snakebite syndromes. Evidence regarding the role of ACHEIs (e.g. neostigmine) in the management of muscle paralysis following neurotoxic snakebite is limited.[21] A beneficial role of ACHEIs is not confirmed by WHO guidelines for envenomation from possible mamba bites.[9] Mamba bites are common causes of severe neurotoxic envenomation in eastern and southern Africa.[9]

Study limitations

Important limitations need to be considered when interpreting the data of our study. First, our analysis was designed retrospectively, which explains why the presenting clinical symptoms of snakebite victims could be determined in only 23% of the patients included in the analysis. Our findings therefore offer insight merely into the differences in management and outcome of patients presenting with different snakebite-associated clinical syndromes. Second, the non-randomised study design precludes conclusions on the true outcome effects of intensive-care interventions, including mechanical ventilation, in critically ill snakebite patients.

Conclusion

Despite the limitations of this study, our results suggest that provision of basic intensive care, including mechanical ventilation, was a feasible treatment option for critically ill snakebite victims presenting with respiratory failure in a rural sSA hospital when adequate antivenom doses were unavailable. An international strategy focused on preventive measures and community engagement to reduce deaths and disability associated with snakebites in sSA is required. Strengthening of context-adapted treatment of critically ill patients, including snakebite victims, at various levels of the referral pathway is important. The provision and administration of efficient and safe antivenoms should be integrated in the clinical care of snakebite victims in rural and peripheral healthcare facilities. Snakebite management protocols and preventive measures need to consider specific requirements of children. Pragmatic operational research can contribute to advance strategies aimed at integrating prevention of snakebites and improving clinical care of snakebite victims.

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Author contributions. HJL was responsible for review of the ICU's database and identification of the specific outcomes of patients presenting with snakebite envenomation, and contributed substantially to the review of data analysis and manuscript development. MWD led the data analysis process, supported by RG and JA. RT was responsible for setting up the ICU's data-

base and contributed to data collection for the study, supported by JA. All co-authors (JA, MWD, RG and RT) supported HJL in writing and reviewing of the manuscript.

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III

Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial

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Summary

Background Fluid resuscitation is the recommended management of shock, but increased mortality in febrile African children in the FEAST trial. We hypothesised that fluid bolus-induced deaths in FEAST would be associated with detectable changes in cardiovascular, neurological, or respiratory function, oxygen carrying capacity, and blood biochemistry.

Methods We developed composite scores for respiratory, cardiovascular, and neurological function using vital sign data from the FEAST trial, and used them to compare participants from FEAST with those from four other cohorts and to identify differences between the bolus (n=2097) and no bolus (n=1044) groups of FEAST. We calculated the odds of adverse outcome for each ten-unit increase in baseline score using logistic regression for each cohort. Within FEAST participants, we also compared haemoglobin and plasma biochemistry between bolus and non-bolus patients, assessed the effects of these factors along with the vital sign scores on the contribution of bolus to mortality using Cox proportional hazard models, and used Bayesian clustering to identify subgroups that differed in response to bolus. The FEAST trial is registered with ISRCTN, number ISRCTN69856593.

Findings Increasing respiratory (odds ratio 1·09, 95% CI 1·07–1·11), neurological (1·26, 1·21–1·31), and cardiovascular scores (1·09, 1·05–1·14) were associated with death in FEAST (all p<0·0001), and with adverse outcomes for specific scores in the four other cohorts. In FEAST, fluid bolus increased respiratory and neurological scores and decreased cardiovascular score at 1 h after commencement of the infusion. Fluid bolus recipients had mean 0·33 g/dL (95% CI 0·20–0·46) reduction in haemoglobin concentration after 8 h (p<0·0001), and at 24 h had a decrease of 1·41 mEq/L (95% CI 0·76–2·06; p=0·0002) in mean base excess and increase of 1·65 mmol/L (0·47–2·8; p=0·0070) in mean chloride, and a decrease of 0·96 mmol/L (0·45 to 1·47; p=0·0003) in bicarbonate. There were similar effects of fluid bolus in three patient subgroups, identified on the basis of their baseline characteristics. Hyperchloraemic acidosis and respiratory and neurological dysfunction induced by saline or albumin bolus explained the excess mortality due to bolus in Cox survival models.

Interpretation In the resuscitation of febrile children, albumin and saline boluses can cause respiratory and neurological dysfunction, hyperchloraemic acidosis, and reduction in haemoglobin concentration. The findings support the notion that fluid resuscitation with unbuffered electrolyte solutions may cause harm and their use should be cautioned. The effects of lower volumes of buffered solutions should be evaluated further.

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Introduction

Both adult and paediatric resuscitation guidelines recommend boluses of intravenous fluid, most commonly crystalloid or colloid solutions, with 20–60 mL/kg bodyweight being recommended in the first hour of resuscitation.[1,2] The practice of volume expansion by rapid bolus infusion was introduced not on the basis of evidence from randomised trials, but on current understanding of the physiology of shock. Patients with sepsis or other forms of shock, whether arising from external blood or fluid losses, internal fluid loss from capillary leakage, or pathological vasodilatation, are thought to be hypovolaemic and thus to have diminished venous return to the heart. Clinical experience has supported this physiological concept because bolus resuscitation is usually associated with improved pulse pressure, warming of the peripheries, and increased urine output. However, clinicians are also aware that some patients deteriorate, rather than improve, after volume resuscitation. Furthermore, patients receiving large volumes of fluid are known to develop generalised oedema,[1,2] often accompanied by increased requirement for high ventilation pressures, unless fluid is removed by haemofiltration or diuresis. Despite these known adverse effects of fluid, bolus fluid resuscitation is so widely accepted in the practice of emergency medicine in resource-rich countries that neither clinicians nor research ethics committees are likely to agree to test the

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Research in context

Evidence before this study

Fluid resuscitation has been recommended initial treatment of sepsis and septic shock for more than 40 years. The practice of fluid resuscitation in sepsis has strong theoretical and physiological justification, because volume expansion is believed to correct the hypovolaemia occurring in sepsis due to capillary leak and pathological vasodilatation, and thus increases cardiac output by achieving a more favourable position on the Starling curve.

We searched PubMed from Sept 1, 1974, to July 31, 2018, using the search term "fluid resuscitation in sepsis" restricting the search to human studies, and English language.

We identified 1827 publications, including reviews, observational studies, and clinical trials. We found numerous observational studies and randomised trials comparing different types of fluid resuscitation, including colloids (albumin, gelatin, dextrans, and starch) and different crystalloids (normal saline, hypertonic saline, Ringer's lactate, and other balanced salt solutions). We identified only one randomised controlled trial (the FEAST trial) in which volume resuscitation by itself was compared with maintenance fluids alone. In the FEAST trial, more than 3000 children with fever and clinical signs of impaired perfusion were randomly assigned to volume resuscitation with boluses of 5% albumin or normal saline, or maintenance fluids alone. The trial was stopped because of increased mortality in the bolus groups. Since FEAST is the only randomised controlled trial comparing bolus volume expansion with a no bolus control group, and showed harm from fluid expansion, it provides unique data through which to understand the physiological effects of fluid resuscitation.

Added value of this study

The findings of the FEAST trial—that volume expansion with 20-40 mL/kg of normal saline or albumin increased mortality in critically ill children, compared with no bolus—has been intensively debated by the intensive care and resuscitation community, and has left practitioners uncertain as to what the best resuscitation practice should be. To date, there has been no clear explanation as to why volume resuscitation was harmful in FEAST. Because FEAST was done in resource-poor hospitals in Africa, where other aspects of intensive care were not available, including mechanical ventilation and inotropic drugs, it provides unique data about the physiological effects of bolus volume expansion without the interference of other intensive care methods.

We compared sequential haemodynamic and vital sign data, haemoglobin, and blood chemistry in the bolus and no bolus groups of FEAST. Using novel composite scores to compare changes in respiratory, cardiovascular, and neurological function between the bolus and no bolus groups, we found that volume expansion with either 5% albumin or normal saline caused worsening of respiratory function and increased signs of raised intracranial pressure, but improved cardiovascular function. Bolus recipients had lower haemoglobin concentrations at 8 h, lower bicarbonate, and increased base deficit and chloride at 24 h after the bolus infusion. Regression modelling using the physiological variables significantly altered by bolus suggest that the increased mortality in FEAST can be explained by bolus-induced worsening in respiratory and neurological function, haemodilution, and hyperchloraemic acidosis.

Implications of all the available evidence

Despite the universal belief that volume expansion with crystalloid or colloidal fluid is beneficial in sepsis, and the inclusion of bolus volume expansion in current treatment recommendations, the FEAST trial showed fluid bolus increased mortality. The results of our analysis of the vital signs, haematological data, and biochemical data from FEAST provide a biologically plausible explanation for the adverse outcomes associated with bolus fluids. A modest bolus (20-40 mL/kg) of normal saline or albumin resulted in prolonged hyperchloraemic acidosis, reduced haemoglobin concentration, and worse respiratory and neurological function in the early hours after infusion, despite transient improvement in cardiovascular function, and explained the increase mortality in bolus recipients. Of these effects, saline-induced hyperchloraemic acidosis was a major contributor to the adverse outcome in bolus recipients. Our data suggest that normal saline and other unbuffered crystalloid solutions should be avoided in resuscitating seriously ill patients. Because volume resuscitation is associated with deterioration of respiratory function and neurological function in some patients, caution in use of fluids might be needed in patients with respiratory or CNS compromise, and trials of lower volumes of buffered solutions are now needed to establish whether the beneficial effects of fluid on cardiovascular function can be achieved with less risk of respiratory and neurological compromise.

practice in a randomised controlled trial with a no-fluid bolus control.

By contrast with practice in resource-rich countries, fluid bolus resuscitation is not routine in Africa and other resource-poor regions. There has been an equipoise in many African hospitals between clinicians who recommend fluid resuscitation and those who avoid rapid fluid bolus resuscitation for fear that it might result in pulmonary or cerebral oedema. It was this equipoise in the use of fluids for resuscitation that motivated the FEAST (Fluid Expansion As Supportive Treatment) trial.[3] In FEAST, 3141 febrile children with signs of under-perfusion in Uganda, Kenya, and Tanzania were randomly allocated to receive 20–40 mL/kg of normal saline or albumin bolus or maintenance only fluids. There was surprise both among the investigators as well as the wider

scientific community when the trial was stopped by the study data and safety monitoring group after 3141 patients had been recruited, because of clear evidence of increased incidence of death in the recipients of bolus fluids.[3]

Since publication of the FEAST trial in 2011, there has been extensive debate about the generalisability of the findings and their implications for practice.[4–14] The surprising finding, that a common medical intervention increased mortality in the only randomised controlled trial ever done to test fluid resuscitation against a no bolus control, has raised several important questions. What were the mechanisms by which fluid resuscitation increased mortality in FEAST? Were the findings specific to the population of patients in east Africa included in the study, or are they relevant to patients globally? Were there subgroups of patients included in the FEAST trial who were adversely affected by bolus, whereas others experienced benefit? Was the adverse effect due to the nature of the fluids used (normal saline and 5% albumin, both high chloride solutions) rather than the volume infused? Should international recommendations for fluid resuscitation be altered on the basis of this trial?

Research ethics committees in Africa and other resource-poor regions are unlikely to approve further trials of fluid resuscitation in light of the increased mortality shown in FEAST. Conversely, neither clinicians nor ethics committees in most resource-rich countries are likely to approve a trial in which fluid bolus is withheld from critically ill patients, because of the widely held belief in the benefits of fluid resuscitation. Many clinicians involved in emergency care in Europe and North America have chosen to disregard the results of the FEAST trial as being unique to the African context and argue that the findings are not relevant in well resourced settings, where the availability of ventilators and inotropes can ameliorate any negative effects of bolus fluids.[9] The findings from FEAST have thus confused current clinical practice in resuscitation, raising the question of whether the current standard intervention to rapidly expand circulating volume is harmful and perhaps increases deaths and admissions to intensive care.

In light of the unresolved questions raised by FEAST, we believed that there was both a need and an obligation to fully use all the available data from the FEAST trial to understand why fluid bolus was associated with increased mortality. We postulated that the increased mortality in bolus recipients resulted from a measurable adverse effect of bolus fluids on cardiovascular function, respiratory function, raised intracranial pressure or neurological function, oxygen carrying capacity, or the biochemical and acid base status of bolus recipients. To test this hypothesis we developed composite scores to measure respiratory function, cardiovascular function, and identify raised intracranial pressure, using sequential vital sign data from FEAST, and compared the function of each system, as well as plasma biochemistry and acid-base balance, in the bolus and no bolus groups of FEAST.

Methods

Study design

We hypothesised that fluid bolus-induced deaths in FEAST would be associated with detectable changes in cardiovascular, neurological, or respiratory function, oxygen carrying capacity, or blood biochemistry. Several scoring systems exist to predict severity and outcome in paediatric intensive care.[15–18] However, these existing scores do not enable evaluation of changes in individual organ systems because they combine markers of dysfunction of multiple organ systems. Furthermore, these scores use blood or intensive care variables that are not routinely available in the low-resource settings where FEAST was done. There are no reliable and established methods to quantify the severity of cardiovascular dysfunction, respiratory dysfunction, or raised intracranial pressure, outside of an intensive care setting. To analyse the effects of fluid bolus on physiological status of each organ system, we developed composite scores to describe respiratory, cardiovascular, and neurological function. We assessed their validity by comparison and analysis of their relationships in all available data from FEAST and four other cohorts of ill children, and then used the composite scores to identify differences in respiratory, neurological, and cardiovascular function between the bolus and no bolus groups of FEAST. We also compared changes in acid-base balance and haemoglobin concentration in bolus and no bolus groups of FEAST. The overall structure of the study and the pre-planned and post-hoc analyses are shown in figure 1.

Participants

We analysed data from FEAST and two published paediatric studies of critically ill children (meningococcal disease in the UK, and cerebral malaria in Malawi)[3,19,20] together with data from two unpublished cohorts (one from South Africa, the other from St Mary's Hospital emergency department in London, UK).

In the FEAST study,[3] between Jan 13, 2009, and Jan 13, 2011, 3170 patients with fever, respiratory distress, or prostration and impaired perfusion were enrolled. 3141 were randomly assigned to either maintenance fluids only (4 mL/kg per h; n=1044), or to receive boluses of 20 mL/kg albumin (n=1050) or normal saline (n=1047) in the first hour, with a further 20 mL/kg if signs of impaired perfusion persisted.[3] Clinical details of patients in FEAST have been described in detail.[3,21,22] Vital signs were assessed in surviving children at 1 h, 4 h, 8 h, 24 h, and 48 h after commencing fluid bolus in the albumin and saline groups, or after randomisation in the control group (appendix p 21).

See Online for appendix

In the UK meningococcal disease study,[19] 148 fatal cases and 354 survivors with meningococcal sepsis in England and Wales were enrolled between Dec 1, 1997, and Feb 28, 1999. The cohort has been described previously.[19]

In the Malawian cerebral malaria cohort, between Jan 4, 2010, and June 5, 2011, 448 children with cerebral

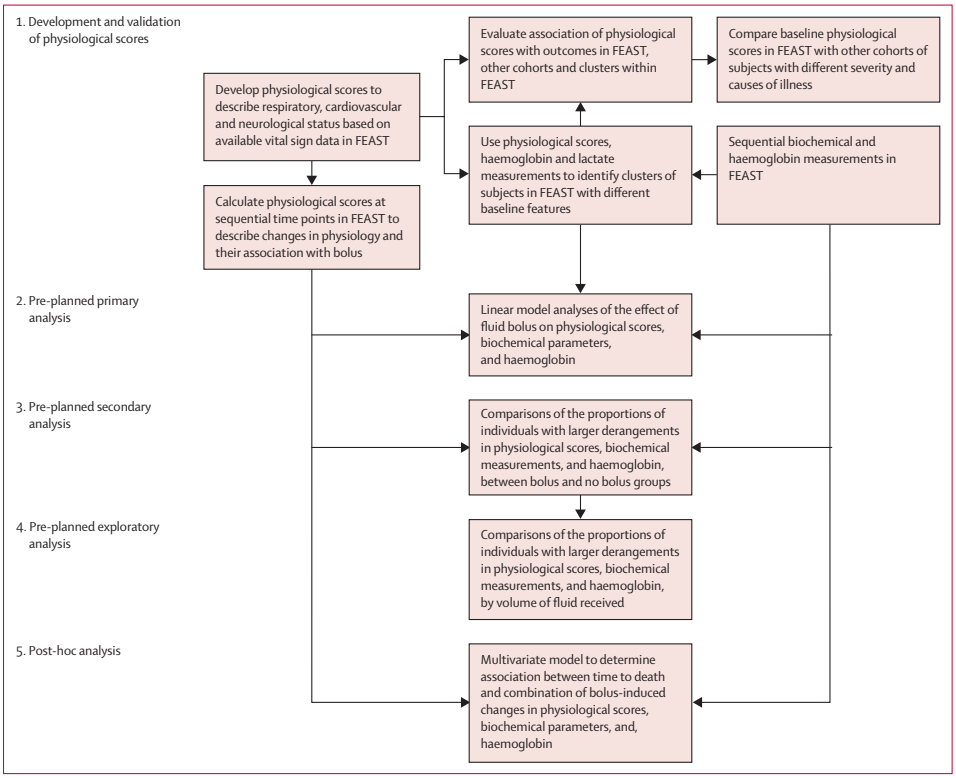

Figure 1: **Study overview**
We developed physiological scores to describe respiratory, neurological, and cardiovascular function, and compared them between FEAST and four additional cohorts of ill children. We assessed their relationships with clinical outcomes. We used the scores to describe sequential changes in each organ system in FEAST and to identify clusters of participants with differing physiological derangements within FEAST. We then assessed the effect of fluid bolus on subsequent physiological scores, haemoglobin, and acid-base biochemistry in FEAST participants using a linear model accounting for baseline values as the primary outcome measure. The proportion of individuals with larger, more clinically important changes in physiological scores and blood parameters were compared in a secondary analysis. The effect of bolus volume on physiological scores, haemoglobin, and biochemical parameters was assessed in pre-planned exploratory analyses. The combined contribution of the effects of bolus on time to death was assessed in a post-hoc analysis.

malaria were admitted to Queen Elizabeth Central Hospital, Blantyre, Malawi, and reported in a study of raised intracranial pressure.[20] Vital signs and clinical variables recorded on admission were related to outcome.

In the South African cohort, 61 children receiving fluid resuscitation for presumed sepsis and gastroenteritis at Red Cross Children's Hospital, Cape Town, South Africa were recruited between Feb 1, 2013, and June 1, 2013. Vital signs and other clinical details were recorded on admission to hospital and related to outcome (admission to intensive care or death).

In the St Mary's cohort, vital sign data and outcome (the need for hospital admission or intensive care admission) were collected for 18 863 children attending the emergency department at St Mary's Hospital, London, UK, from June 10, 2014, to March 9, 2015.

All studies were approved by the institutional review board of the relevant centre. Details of the recruitment procedure, consent procedures, ethics, and institutional approvals for the FEAST, meningococcal, and Malawian cerebral malaria studies have been reported.[3,19,20] Access to the FEAST trial data was provided after a formal request to the trial study group. Data collection for the South African sepsis cohort and St Mary's Hospital cohort were approved by the local research ethics committee of University of Cape Town (HREC REF 025/2013) and UK (14/LO/0266), respectively; in accordance with these approvals, written informed consent was obtained only for participants who had additional data or samples collected beyond those necessary for routine clinical care. The data from each study were made available with approval of the individual country investigators. The

analysis of factors affecting outcome in each study were covered by the ethics approval of each study.

Outcomes

We analysed the distribution of respiratory, cardiovascular, and neurological function scores among FEAST participants and within each of the four cohorts, and for FEAST compared scores between those who received bolus and those who did not. We used logistic regression to calculate the odds of adverse outcome (death in FEAST and the UK meningococcal disease cohort, neurological sequelae or death in the Malawian cohort, intensive care admission or death in the South African cohort, and admission to hospital or intensive care admission in the St Mary's cohort) for each ten-unit increase in baseline score. Within FEAST participants, we examined the effect of bolus on the proportion of patients with extreme derangement of vital sign scores or physiological parameters, and assessed the effect of volume of fluid administered. Finally, we used Bayesian analysis to identify subgroups with differing physiological derangement who might differ in response to fluids, and to explore how the multiple simultaneous physiological changes caused by fluid bolus were associated with excess deaths in bolus recipients.

Procedures

The physiological basis and development of composite scores for respiratory function, cardiovascular function, and detection of raised intracranial pressure and neurological function are described in detail in the web appendix (pp 3–6).

To assess respiratory compromise we used respiratory rate (which increases as respiratory function worsens) and oxygen saturation (which decreases as respiratory function worsens). Vital signs were normalised as described in the appendix, with published normal values. We converted age-adjusted degree of tachypnoea and pulse oximetry measurements to the same direction of effect and weighted the contribution of oxygen saturation:

Respiratory score=(respiratory rate−mean respiratory rate for age)+5×(100−oxygen saturation)

Cardiovascular responses to developing shock maintain blood pressure with vasoconstriction and increasing heart rate. If these fail, blood pressure falls. We combined age-adjusted degree of tachycardia, age-adjusted degree of hypotension, and weighted peripheral capillary refill time into a measure of cardiovascular compromise:

Cardiovascular score=(heart rate−mean heart rate for age)+(mean systolic blood pressure for age−systolic blood pressure)+25×(capillary refill time)

Raised intracranial pressure is associated with decreasing conscious level, bradycardia, and hypertension (the latter two are components of Cushing's triad).[23–25] We combined weighted level of consciousness measured on the AVPU scale (alert=0; responds to verbal stimulus=1; responds to painful stimulus=2; unresponsive=3),[26] and age-adjusted degree of hypertension, and age-adjusted degree of bradycardia:

Neurological score=(blood pressure−mean blood pressure for age)+(mean heart rate for age−heart rate)+25×(AVPU coma scale)

In FEAST, scores were calculated at baseline (before commencing fluid administration) and 1 h, 4 h, 8 h, 24 h, and 48 h after commencing fluid bolus or maintenance fluids. In the other cohorts, only baseline data (ie, at enrolment) were used.

In FEAST, haemoglobin concentration and plasma lactate were measured at baseline, 8 h, and 24 h; base excess, pH, and electrolytes were measured at baseline and 24 h.[3]

Statistical analysis

All available data in each dataset were used (appendix pp 21, 22), with the exception of implausible blood biochemistry values in FEAST, which were excluded (base excess less than −30 mEq/L [n=2]; chloride <80 mmol/L [n=1]; bicarbonate=0 mmol/L [n=1]).

We calculated the odds of adverse outcome for each ten-unit increase in baseline score using logistic regression. In FEAST and the UK meningococcal disease cohorts the outcome was death; in the Malawi cohort the outcome was neurological sequelae or death; in the South African cohort the outcome was admission to intensive care, or death; in the St Mary's Hospital cohort the outcome was admission to hospital or intensive care.

To show the association of each physiological score with disease severity, and to gain insight into the association of the scores with specific pathophysiological phenotypes such as cerebral malaria and septic shock, we compared the distribution of scores between cohorts using the Mann-Whitney test.

Saline and albumin bolus were equally associated with increase in mortality in FEAST.[3] Therefore we compared physiological scores and blood parameters between the combined group of albumin and saline-randomised individuals with those randomised to no bolus in an intention-to-treat analysis. For the primary analysis we used linear regression, controlling for baseline values (before starting fluid), to detect mean differences in physiological scores and blood variables between the bolus and no bolus groups at sequential timepoints after the start of fluid bolus or maintenance fluid (no bolus group) administration.

To examine whether bolus was associated with an increased proportion of patients with extreme derangement of physiological parameters we created separate bins across the distribution of each variable, and then calculated the relative risk for bolus recipients versus no bolus recipients being in each bin. We did this for both change from baseline value, and for absolute values of each parameter.

To assess the effect of volume of fluid administered, we did a secondary analysis based on the actual volume of fluid boluses received within the first 2 h. On the basis of

	Setting	Total (n)	Entry criteria	Age (months)		Sex		Outcome		
				n	Median (IQR)	n	Male, n (%)	n	Adverse outcome	Adverse outcome, n (%)
FEAST	Kenya, Uganda, and Tanzania	3170	Fever and respiratory distress or prostration and impaired perfusion	3170	24 (13–38)	3170	1705 (54)	3170	Death	315 (10)
Meningococcal disease	England, Wales, and Northern Ireland, UK	502	*Neisseria meningitidis* culture or PCR positive or purpura fulminans without other cause	499	39 (13–166)	365	192 (53)	502	Death	148 (29)
Cerebral malaria	Blantyre, Malawi	448	Blantyre coma score ≤2 with *Plasmodium falciparum* parasitaemia and no other discernible cause of coma	448	45 (29–67)	448	233 (52)	448	Death or neurological sequelae	106 (24)
South Africa	Cape Town, South Africa	61	Suspected septic shock or severe gastroenteritis and clinician's decision to give fluid resuscitation	61	5 (1–9)	61	36 (59)	61	Death or intensive care admission	20 (33)
St Mary's Hospital emergency department	London, UK	18 863	Emergency department presentation	18 862	48 (18–110)	18 861	10 467 (55)	18 717	Admission to hospital ward or intensive care unit	1933 (10)

Table 1: **Clinical details of cohorts studied**

the bimodal distribution, we categorised low volume as less than 30 mL/kg and high volume as 30 mL/kg or more. Because the decision to administer more than 20 mL/kg (initial bolus) was not randomised but was based on clinical assessment of ongoing impaired perfusion, we anticipated some bias due to severity of illness at baseline. We therefore analysed both change from baseline of each physiological score, biochemical variable, and haemoglobin, as well as the actual distribution observed in high-volume and low-volume bolus groups.

To identify subgroups with differing physiological derangement who might differ in response to fluids, we used Bayesian Dirichlet process clustering as implemented in the R package PreMiuM,[27] applied to baseline physiological scores and haemoglobin concentration and lactate measurements in all participants recruited to FEAST (appendix pp 6, 7). The modelling assumes variables are distributed as multivariate normal distributions within each cluster. We applied Cox proportional hazards regression to each identified cluster to compare survival times between the bolus and no bolus groups. In FEAST stratum A, we used Kaplan-Meier plots to visualise survival over time. We used Spearman correlation to assess the relationship between haemoglobin and lactate.

To explore how the multiple simultaneous physiological changes caused by fluid bolus were associated with excess deaths in bolus recipients (the primary finding in FEAST) we examined the relationship between death and the combination of physiological scores, base excess, bicarbonate, chloride, and haemoglobin concentration in principal component analysis and Cox proportional hazard regression models (appendix pp 6–8). We built Cox proportional hazard models for time of death using bolus or no bolus, physiological scores, and imputed estimates of haemoglobin concentration and biochemical values at 1 h after bolus administration (appendix pp 7, 8). Full details of the imputation and basis for minimal and larger estimates of each value are shown in the appendix (pp 7, 8, 19, 28–31). The initial model included only bolus alone and additional covariates were added iteratively to the models in order of their association with outcome using a forward selection approach. After each iteration, we report the resulting hazard ratio for time of death. We repeated the procedure using the individual components of each physiological score rather than the composite scores, to identify the contribution of each variable to the increased mortality in bolus recipients. For comparison, we also built a multivariable model using measured baseline values of physiological scores and blood parameters. All statistical analyses were done in R (version 3.2.2).

The FEAST trial is registered with ISRCTN, number ISRCTN69856593.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Details of each cohort are shown in table 1. In the FEAST study, median physiological scores were 105 (IQR 86–124) for cardiovascular function, 53 (37–79) for respiratory function, and 25 (8–47) for neurological function. Patients in FEAST had significantly higher values of all physiological scores than the St Mary's Hospital cohort (57 [IQR 50–67] for cardiovascular function, 5 (0–12) for respiratory function, and 11 (3–20) for neurological function), and they had higher respiratory

scores than all other cohorts (p<0·0001; appendix p 9). Neurological scores were highest in the Malawian cerebral malaria cohort (median score 75, IQR 55–78; appendix p 9). FEAST patients had cardiovascular scores similar to those in the Gram-negative sepsis meningococcal cohort (median score 100, IQR 69–157; appendix p 9).

Physiological scores in FEAST were highest in the first hours following admission, and decreased over the next 48 h (appendix p 9). Median physiological scores, at baseline and 48 h, respectively, were 105 (IQR 86–124) and 52 (39–65) for cardiovascular score, 53 (37–79) and 18 (11–27) for respiratory score, and 25 (8–47) and 4 (0–13) for neurological score. Patients who subsequently died had significantly higher respiratory and neurological scores than survivors at all timepoints up to 24 h (appendix p 9). Cardiovascular score was significantly higher in fatal cases than in survivors at baseline, was not significantly different at 1 h after administration of initial fluid bolus (if received), but was then significantly higher after 4 h or more in those dying than in survivors (appendix p 9).

In FEAST, odds of death for each ten-unit increase in baseline score was 1·09 (95% CI 1·07–1·11) for respiratory score, 1·26 (1·21–1·31) for neurological score, and 1·09 (95% CI 1·05-1·14) for cardiovascular score (all p<0·0001; appendix p 22). The associations between physiological scores and outcome measures in the other cohorts are shown in the appendix (p 22).

To determine the effect of fluid bolus on physiological scores, biochemical parameters, and haemoglobin concentration, we used linear regression analysis to calculate the mean differences, adjusted for baseline value, between those randomly assigned to receive bolus or no bolus in FEAST. We combined the albumin and saline groups because they had similar effects on mortality in FEAST.[3] Mean respiratory score was 3·45 (95% CI 0·90–6·01; p=0·0080) higher at 1 h and 2·3 (0·31–4·3; p=0·024) higher at 4 h in children randomly assigned to receive bolus than in those who received no bolus, but there was no significant difference between groups at 12 h (table 2). Fluid bolus increased the mean neurological score at 1 h by 2·64 (95% CI 0·76–4·52, p=0·0060) and there was no significant difference at 4 h and 12 h (table 2). Conversely, fluid bolus decreased the mean cardiovascular score at 1 h by 2·17 (95% CI 0·57–3·78, p=0·0080; table 2); there was no significant difference between groups at 4 h and 12 h. After 4 h, there were no significant differences in physiological scores (table 2). In a post-hoc analysis, we analysed albumin and saline groups separately (appendix p 23). With the exception of respiratory score at 8 h, which was more increased in albumin recipients than in saline recipients, there were no significant differences between participants who received saline and those who received albumin (appendix p 23). Bolus decreased mean haemoglobin concentration at 8 h by 0·33 g/dL (95% CI 0·20–0·46, p<0·0001). Bolus was not associated with a change in blood lactate concentrations at 8 h or 24 h but was associated with a decrease in mean plasma bicarbonate by 0·96 mmol/L (0·45 to 1·47, p=0·0003), a decrease in mean base excess by 1·41 mEq/L (0·76 to 2·06, p<0·0001), and an increase in mean chloride by 1·65 mmol/L (95% CI 0·47 to 2·83, p=0·0070) in patients surviving to 24 h (table 2).

To assess whether bolus induced larger changes in some individuals, we compared the proportions of individuals in different segments of the distribution of each variable between the bolus and no bolus groups (figure 2; appendix p 10). Compared with those who did not receive bolus, individuals who received bolus had an increased risk of a large or very large increase in respiratory score and neurological score at 1 h, and of a large or very large decrease in cardiovascular score at 1 h (figure 2). The bolus-associated changes in respiratory score persisted at 4 h (appendix p 10). When absolute values of scores at 1 h and 4 h were considered, rather than change from baseline, a greater proportion of the bolus group had high respiratory and neurological scores than in the no bolus group, whereas a smaller proportion had high cardiovascular score (appendix pp 11, 12). Larger

	n/N (%)	Effect size* (95% CI); p value
Respiratory score		
1 h	2925/3102 (94·3%)	3·45 (0·90 to 6·01); p=0·0080
4 h	2884/3025 (95·3%)	2·31 (0·31 to 4·31); p=0·024
12 h	2838/2938 (96·6%)	1·58 (–0·29 to 3·46); p=0·10
Neurology score		
1 h	2992/3102 (96·5%)	2·64 (0·76 to 4·52); p=0·0060
4 h	2933/3025 (97·0%)	1·05 (–0·68 to 2·79); p=0·23
12 h	2881/2938 (98·1%)	0·322 (–1·30 to 1·94); p=0·70
Cardiovascular score		
1 h	3010/3102 (97·0%)	–2·17 (–3·78 to –0·57); p=0·0080
4 h	2948/3025 (97·5%)	–0·30 (–1·93 to 1·33); p=0·72
12 h	2897/2938 (98·6%)	0·10 (–1·52 to 1·72); p=0·90
Haemoglobin (g/dL)		
8 h	2771/2974 (93·2%)	–0·33 (–0·46 to –0·20); p<0·0001
24 h	2723/2882 (94·5%)	–0·21 (–0·35 to –0·08); p=0·0010
Lactate (mmol/L)		
8 h	2737/2974 (92·0%)	–0·12 (–0·33 to 0·092); p=0·27
24 h	2657/2882 (92·2%)	–0·011 (–0·21 to 0·19); p=0·92
Base excess (mEq/L)		
24 h	857/2882 (29·7%)	–1·41 (–2·06 to –0·76); p<0·0001
Bicarbonate (mmol/L)		
24 h	858/2882 (29·8%)	–0·96 (–1·47 to –0·45); p=0·0003
Chloride (mmol/L)		
24 h	840/2882 (29·1%)	1·65 (0·47 to 2·83); p=0·0070

Results of linear regression analysis comparing albumin or saline bolus with no bolus controls, controlling for respective baseline levels. Times shown are the hours after start of infusion. Proportions are given as a percentage of individuals with data from those alive at that timepoint. *Mean change in the variable relative to the no bolus control. A positive effect size indicates an increase in the parameter in bolus recipients; a negative effect size indicates a decrease in the parameter in bolus recipients, relative to the no bolus group.

Table 2: **Changes in physiological scores and blood parameters associated with fluid bolus in FEAST**

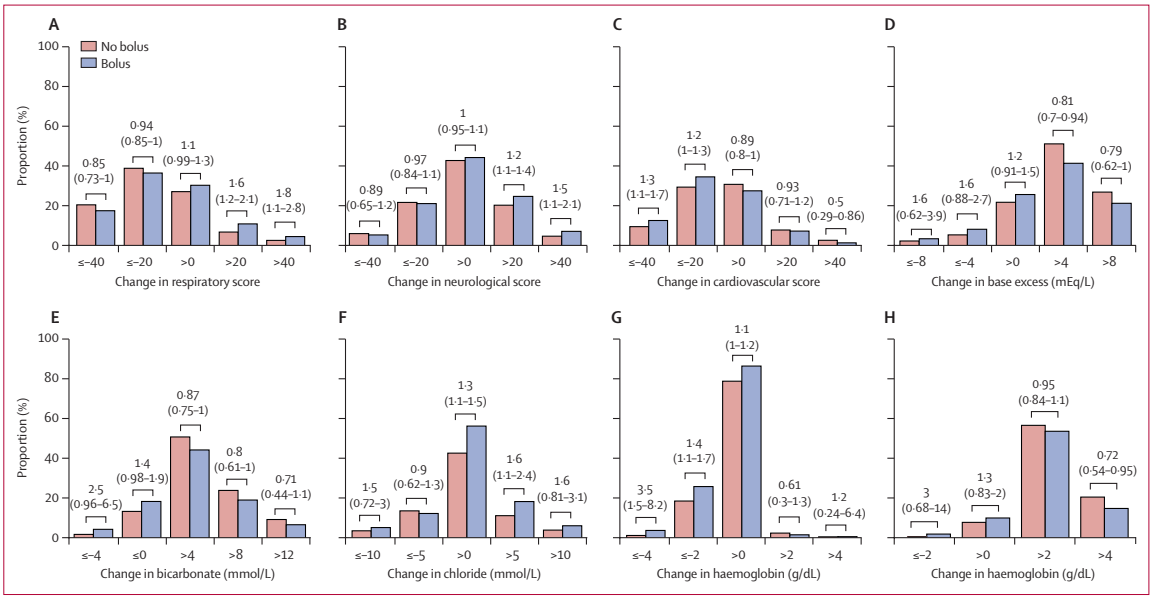

Figure 2: **Changes in physiological scores and blood measures associated with fluid bolus**

The proportion of individuals in FEAST with different magnitudes of change from baseline in physiological scores and blood measurements are shown according to whether they were randomly assigned to receive no fluid bolus (red bars) or fluid bolus (blue bars). Panels A–C show changes in physiological scores between baseline and 1 h after starting fluid infusion. Panels D–F show changes in biochemical measures from baseline to 24 h. Panels G and H show change in haemoglobin concentration from baseline to 8 h in non-transfused (G) and transfused (H) participants. Negative values indicate decrease from the baseline, and positive values indicate increase from baseline. Values above the bars show relative risk (95% CI) for comparison of proportions between bolus and no bolus groups.

decreases from baseline in base excess and bicarbonate, and larger increases in chloride were observed in bolus recipients (figure 2D–F). A greater proportion of bolus recipients had very low haemoglobin concentration (<7·5 g/dL and <5 g/dL) at 8 h (appendix p 11).

In an exploratory analysis, we assessed the effect of low or high volume bolus on the distribution of physiological scores and blood parameters. At 4 h, the first observation after completion of the high volume bolus, there were higher respiratory and neurological scores in patients who received high volume (≥30 mL/kg) bolus (appendix p 13). However, the distribution of cardiovascular scores at 4 h was similar in low and high volume recipients (appendix p 13). There were lower base excess and bicarbonate, higher chloride, and lower haemoglobin concentration (but only in untransfused participants) in the high-volume bolus recipients (appendix p 13). Findings were similar when change from baseline was considered (appendix p 14).

The biochemical changes we observed in FEAST suggested that boluses of albumin or saline could cause hyperchloraemic metabolic acidosis. To explore this further, we did a post-hoc analysis of the effect of bolus on pH and respiratory compensation. 719 (35%) of 2082 FEAST participants with pH measurements at baseline had acidosis (pH<7·35; appendix p 15), and the mortality rate for those with baseline acidosis was much higher than for those with pH of 7·35 or higher. Among survivors in the bolus group, the relative risk of being acidotic at 24 h was 1·4 (95% CI 1·0–1·9) compared with the no bolus group. There was a significant negative correlation between chloride and pH, with a stronger effect of chloride on pH in the bolus group (appendix p 15). Low pH suggests that respiratory compensation mechanisms have been overwhelmed, so we explored the respiratory response at early timepoints, when the majority of deaths occurred in acidotic patients. Respiratory rates were increased at baseline and 1 h, relative to normal ranges for healthy children (appendix p15). Oxygen saturations decreased more in bolus recipients at 1 h, whereas there were no differences between the bolus and no bolus groups in the change in respiratory rate (appendix p 15).

We identified three clusters of patients on the basis of their baseline characteristics (figure 3A). Cluster one (n=1991) had least derangement in physiological scores, haemoglobin concentration, and lactate. Cluster two (n=795) comprised patients with severe anaemia (haemoglobin concentration <5 g/dL), and high lactate and cardiovascular score. Cluster two also had greater base deficit, lower bicarbonate, and high chloride concentrations (appendix p 17). Cluster three (n=384) was characterised by

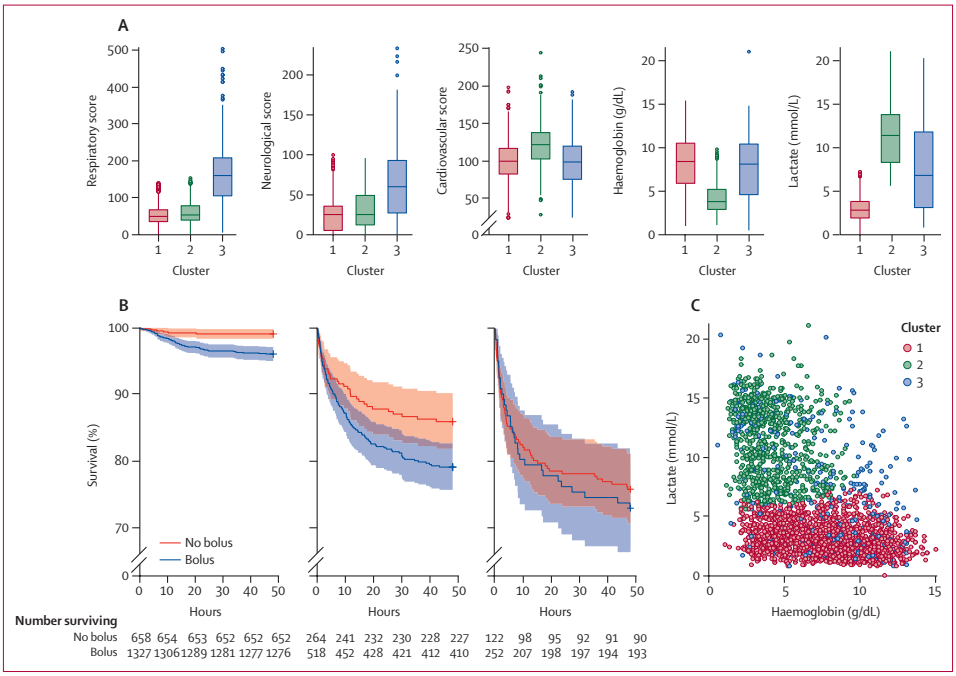

Figure 3: **Bayesian cluster analysis of FEAST**

(A) Distributions of the physiological scores, haemoglobin concentrations, and lactate concentrations by cluster. Boxes show median (coloured line) and IQR; whiskers extend up to 1·5 times IQR. Cluster one, n=1991; cluster two, n=795; cluster three, n=384. (B) Survival curves for no bolus (red line) or bolus (blue line) recipients in each cluster in FEAST stratum A. Cluster one, bolus n=1327, no bolus n= 658; cluster two, bolus n=518, no bolus n=264; cluster three, bolus n=252, no bolus n=122. Dotted lines indicate 95% CIs. (C) Correlation between baseline haemoglobin and lactate concentrations (Spearman p<0·0001, r_s–0·56) with individual participants coloured by cluster (cluster one [red] n=1991; cluster two [green] n=795; cluster three [blue] n=384).

extremely high respiratory and neurological scores, but better maintained haemoglobin concentration.

The clusters differed markedly in mortality (figure 3B). In cluster one, six (1%) of 658 participants in the non-bolus group died, and 51 (4%) of 1327 died in the bolus group. In cluster two, 37 (14%) of 264 patients in the non-bolus group died, and 108 (21%) of 518 died in the bolus group. Mortality was highest in cluster three: 32 (26%) of 122 participants in the non-bolus group died, and 59 (23%) of 252 in the bolus group died.

Considering all participants, there was a negative correlation between haemoglobin and lactate concentrations (Spearman r=–0·56, p<0·0001; figure 3C). Associations between bolus and respiratory score, neurological score, haemoglobin concentration, and blood biochemistry in clusters one and two were consistent with those seen in FEAST overall (appendix pp 24–26). The association between bolus and changes in blood parameters and physiological scores in each cluster are shown in the appendix (pp 25–27).

We reasoned that the multiple physiological changes induced by bolus might act in combination to explain the higher mortality observed in the bolus group, and investigated this in post-hoc analyses. Principal component analysis using the physiological scores and predicted values of blood parameters at 1 h showed that the distribution of fatal cases was distinct from survivors and appeared related to the effects of bolus (appendix p 18). Baseline values of these variables predicted deaths in both bolus and no bolus groups, but there were more observed deaths in the bolus group, indicating that the baseline values of the covariates did not explain the difference in mortality (as expected in a randomised trial; appendix p 32). However, when we used the 1 h post-bolus values to predict deaths, using either conservative or more realistic estimates of the biochemical changes induced by bolus at 1 hour (appendix pp 7, 8, 28–32), we found that there was no longer a significant difference between the bolus and no bolus groups (figure 4; appendix p 32). This finding indicates that the covariates in the model can explain all of the difference in observed mortality between bolus and no bolus groups of the trial. We found that after bolus, the neurological score, base excess, and respiratory score were the major determinants of the increased death rate from

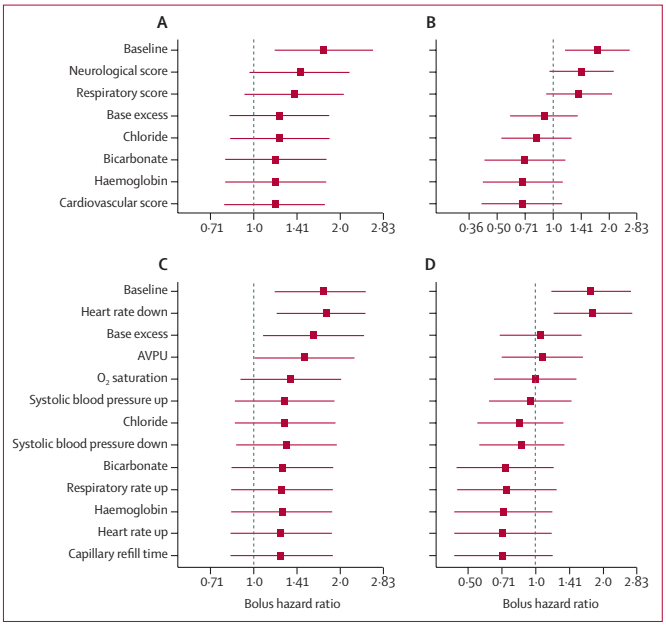

***Figure 4*: Contribution of physiological derangements to excess mortality due to bolus**
In post-hoc analyses, we calculated hazard ratios for bolus versus no bolus on time of death in Cox proportional hazard models, sequentially incorporating additional explanatory covariates (in order from top to bottom of each list), showing how the effect of bolus on death is mediated by observed changes in physiology and blood parameters (A–D). Up or down refers to the direction of change from the age-related mean values, which contribute to different physiological scores. (A) The covariate list includes physiological scores at 1 h and conservative (data-derived) estimates of the effect of bolus on blood parameters at 1 h. (B) The covariate list uses literature-derived values for the changes in acid-base biochemistry parameters. (C) The covariate list includes the component variables of the physiological scores at 1 h and conservative (data-derived) estimates of the effect of bolus on blood parameters at 1 h. (D) The covariate list uses literature-derived values for the changes in acid-base biochemistry parameters. Analyses in A–D are based on 1898 subjects with complete data for physiological scores at 1 h and baseline biochemical parameters. AVPU= Alert, Responds to Voice, Responds to Pain, Unresponsive.

bolus using either minimal (figure 4A) or more realistic estimates (figure 4B) of the post-bolus biochemical values (appendix). When the individual components of each score were included in the models, the post-bolus AVPU score, base excess, and oxygen saturation made the largest contribution to explaining the excess deaths (figure 4C, 4D). We summarised these findings into a physiological model proposing how the adverse effects of bolus fluids could increase mortality (figure 5).

Discussion

The physiological scores we developed provide a tool to quantify changes in respiratory, cardiovascular, and neurological function in response to bolus fluids in FEAST. The scores discriminated between cohorts of patients with infections affecting different organ systems and were generally predictive of outcome, showing their use as objective measures of organ system derangement. Using these physiological scores and available blood measurements, we observed six deleterious effects of fluid bolus: respiratory and neurological scores increased at early timepoints; haemoglobin concentration decreased (particularly in patients who did not receive blood transfusion); base deficit and chloride concentrations increased, and plasma bicarbonate decreased (changes consistent with hyperchloraemic acidosis). Although the linear regression analysis showed a modest, but significant, change in the mean value of each variable, there were much greater changes observed in some individuals, with increased proportions of bolus recipients having extreme adverse physiological derangement in physiological scores, haemoglobin concentration, and blood chemistry. Most of these changes were greater in patients receiving higher fluid volumes. The changes in physiological scores were most evident at early timepoints, but early deaths and the increased mortality in bolus recipients makes evaluation of later timepoints difficult. The only beneficial physiological change observed was a reduction of cardiovascular score, in keeping with the impression of clinicians that perfusion improved during fluid resuscitation.

When we included the bolus-induced changes in respiratory function, cardiovascular function, neurological function, and biochemical changes in Cox survival models, the increased mortality in bolus recipients in FEAST was explained by the physiological changes we identified. Analysis of the effect of each component in the models showed that the excess deaths in bolus recipients were largely explained by worsening neurological score (or raised intracranial pressure), increased base deficit, and worsening respiratory score. Of the individual components analysed, bolus-induced increased base deficit, worsening conscious level, and oxygen saturation were the major contributors to the excess mortality associated with bolus.

Since the 1990s, there have been increasing reports, including small case studies, randomised trials in healthy volunteers and patients, and experimental studies in animals that have documented hyperchloraemic acidosis after infusion of unbuffered salt solutions (appendix pp 28–31).[30–33] Hyperchloraemic acidosis is an inevitable consequence of the infusion of unbuffered sodium chloride solutions, predicted by the Stewart equation of acid-base balance[28,29] and confirmed in the extensive literature. Although many small studies comparing balanced salt solutions (which contain acetate or lactate as a source of anion) with normal saline have documented saline-induced hyperchloraemic acidosis, recent large clinical trials also reported increased mortality and worsening renal outcome in adults receiving normal saline as compared with balanced salt solutions.[34,35] Our finding that the bolus-induced hyperchloraemic acidosis and decreased base excess was a major contributor to the increased mortality in bolus recipients suggests that much of the adverse effect of bolus in FEAST was due to the nature of the fluids used.

Worsening respiratory function and increase in signs of raised intracranial pressure, which we documented in

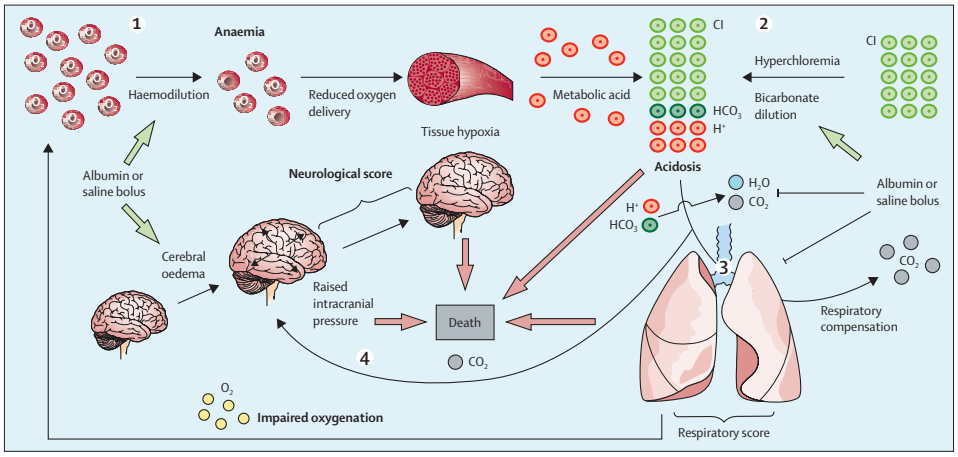

Figure 5: **Proposed physiological model of the adverse effects of fluid bolus**
Bolus fluid reduces haemoglobin concentration, resulting in decreased tissue oxygenation, increasing anaerobic metabolism, and metabolic acidosis. According to the Stewart model, maintenance of normal plasma pH is controlled by (1) the strong ion difference (charge difference between strong cations (Na^+, K^+, Ca^{2+}, and Mg2+), and strong anions (Cl– and lactate–); (2) pCO_2 and (3) charge from weak acids (phosphate, albumin).[28,29] Bolus of normal saline or 5% albumin (which have similar electrolyte content) caused hyperchloraemia and dilution of bicarbonate, resulting in a reduction in the strong ion difference. Hyperchloraemic acidosis increases the need for respiratory compensation through increased carbon dioxide excretion to maintain pH. Worsening of respiratory function due to bolus results in hypoxia (as evidenced by low oxygen saturation and increased respiratory score). This outcome, together with an inability to increase respiratory rate, impairs excretion of carbon dioxide (not shown in our study). Increasing carbon dioxide causes cerebral vasodilation, resulting in increased intracranial pressure. Fluid bolus might also directly cause cerebral oedema. The combination of adverse effects on haemoglobin concentration, acidosis, and respiratory and neurological function induced by modest albumin or saline fluid boluses might overwhelm compensatory mechanisms in the most severely ill patients, resulting in increased mortality.

bolus recipients, are well known effects of fluid administration in some critically ill patients. Indeed, many guidelines for management of shock recommend intubation, and elective mechanical positive pressure ventilation for patients who remain with signs of shock after initial bolus volume infusion because of the recognition that continued fluid resuscitation is likely to cause respiratory deterioration.[1,36] However, our finding that small volumes (20–40 mL/kg) of normal saline or albumin, which are routinely administered to underperfused children in emergency departments, cause worsening of respiratory function and decrease in oxygen saturation suggest that even modest volumes of fluid might have detrimental effects in some children despite the observable improvement in perfusion, which was also manifested in FEAST as improving cardiovascular score. Our findings raise the possibility that administration of fluid bolus to underperfused patients might increase the need for intensive care admission because of worsening oxygenation.

The worsening neurological score in bolus recipients and the contribution of deteriorating neurological score to the excess mortality in bolus recipients is also an expected effect of bolus fluids in patients who have increased intracranial pressure. More than 50% of the patients included in FEAST had severe malaria, and many of these patients had evidence of cerebral malaria. Evidence of raised intracranial pressure has been well documented in cerebral malaria by direct measurement,[37] MRI scan,[20] and by clinical findings.[38] Both fluid volume and the hyperchloraemic acidosis induced by the saline and albumin used in FEAST could have contributed to the worsening of consciousness and neurological score in bolus recipients (figure 5). Although patients with neurological diseases such as cerebral malaria and meningitis comprise a smaller proportion of critical illness in resource-rich settings, our finding that worsening neurological score occurred in bolus recipients suggests that volume resuscitation should be used with great caution in patients presenting with neurological illness, and unbuffered salt solutions should be avoided.

Our cluster analysis revealed heterogeneity within FEAST. The majority of patients (cluster one), had least severe derangement of all three physiological scores, adequate haemoglobin concentrations, and remarkably low mortality in the absence of bolus. Fluid bolus in this cluster caused worsening of respiratory and neurological function, reduced haemoglobin concentration and increased acidosis. The second cluster, characterised by low haemoglobin concentration, high lactate concentration, and high cardiovascular score, identified patients with severe anaemia. The inverse relationship observed between haemoglobin and lactate concentrations, and lower bicarbonate and base excess suggests that the baseline hyperlactataemia and metabolic acidosis is largely driven by impaired oxygen carrying capacity. In this cluster,

bolus fluids caused worsening of respiratory and neurological function and increased acidosis. The third cluster, characterised by high respiratory and neurological scores had high mortality (23–26%). Patients in the bolus group had lower haemoglobin concentrations and higher chloride concentrations than those in the non-bolus group.

Identification of clusters within the large FEAST cohort of ill children has important therapeutic implications. The low mortality in the absence of bolus fluids in cluster one suggests that this group did not require any additional intervention, and most would recover with treatment of the infection alone. In cluster two, in which anaemia was the major problem, we believe blood transfusion was required, and bolus probably worsened tissue oxygen delivery. In cluster three, in which respiratory failure and neurological impairment were the main physiological derangements, we believe that respiratory support was needed to reduce mortality.

Combination of the physiological derangements caused by bolus explained mortality better than the pre-bolus values of the same parameters, indicating that through their combined effects, the bolus-induced changes plausibly explain the effect of bolus on mortality in FEAST (figure 4). Because the physiological changes identified are likely to be similar in all settings, our findings have implications for fluid resuscitation in both developed and resource-limited settings, although the magnitude of effect may differ because the severity of anaemia in FEAST participants might have increased the relative importance of haemodilution.

The findings in our analysis differ from the previous analysis of modes of death in FEAST[9,22] and an ovine model,[39] which concluded that worsening cardiovascular shock was the major adverse effect of bolus. The earlier study[22] used increased plasma lactate concentration as part of the definition of cardiovascular shock. Our analysis found that plasma lactate was negatively correlated with haemoglobin concentration, and thus use of lactate as a biomarker of cardiovascular shock in the previous analysis gave an incorrect indication of the prevalence of cardiovascular shock.

Our study has several limitations. Although our physiological scores are associated with outcome in multiple different cohorts, they have not been independently validated. In particular, the weightings were chosen to reflect the perceived importance of each variable as a measure of organ system function. They were not derived from the data or from previous studies. The scores should be seen as means of studying changes in physiology between arms of a trial, rather than as outcome predictors, for which there are already a number of scoring systems available.[15–18] FEAST was done in settings in which intensive care and mechanical ventilation were not available. Although the physiological changes induced by bolus are likely to be seen in all settings, caution is needed in extrapolating associations with mortality to resource-rich settings, in which some of the adverse effects of bolus fluids could be mitigated by mechanical ventilation and neuro-intensive care. Furthermore, because of the design of the trial, we cannot exclude that the associations we have reported between greater physiological derangements and larger volumes of administered fluid are confounded by the indication—ie, administration of larger volumes of fluid to participants with more deranged physiology. An additional limitation is that acid-base balance was only measured on admission and at 24 h, by which time most deaths had occurred, and many patients had no data at the 24 h timepoint. To include the effect of bolus on acid-base balance, we imputed the earlier timepoints from the 24 h differences, and used published values to produce a range of estimates of the extent of acidosis at earlier time points. We believe the assumptions used in the imputation provide reliable estimates of the earlier values.

The FEAST trial included children with widely differing diseases and underlying physiology. We found that fluid bolus achieved the intended improvement in cardiovascular function at the cost of worsening respiratory and neurological function, acidosis, and reduced haemoglobin. Our finding that within FEAST there are clusters with differing physiological derangements suggests particular need for caution in fluid administration to patients with established respiratory failure, neurological failure, severe acidosis, or anaemia, and the need for better detection and specific management of the physiological derangements in each individual patient. The physiological scores we have developed might be useful in identifying derangement in specific organ systems.

The combination of adverse physiological effects we observed, associated with both albumin and saline bolus, raises questions about both the volume and type of fluid used in resuscitation. Balanced salt solutions such as Ringer's lactate or plasmalyte (which have electrolyte compositions closer to plasma than normal saline, and lactate or acetate as major anions) are associated with more rapid resolution of acidosis than 0·9% saline, and in recent clinical trials they were associated with improved outcomes.[34,35,40] Our finding that worsening hyperchloraemic acidosis was a major contributor to the excess deaths in FEAST suggests that unbalanced salt solutions such as normal saline and 5% albumin should be avoided in seriously ill patients and replaced with balanced salt solutions. However, other fluids are likely to have the same adverse effects on respiratory function, oxygen carrying capacity, and perhaps neurological function that we have observed with albumin and saline in FEAST. Trials are needed to establish if balanced electrolyte solutions and lower volumes than currently recommended will allow the benefits of fluid on cardiovascular function to be achieved without the adverse effects observed in FEAST.

Contributors

ML, AJC, and CJH led the study, analysed the data, and wrote the first draft of the manuscript. CW, SN, HJL, NN, MM, AA, HB, CAM, AB, and RGN collected the data. All co-authors provided a full review of the Article, are

fully responsible for all content and editorial decisions, were involved in all stages of manuscript development, and have approved the final version.

Declaration of interests

We declare no competing interests.

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Annex I

THE LANCET
Respiratory Medicine

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Levin M, Cunnington AJ, Wilson C, et al. Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial. *Lancet Respir Med* 2019; published online June 10. http://dx.doi.org/10.1016/S2213-2600(19)30114-6.

Web appendix: Adverse effects of saline or albumin fluid bolus in resuscitation: Evidence from re-analysis of the FEAST trial

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Detailed methods

Relationship to the FEAST trial and analysis plan

The present study was not planned as a pre-specified analysis of the FEAST trial. The present study represents a hypothesis-based reanalysis of the trial data. The primary hypothesis was that bolus fluids produce measurable changes in cardiovascular function, respiratory function, raised intracranial pressure or neurological function, oxygen carrying capacity, biochemical and acid-base status. The secondary hypothesis was that if these changes are detectable, they can explain the excess mortality associated with bolus fluid in the FEAST trial. To evaluate both of these hypotheses, multiple analyses (detailed below) were performed in order to justify the methodological approaches for detection of the changes in organ system function and to assess whether any effects attributed to bolus were consistent with expected relationships with the volume of bolus-fluids received, known mechanisms of acid-base derangement, and between subgroups of patients.

Assessment of changes in physiology and blood parameters

FEAST collected data on respiratory rate, pulse rate, blood pressure, capillary refill time and level of consciousness sequentially throughout the trial at baseline, 1, 4, 8, 24 and 48 hours[1]. Haemoglobin and lactate concentrations were measured at baseline, 8 and 24 hours.[1] Plasma chemistry and acid-base balance were measured at baseline and 24 hours.[1]

Our first challenge in attempting to establish the mechanisms by which fluid increased mortality in FEAST was to identify a methodology for detecting changes in each organ system in bolus recipients using the data available from the trial.

There are currently no "gold standard" methods to quantify respiratory function, neurological function or cardiovascular function in critically ill children based on clinical features, although multiple international guidelines indicate that respiratory rate, pulse rate, blood pressure, capillary refill time and level of consciousness should be used to guide management. We postulated that combinations of these variables would provide objective and quantitative indicators of respiratory, neurological and cardiac function, in a similar manner to which experienced clinicians subconsciously assimilate them each time they assess a seriously ill patient**.** As blood pressure, heart rate, and respiratory rate vary greatly in children of different age, we adjusted for age by calculating the deviation from the age-related mean values for healthy children. Mean values for heart rate and respiratory rate and blood pressure were derived from published tables.[2, 3]

We note that the intended purpose of each score was to enable comparison of changes in organ function between the bolus and no bolus arms of the randomised controlled trial, and to compare physiological derangement between different studies. Recognising that there is no absolute measure against which to calibrate each score, the weightings of oxygen saturation, coma score and capillary refill time were chosen to reflect the clinical importance of each component of the score. We acknowledge that different weightings might enable better prediction of outcome in individual studies, however our aim was to develop an objective tool for comparison between arms and studies, and not to develop a new predictor of outcome.

Heart rate and blood pressure deviations from the age-related means were considered to have different implications for cardiovascular and neurological status, since low blood pressure and high heart rate are features of circulatory failure whilst rising blood pressure and falling heart rate are features of raised intracranial pressure. Thus only physiologically adverse deviations contributed to each score, and otherwise the difference was set to zero as explained for each score below.

Developing a composite measure for cardiovascular function

Measurement of cardiac function is routinely undertaken using echocardiography or thermodilution catheter in an intensive care setting. However these methods were not available in FEAST. Furthermore, shock is defined as a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells; a state in which the circulation is unable to deliver sufficient oxygen to meet the demands of the tissues resulting in cellular dysfunction.[4] Therefore it is not solely defined by or dependent on cardiac output. Remarkably neither adult nor paediatric guidelines for clinical recognition of shock have an objective quantification of the severity of shock (see table below). In some guidance more severe cases are recognized by being refractory to fluid volume expansion[5] thus defining severity by the very intervention shown to be associated with increased mortality in FEAST. Clinical recognition of shock is based not only on markers of cardiac output (such as heart rate and blood pressure) but on evidence of impaired perfusion of tissues and organs, such as change in mentation,

oliguria or rising blood lactate.[4, 5] Furthermore FEAST included a large proportion of patients with presumed cerebral malaria and meningitis[1, 6] so changes in mentation may not only be caused by impaired cardiovascular function or perfusion but by the underlying disease process. Furthermore, changes in urine output were not recorded as this is difficult without indwelling catheters. Lactate, which is the most commonly used marker of tissue under perfusion in most shock algorithms, was also found to be unreliable in the African setting because we found it was closely correlated with the level of haemoglobin and thus more a reflection of anaemia than cardiovascular perfusion.

Criteria for clinical recognition of shock (modified from Houston et al.[7])

Guideline	Clinical criteria	Age group
Advanced Paediatric Life Support (APLS)[8]	Compensated: normal blood pressure (BP), but capillary refill time (CRT) >2 s, mottled peripheries, peripheral cyanosis Decompensated: as above but with hypotension, decreased mental status	Paediatric
American Academy of Critical Care Medicine – Paediatric Advanced Life Support (ACCM-PALS)[9]	Septic shock: Suspected infection (hypo- or hyperthermia) and clinical signs of inadequate perfusion including any of: decreased or altered mental status; CRT >2 s (cold shock) or flash CRT (warm shock), diminished (cold shock) or bounding (warm shock) peripheral pulses, mottled cool extremities (cold shock), or decreased urine output (<1 ml/kg/hr)	Paediatric
World Health Organization (WHO)[10]	Shock: cold hands, capillary refill time longer than 3 s, high heart rate with weak pulse, and low or unmeasurable blood pressure	Paediatric
Fluid Expansion As A Supportive Therapy (FEAST) study[1]	History of fever and temperature ≥37·.5 °C or <36·.0 °C and impaired consciousness (prostration or coma) and/or respiratory distress Stratum A (impaired perfusion) Plus ≥1 of: CRT >2 s; lower limb temperature gradient; weak pulse; tachycardia (defined) Stratum B (decompensated shock): Systolic BP <50 mmHg if < 12 months old; <60 mmHg if 1–5 years old; <70 mmHg if > 5 years old	Paediatric
International pediatric sepsis consensus conference definitions[11]	Sepsis: SIRS (2 of 4 of: core temp > 38·5 or < 36 °C; tachycardia or bradycardia if <1yr; tachypnea; elevated or depressed leukocyte count) in the presence of or as a result of suspected or proven infection Septic shock: Sepsis and cardiovascular organ dysfunction	Paediatric
Sepsis 3[12]	Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction defined as an increase in the SOFA score of 2 points or more Septic shock: Sepsis and both persistent hypotension requiring vasopressors and lactate ≥2 mmol/L despite adequate volume resuscitation	Adult
Sepsis 2[13]	Sepsis: suspected or documented infection with change to some of the following: General variables; inflammatory variables; haemodynamic variables; organ dysfunction variables ; tissue perfusion variables. Severe sepsis: sepsis complicated by organ dysfunction Septic shock: persistent arterial hypotension unexplained by other cause	Adult

These clinical indicators of cardiovascular system dysfunction are rarely synthesised into quantitative measures which would allow comparison of organ function between individuals or sequentially over time. The widely used shock-index was devised based on the logical but arbitrary belief that heart rate divided by systolic blood pressure should provide a better indicator of cardiovascular status than either alone,[14] but was not empirically derived based on data. For application to children it has required modifications to account for age-related variation in normal values,[15] and it does not include any measure of perfusion.

We concluded there was no optimal or accepted method for quantifying differences in shock or cardiovascular function between the bolus and no bolus arms of FEAST, and that we needed to develop novel methods that could be used to identify the effect of bolus on shock /cardiovascular function (as well as for each of the other organ systems, described below) using the available data.

We reasoned that an overall assessment of cardiovascular function could be made by combining heart rate and blood pressure with capillary refill time, which is a well-established marker of perfusion, as all three variables were recorded sequentially in FEAST. Heart rate rises while blood pressure falls as shock evolves, so heart rate and blood pressure can be combined as markers of cardiac function by converting them to the same direction of effect. As all vital signs are age related we also adjusted blood pressure and heart rate to detect a rise in heart rate above the mean normal for age and a fall in blood pressure below the mean normal for age. As capillary refill time is typically in the range of 0 to 5 seconds, while heart rate and blood pressure extend over much larger numerical ranges, we weighted capillary refill time so that it could make an approximately equal contribution to an overall score for cardiovascular function.

The conventional method for assigning weightings in predictive scores is to derive the weightings from the associations between the data and the outcome of interest, and then test the assigned weightings on an independent

and external data set. However, as we were aiming to characterise the changes in organ system function induced by bolus fluids, rather than aiming to identify the best predictor of outcome (death in the case of FEAST), there was no gold standard outcome against which to evaluate the weightings of each variable. The clinical definitions of shock listed above include a range of variables, but provide no method for quantifying the severity of derangement. We concluded that empiric assignment of weighting for capillary refill time to enable a contribution equivalent to that of blood pressure and pulse rate was appropriate. Further evidence on the utility of the score could be gained by comparison of the composite score between cohorts, and evaluation of the weightings can be achieved in modelling the effect of each variable in survival models (see below). The composite score we used was:

Composite cardiovascular score

Cardiovascular score = (heart rate - mean heart rate for age) + (mean blood pressure for age – blood pressure) + 25(capillary refill time)

If the heart rate was less than the mean heart rate for age, the term (heart rate - mean heart rate for age) was set to zero, so that only increased heart rates contributed to the score. If the blood pressure was greater than the mean blood pressure for age, the term (mean blood pressure for age - blood pressure) was set to zero, so that only decreased blood pressure contributed to the score.

Developing a composite measure for respiratory function

Assessment of respiratory function is often achieved by assessment of the adequacy of oxygenation (comparing the ratio of inspired oxygen to arterial oxygen in ventilated patients) and of carbon dioxide excretion. However, accurate evaluation of respiratory function is more difficult in patients who are not mechanically ventilated as widely differing oxygen concentrations are delivered when using face mask or nasal cannula. Clinical assessment of respiratory function in settings other than intensive care units is generally undertaken by observing the rate of breathing, respiratory effort and the depth of breathing and by pulse oximetry. Depth of breathing and respiratory effort are highly subjective and difficult to quantify but respiratory rate and pulse oximetry are reliably measured and were recorded sequentially during the first 48 hours of the FEAST trial. We reasoned that an overall assessment of respiratory function could be made by combining in a composite score, respiratory rate (which rises as respiratory function is compromised) with oxygen saturation (which declines) by converting them to the same direction of effect**.** As oxygen saturation declines over a more limited range than the changes in respiratory rate and as there may be more clinical significance to a declining oxygen saturation, we weighted contribution of declining oxygen saturation in a combined score.

Composite respiratory score

Respiratory score = (respiratory rate - mean respiratory rate for age) + 5(100 - oxygen saturation)

If the respiratory rate was less than the mean respiratory rate for age, the term (respiratory rate - mean respiratory rate for age) was set to zero, so that only increased respiratory rates contributed to the score.

Developing a composite measure for raised intracranial pressure and neurological status

How to detect raised intracranial pressure (ICP) is the most difficult challenge in evaluating the possible mechanisms for increased death in bolus recipients. The only reliable method for detecting raised intracranial pressure is by directly inserted intracranial pressure transducer, and there is no established method to detect or monitor raised ICP outside an intensive care setting[16]. Detection of raised ICP using MRI or CT scan is notoriously unreliable unless the changes are extremely severe. In practice, suspicion of raised intracranial pressure is raised clinically in patients who have declining levels of consciousness and who also show evidence of brainstem compression of centers controlling respiration, blood pressure and heart rate. Patients who show paradoxical bradycardia, rising blood pressure and declining consciousness or abnormal respiratory patterns (components of Cushing's triad[17-19]) are considered to have features of raised intracranial pressure and generally managed in intensive care units with intracranial monitoring and brain imaging. We postulated that the same clinical variables used by clinicians to detect raised intracranial pressure clinically could be combined in a single score combining rising blood pressure, falling heart rate and declining consciousness. As with the cardiovascular score, we converted the rising blood pressure and falling heart rate to the same direction of effect, and normalized rising blood pressure and falling heart rate using age-related means. As coma was measured by the AVPU (awake (A), response to voice (V), response to pain (P), unresponsive (U)) scale over a much smaller range than blood pressure and heart rate we weighted its contribution in order to capture its contribution to the overall score.

FEAST utilised two different coma scores,[1] at baseline the Blantyre Coma Score[20] was recorded which summates three measures of responsiveness: motor (able to localize=2, withdraws from pain=1; unresponsive=0), eye movement (follows=1; unresponsive=0), and voice (appropriate response=2, inappropriate or groaning=1, unresponsive=0), giving a total score from 0 to 5 which decreases with severity. At later time points the AVPU scale was used. In order to contribute to neurological score the AVPU categories were given numerical values A=0, V=1, P=2, U=3. In order to enable comparison of baseline with later time points we converted baseline Blantyre Coma Score to AVPU as follows:

Blantyre Coma Score	AVPU scale	Numerical score
5	A	0
4	V	1
3	V	1
2	P	2
1	U	3
0	U	3

We weighted the contribution of AVPU to reflect its expected importance as an indicator of impaired neurological function.

Composite neurological score

Neurological score = (blood pressure - mean blood pressure for age) + (mean heart rate for age – heart rate) + 25 (AVPU score).

If the blood pressure was lower than the mean blood pressure for age, the term (blood pressure - mean blood pressure for age) was set to zero, so that only increased blood pressure contributed to the score. If the heart rate was greater than the mean heart rate for age, the term (mean heart rate for age - heart rate) was set to zero, so that only decreased heart rates contributed to the score.

Clustering algorithm

Individuals were clustered using their physiological scores and haemoglobin and lactate measures at baseline. Treatment and outcome were not included in the clustering. Clustering was implemented using a Bayesian multivariate normal mixture of Dirichlet process (MDP) model as implemented in the R package PreMiuM.[21,22] In our implementation each cluster in the mixture is a multivariate normal distribution representing the distribution of the measures within the cluster. An advantage of a MDP model is that the number of clusters is unknown and inferred from the data and inference is made by sampling from the posterior distribution using Markov chain Monte Carlo (MCMC). PreMiuM calculates an optimum single clustering and assignment of individuals to the clusters from the posterior samples it simulates; firstly it calculates a similarity matrix between all pairs of individuals based on the posterior mean of the number of times each pair is assigned to the same cluster. Individuals are then robustly assigned to clusters in a way consistent with the similarity matrix for all possible number of clusters. The optimal number of clusters is determined by the partition which maximises the average silhouette width. We used the single optimal clusters and assignments in all subsequent analyses. The optimal number of clusters determined by the algorithm is driven by the prior distribution assigned to the within cluster covariance; the more prior weight assigned to larger variances the fewer the clusters as more variation is allowed within each cluster. The default settings of the program resulted in eight clusters, increasing the prior within cluster variance by a factor of ten relative to the default values resulted in three clusters which we deemed to be more interpretable and therefore used in subsequent analyses.

Principal component analysis

Principal component analysis (PCA) was performed on the matrix of respiratory, neurological and cardiovascular scores at one hour and baseline base excess, bicarbonate, chloride and haemoglobin in the no bolus group; in the bolus group, to account for changes in the blood parameters which were not measured at one hour, values were adjusted by the observed mean shifts at 24 hours in biochemical variables (base excess -1.41, bicarbonate -0.96, chloride +1.65) and at 8 hours for haemoglobin (-0.32). This represents a conservative estimate of the change in these variables in the bolus group at one hour. Data was standardized such that all covariates had mean zero and standard deviation of one before PCA. Only samples with complete measures for all seven covariates were used, n=1901. The principal component loadings are weights representing the contribution of each of the seven covariates to each principal component. The loadings V are calculated as follows:

$$V = X^T U D^{-1/2}$$

where V are the PC loadings, X is the data matrix, U is the matrix of PCs and D is the diagonal matrix of eigenvalues.

Evaluation of the effect of bolus-induced changes in blood parameters on survival

Evaluation of changes in plasma chemistry and acid-base balance due to bolus

Acid-base balance and plasma chemistry were only measured on admission (before bolus fluids were administered) and again 24 hours later. We therefore had no data on the actual values for plasma chemistry and acid-base status in the early hours of the trial when most of the deaths were occurring. Furthermore by 24 hours, when the second measurement of plasma biochemistry was undertaken, the majority of deaths in the study had already occurred. Therefore we used two approaches to estimate the likely biochemical and acid-base status immediately after bolus-administration. First we used the difference in these parameters between surviving bolus and no bolus recipients at 24 hours to calculate a conservative estimate of the change in these parameters immediately after bolus administration. Second we used a literature-based estimate of the likely magnitude of change due to albumin or saline bolus.

Supporting the first approach, as shown in webextra Figure 10, baseline levels of bicarbonate, chloride and base excess were highly correlated with the levels at 24 hours in surviving patients. However, as shown in webextra Figure 11, patients with more severe derangement of base excess, bicarbonate and chloride at baseline had a greater change between 0 and 24 hours than those with less derangement. We concluded that the linear interpolation of the earlier time points from the 24 hour data was likely to significantly under estimate the change at the earlier time point. Examination of the 24 hour blood sample results (Table 1 in the main manuscript) showed clear evidence of worse hyperchloraemic acidosis in bolus recipients, who had significantly lower plasma bicarbonate and increased base excess and chloride as compared to the no bolus controls. As increased base excess was a strong predictor of death and those patients who went on to die had lower base excess and bicarbonate at baseline than survivors, the 24 hour values available were likely to significantly underestimate the extent of bolus-induced acidosis due to the higher death rate in bolus recipients by 24 hours.

In order to estimate the bolus-induced changes at early time points we first used linear interpolation to estimate the one hour value for base excess, chloride and bicarbonate based on the levels observed at baseline and 24 hours in the bolus and no bolus arms and a linear change in the levels from 1 to 24 hours:

Imputation of base excess (be) at 1 hour

be(1hr) = be(baseline) + slope + I(bolus) x (be(24hrs, bolus arm) - be(24hrs, no bolus arm))
where:
slope = (be(24hrs, no bolus arm) - be(baseline, no bolus arm)) / 24
I(bolus) = 1 for bolus sample and 0 otherwise

Chloride and bicarbonate were imputed similarly.
Haemoglobin was imputed using the values at 8 hours rather than 24 hours, in subjects who had not received blood transfusion.

Because the first approach is likely to underestimate the effects of albumin and saline on biochemical and acid-base status we also sought evidence from published studies to establish what changes should be expected at one hour after bolus. There is an extensive literature dating from the 1990s reporting hyperchloraemic acidosis occurring in recipients of normal saline or other high chloride containing solutions or comparing these solutions with buffered salt solutions (web extra Table 8). These studies include administration of crystalloids to healthy volunteers; administration of crystalloid solutions to patients undergoing a range of surgical conditions including both adults and children and ranging from gynaecological procedures, general surgical procedures, renal surgery and cardiac surgery; and studies in experimental animals. These studies establish that administration of normal saline and other high chloride containing fluids is invariably followed by hypochloraemic acidosis with a rise in chloride, decline in plasma bicarbonate and decrease in base excess occurring concurrently with the infusion and maximal immediately after the infusion. While the extensive literature has used a range of different infusion rates and volumes, those studies which have had comparable fluid volumes and rates to the 20-40 ml/kg infused during FEAST have shown decrease in base excess of approximately 5 mmol/l, a decline in bicarbonate of approximately 5 mmol/l and an increase in chloride of approximately 10 mmol/l in recipients of high chloride containing fluids. We therefore concluded there is strong evidence from the literature and our own data that the changes we have

detected in bolus recipients at the 24 hour time points are a minimum estimate of a predictable change induced by saline and albumin at earlier time points.
In order to provide a more realistic estimate based on the factors discussed above, we also estimated the 1 hour values for base excess, bicarbonate and chloride based on the reported changes after saline infusion in the many studies reported and summarised in web extra Table 8. We used the changes reported in those studies most similar to FEAST in the volume and timing of infusion.
Thus the estimates used in our analysis to impute the change in parameters from baseline to1 hour were as follows:

	No bolus	Data estimate in bolus recipients	Literature estimate in bolus recipients
Base excess mEq/L	+0·217	-1·025	-5
Chloride mmol/L	+0·011	+1·577	+10
Bicarbonate mmol/L	+0·194	-0·66	-5
Haemoglobin g/L	+0.03	-0.339	NA (-0.339*)

*The change in haemoglobin was derived only from data, and not from literature values, because measurements were available at 8 hours.

Cox proportional hazards regression modelling
To explore whether the changes induced by bolus at one hour could explain the adverse effect of bolus we built Cox proportional hazards survival models with the outcome as time of death. The baseline model contained only bolus as a covariate, covariates were added iteratively, and at each iteration the covariate with the smallest p-value for association with time of death in the multivariate survival model was added, until all covariates were added. In addition to a model using baseline variables, four sets of explanatory covariates representing the one hour time point were considered.

Covariate set 1
The first set of covariates contained the three scores at 1 hour and imputed levels for base excess, chloride, bicarbonate and haemoglobin based on the levels observed at baseline and 24 hours in the bolus and no bolus arms and a linear change in the levels from 1 to 24 hours.

Covariate set 2
In this set of covariates we used the scores and haemoglobin estimate as in covariate set 1 and imputed levels for base excess, chloride and bicarbonate in the bolus arm based on estimates of the effects of bolus on these blood parameters derived from published articles.

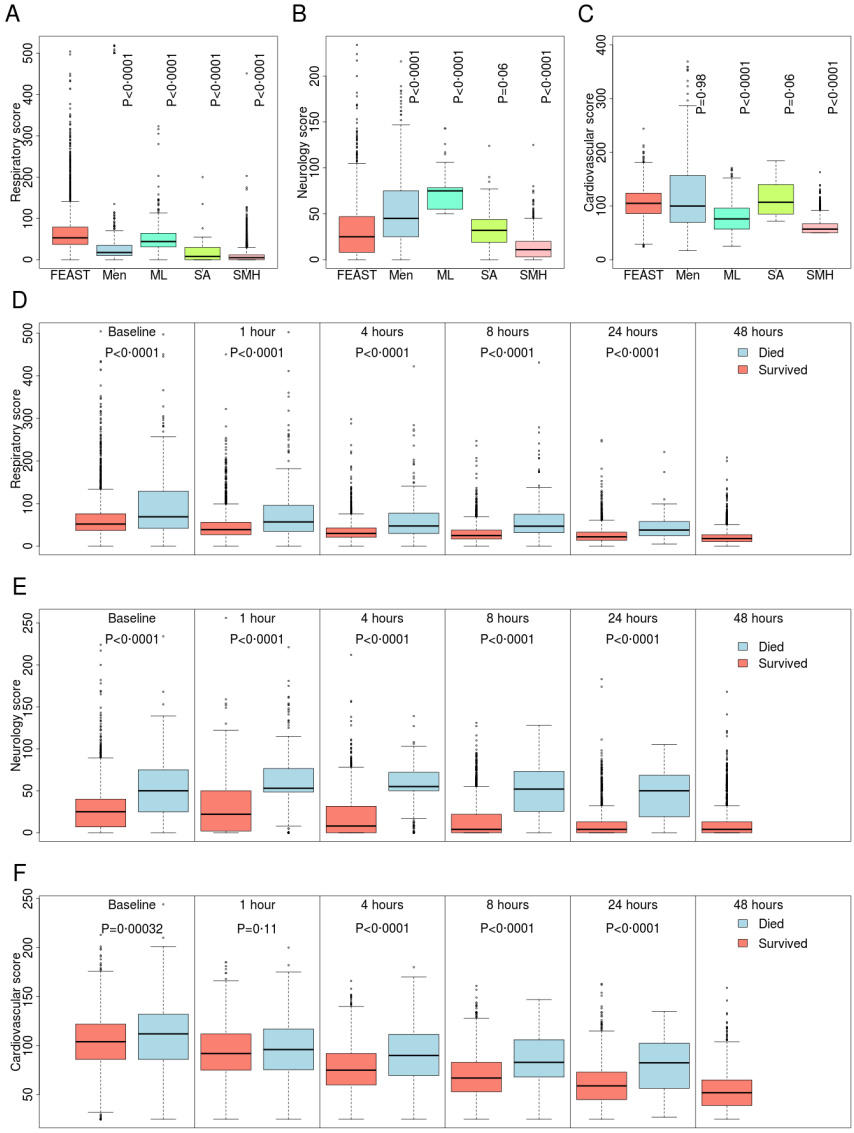
Estimates in the no bolus arm were the same as those used in covariate set 1.

Covariate set 3
The third set of covariates contained the individual components of the score and the imputed blood levels used in covariate set 1. The individual components of the score were respiratory rate above the norm for age, systolic blood pressure above and below the norm for age and heart rate above and below the norm for age.

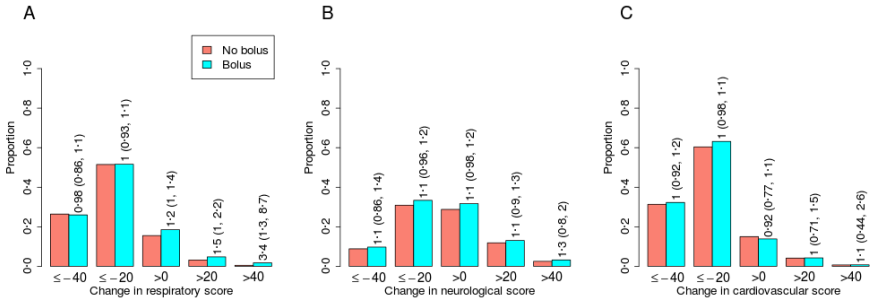
Covariate set 4
Individual components of the score as used in covariate set 3 and the literature based estimates of the effects of bolus on the blood markers as used in covariate set 2.

The above models were refit including bolus as an additional explanatory covariate to calculate the hazard ratio for bolus under each model.

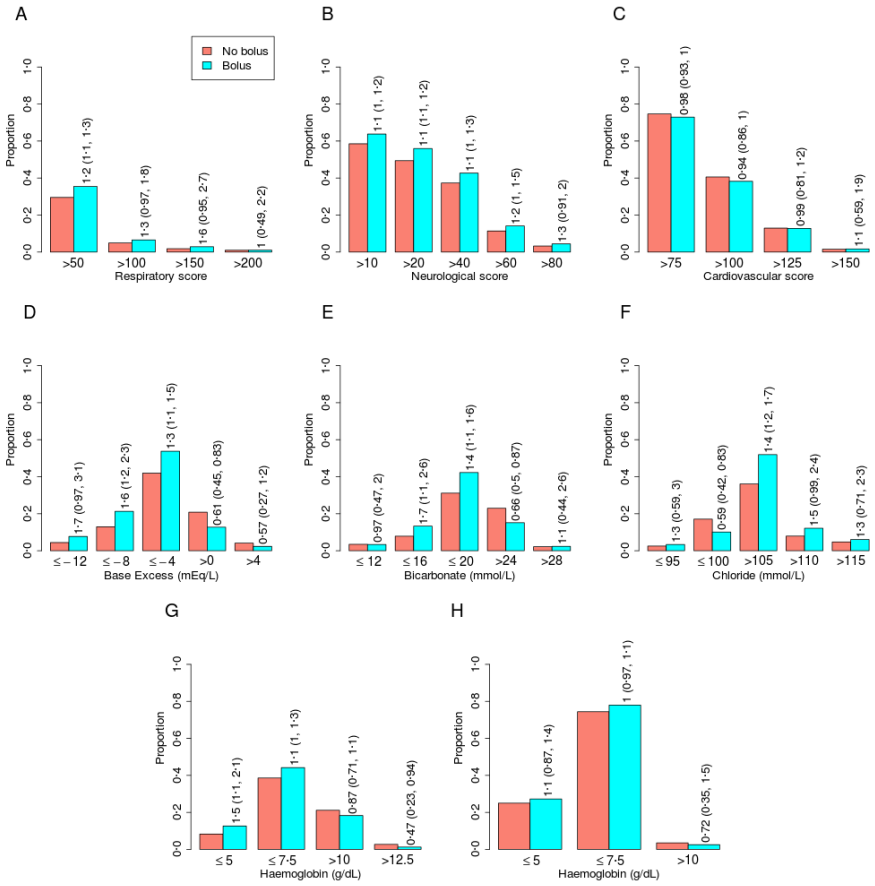
Web extra Figures



Web extra Figure 1. Physiological scores associated with aetiology and severity of illness across cohorts and sequential changes over time in FEAST
Respiratory (A), neurological (B) and cardiovascular (C) scores in FEAST and 4 other cohorts (Men, UK Meningococcal cohort; ML, Malawian cerebral malaria cohort; SA, South African sepsis cohort; SMH, St Mary's Hospital emergency department cohort). D-F show sequential changes in the FEAST cohort in respiratory (D), neurological score (E) and cardiovascular (F) scores at time points from admission baseline to 48 hours. Survivors are shown in red, cases dying in the next time period are shown in blue. Boxes show median and IQR; whiskers extend up to 1·5-times IQR. P for two-sided Mann-Witney test, unadjusted for multiple comparisons.

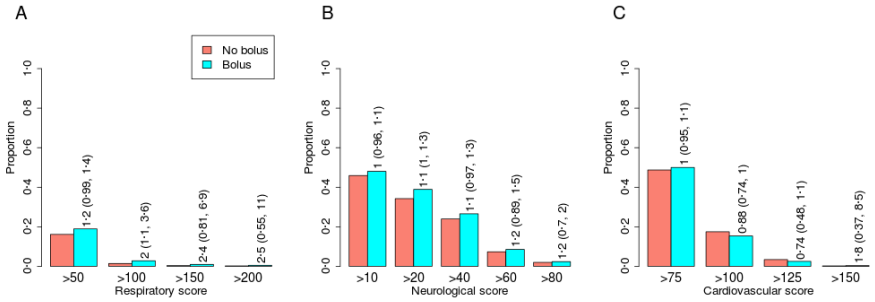


Web extra Figure 2. Change in physiological scores from baseline to 4 hours.
The proportion of individuals in FEAST with different magnitudes of change in physiological scores from baseline to four hours, compared between those randomized to no bolus (red bars) or bolus (blue bars). Negative values indicate decrease from the baseline, and positive values indicate increase from baseline. Values above bars show relative risk (95% CI) for comparison of proportions between bolus and no bolus groups.

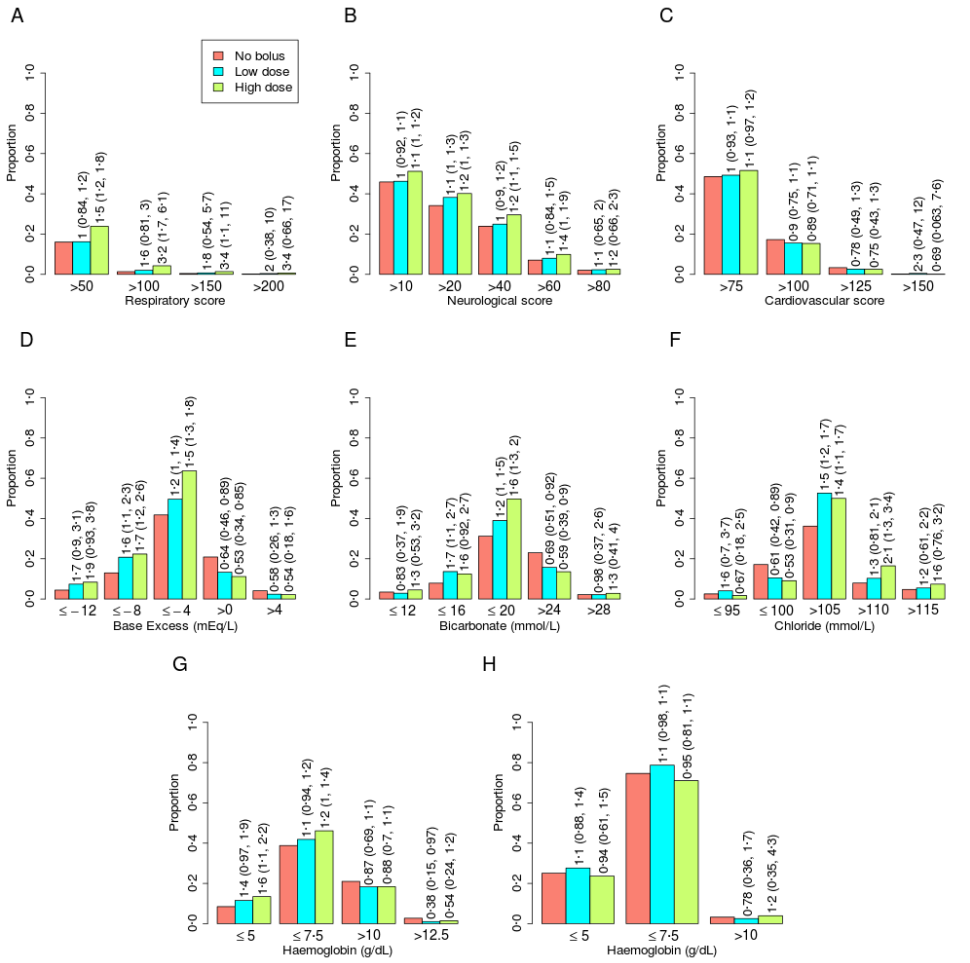


Web extra Figure 3. Distribution of physiological scores and blood parameters at first observation after randomization in FEAST.

Comparison of the proportion of individuals in FEAST with indicated values of physiological scores and blood measurements at the next observation after initiation of fluid bolus (blue) or no fluid bolus (red). A-C show physiological scores at 1 hour. D-F show biochemical measures at 24 hours. G and H show haemoglobin concentration at 8 hours in non-transfused (G) and transfused (H) subjects. Values above bars show relative risk (95% CI) for comparison of proportions between bolus and no bolus groups.

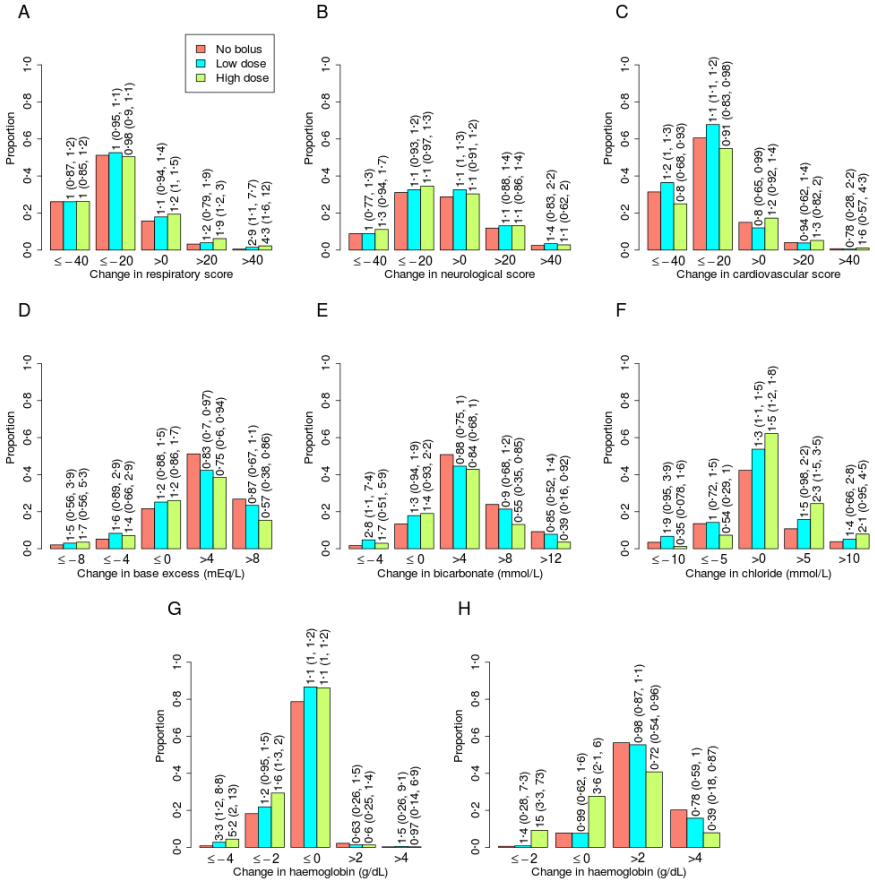


Web extra Figure 4. Distribution of physiological scores at 4 hours in FEAST.
Comparison of physiological scores at 4 hours after initiation of fluid bolus (blue) or no fluid bolus (red). Values above bars show relative risk (95% CI) for comparison of proportions between bolus and no bolus groups.

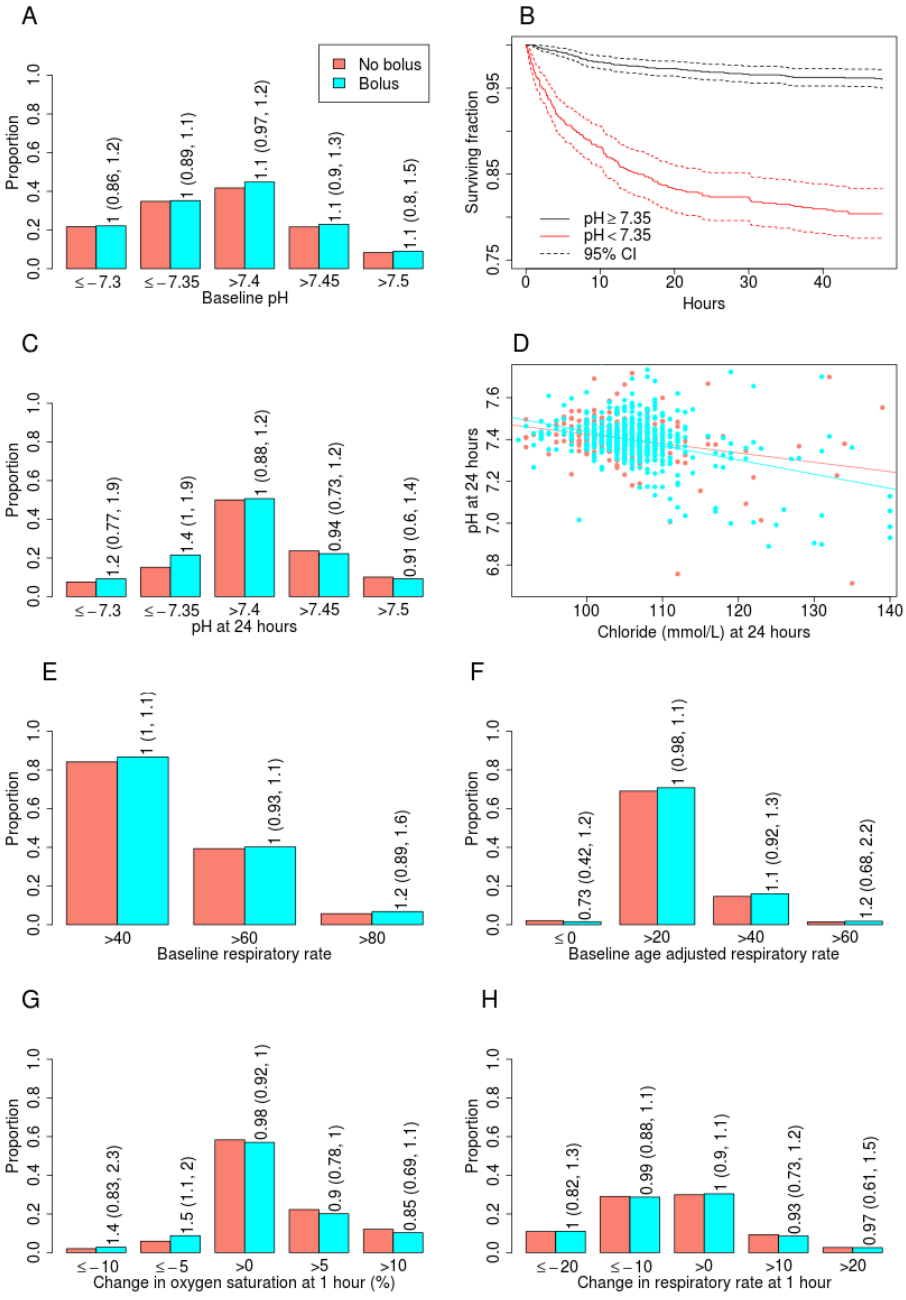


Web extra Figure 5. Distribution of physiological scores and blood parameters associated with volume of fluid bolus administered in FEAST.

The proportion of individuals in FEAST with indicated values of physiological scores and blood measurements at the next observation after completion of bolus fluids in all groups, in those who received high volume bolus (≥30ml/kg, green bars), low volume bolus (<30ml/kg, blue bars), or no bolus (red bars). A-C show physiological scores at 4 hours after bolus initiation. D-F show biochemical measures 24 hours after bolus initiation. G-H show haemoglobin concentration 8 hours after bolus initiation in non-transfused (G) and transfused (H) subjects. Values above bars show relative risks (95% CI) for comparison of proportions between low volume or high volume bolus groups vs no bolus groups.

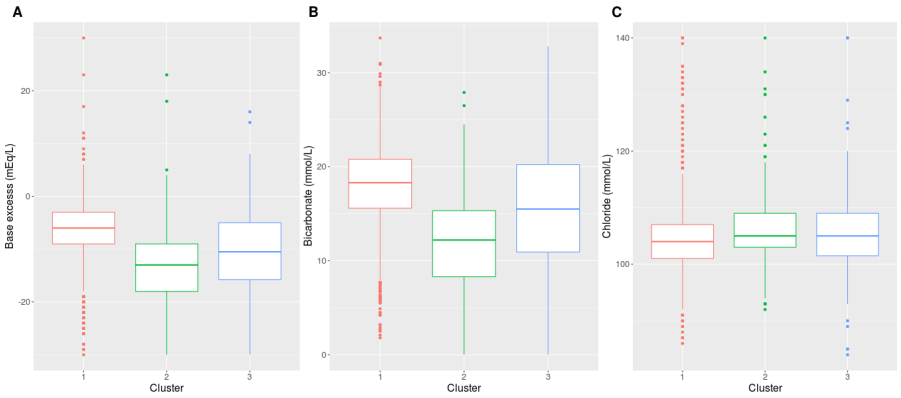


Web extra Figure 6. Changes from baseline to next observation for physiological scores and blood measures according to volume of fluid bolus received in FEAST.
Comparison of the proportion of individuals in FEAST with different magnitudes of change in physiological scores and blood measurements according to whether they received high volume bolus (≥30ml/kg, green bars), low volume bolus (<30ml/kg, blue bars) or no bolus (red bars). A-C show changes in physiological scores between 0 and 4 hours. D-F show changes in biochemical measures from baseline to 24 hours. G and H show change in haemoglobin from baseline to 8 hours in non-transfused (G) and transfused (H) subjects. The change from baseline is shown for each segment of the distribution. Negative values indicate decrease from the baseline, and positive values indicate increase from baseline. Values above bars show relative risks (95% CI) for comparison of proportions between low volume or high volume bolus groups vs. no bolus groups.

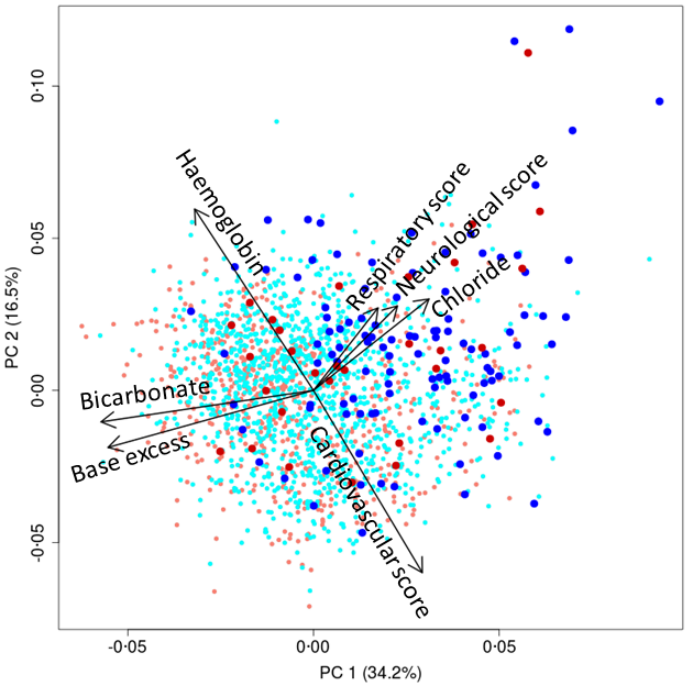


Web extra Figure 7. Hyperchloraemic acidosis in FEAST.
A shows distribution of pH at baseline in FEAST subjects according to whether they were randomized to no fluid bolus (red bars) or fluid bolus (blue bars). B shows survival in FEAST by baseline pH (black line, pH ≥7·35; red line pH <7·35; dotted lines 95% CI; Cox proportional hazards model with random effects for site; n=2082, 195 total events, p<0·0001). C shows proportion of individuals with indicated values of pH at 24 hours for no fluid bolus (red bars) or fluid bolus groups (blue bars). D shows correlation between chloride

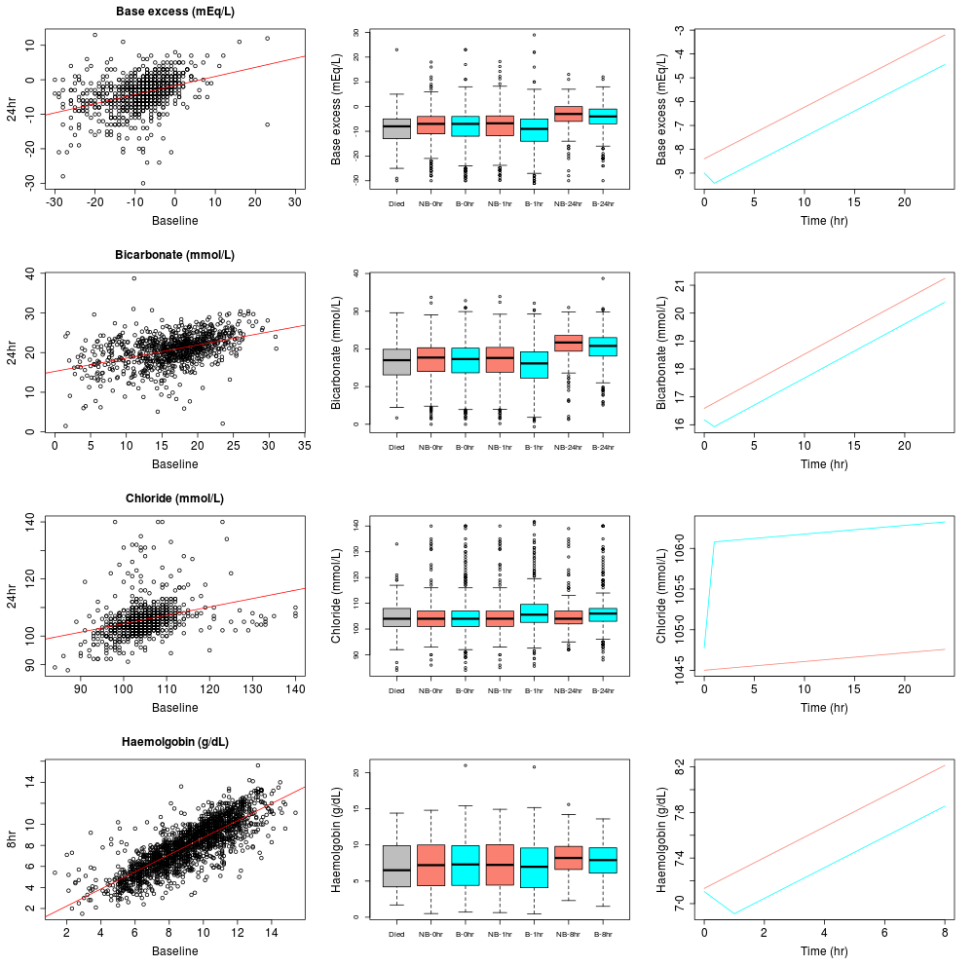
concentration at 24 hours and pH at 24 hours shown by whether subjects were randomized to no fluid bolus (red dots and regression line, Pearson r=-0·28 (95% CI -0·38 to -0·17), p<0·0001) or fluid bolus (blue dots and regression line, Pearson r=-0·41 (95%CI -0·47 to -0·33), p<0.0001); p=0.05 for comparison of correlation coefficients using the z-test. E shows baseline respiratory rate and F the respiratory rate above mean for age. G-H show the proportion of individuals with different magnitudes of change from baseline to one hour in oxygen saturation (G) and respiratory rate (H) according to whether they were randomized to no fluid bolus (red bars) or fluid bolus (blue bars). Values above bars show relative risks (95% CI) for comparison of proportions between bolus vs no bolus groups.



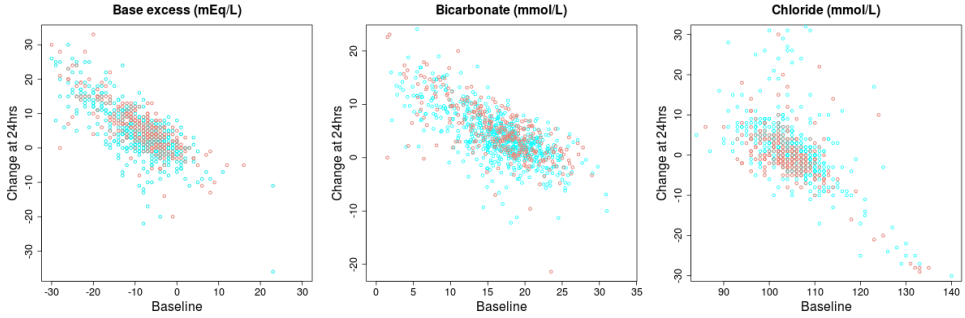
Web extra Figure 8. Biochemical measurements in clusters within FEAST.
Comparison of the distributions of baseline biochemical measurements by cluster within FEAST. Boxes show median and IQR; whiskers extend up to 1·5-times IQR.



Web extra Figure 9. Principle component plot using physiological scores and blood parameters. Principal component (PC) analysis using the respiratory, neurological and cardiovascular scores at 1 hour after bolus, and conservative (data-derived) estimates of haemoglobin and biochemical values at 1 hour based on their values at 8 and 24 hours respectively (light red, no bolus, survivors; large dark red, no bolus, fatal cases; light blue, bolus, survivors; large dark blue, bolus, fatal cases). The principal component loadings (arrows) indicate the contributions of increasing values of each variable. Analysis is based on 1898 subjects with complete data for physiological scores at 1 hour and baseline biochemical parameters.



Web extra Figure 10. Imputation of blood parameters based on relationships between baseline and 24 hour values.
Relationships between baseline values and those at next measurement for base excess, chloride and bicarbonate (all 24 hours) and haemoglobin (8 hours) (first column of panels). Distribution of blood parameter values in subjects who died and those who survived at baseline, imputed from data at 1 hour, and at next measurement (second column of panels; NB (red), no bolus; B (blue), bolus; boxes show median and IQR; whiskers extend up to 1·5-times IQR). Illustration of imputation of values in bolus group based on difference in values between baseline and next measurement in no bolus group, and difference between bolus and no bolus groups at the second measurement timepoint (third column of panels).



Web extra Figure 11. Relationship between baseline values and change at 24 hours for biochemical parameters.
Relationships between values at baseline and change from baseline to 24 hours for blood base excess, bicarbonate and chloride. Blue, bolus recipients; red no bolus.

Web extra Tables

Web extra Table 1. Numbers (%) of surviving subjects at each time point in FEAST Stratum A with available data for each variable.

	Baseline	1 hour	4 hours	8 hours	24 hours	48 hours
Surviving	3141	3102	3025	2974	2882	2844
Systolic blood pressure	3100 (99)	3037 (98)	2975 (98)	2923 (98)	2830 (98)	2772 (97)
Capillary refill time	3137 (100)	3078 (99)	3004 (99)	2950 (99)	2854 (99)	2787 (98)
Conscious level	3123 (99)	3069 (99)	2998 (99)	2943 (99)	2847 (99)	2776 (98)
Oxygen saturation	3038 (97)	3030 (98)	2979 (98)	2930 (99)	2834 (98)	2772 (97)
Heart rate	3141 (100)	3077 (99)	3002 (99)	2950 (99)	2853 (99)	2786 (98)
Respiratory rate	3124 (99)	3056 (99)	2997 (99)	2945 (99)	2845 (99)	2778 (98)
Respiratory score	3022 (96)	3008 (97)	2974 (98)	2925 (98)	2826 (98)	2763 (97)
Cardiovascular score	3096 (99)	3037 (98)	2975 (98)	2923 (98)	2829 (98)	2772 (97)
Neurological score	3082 (98)	3028 (98)	2969 (98)	2917 (98)	2822 (98)	2762 (97)
Hemoglobin	3054 (97)	0 (0)	0 (0)	2785 (94)	2744 (95)	0 (0)
Base excess	2070 (66)	0 (0)	0 (0)	0 (0)	914 (32)	0 (0)
Bicarbonate	2080 (66)	0 (0)	0 (0)	0 (0)	912 (32)	0 (0)
Chloride	2067 (66)	0 (0)	0 (0)	0 (0)	909 (32)	0 (0)

Web extra Table 2. Associations between physiological scores and outcome* in FEAST and 4 other cohorts.

Cohort	n (% all subjects)	Odds ratio for outcome per 10-unit increase in score	95% CI	P value
Respiratory score				
FEAST	3037 (96)	1·09	(1·07, 1·11)	<0·0001
Malawi	357 (80)	1·04	(0·99, 1·1)	0·13
South Africa	61 (100)	1·2	(0·97, 1·47)	0·089
Meningococcal	363 (72)	1·32	(1·19, 1·45)	<0·0001
SMH	13934 (74)	1·6	(1·54, 1.66)	<0·0001
Neurology score				
FEAST	3096 (98)	1·26	(1·21, 1·31)	<0·0001
Malawi	411 (92)	1·24	(1·08, 1·43)	0·0030
South Africa	61 (100)	1·6	(1·2, 2·14)	0·0010
Meningococcal	399 (79)	1·04	(0·99, 1·09)	0·16
SMH	2414 (13)	1·07	(0·97, 1·19)	0·16
Cardiovascular score				
FEAST	3110 (98)	1·09	(1·05, 1·14)	<0·0001
Malawi	411 (92)	1·19	(1·1, 1·28)	<0·0001
South Africa	61 (100)	1·04	(0·88, 1·22)	0·66
Meningococcal	333 (66)	1·08	(1·04, 1·12)	<0·0001
SMH	1509 (8)	1·3	(1·19, 1·42)	<0·0001

*Outcomes were defined as death in FEAST and the Meningococcal cohorts, death or neurological disability in the Malawian cohort, admission to intensive care in the South African cohort and admission to hospital or intensive care in the SMH emergency department cohorts. n, number of subjects with complete data available to calculate each score at baseline.

Web extra Table 3. Changes in physiological scores and blood parameters associated with albumin bolus or saline bolus in FEAST.

	Saline				Albumin				Albumin vs. saline
	n	Effect size	95% CI	p	n	Effect size	95% CI	p	p
1 hour									
Respiratory score	970	2·73	-0·23, 5·68	0·071	976	4·18	1·23, 7·13	0·0056	0·34
Neurological score	995	3·49	1·32, 5·67	0·0017	996	1·79	-0·39, 3·96	0·11	0·12
Cardiovascular score	1003	-2·34	-0·49, -4·20	0·014	1003	-2.0	-0·15, -3·86	0·035	0·72
4 hours									
Respiratory score	957	1·29	-1·02, 3·60	0·273	962	3·32	1·01, 5·63	0·0049	0·086
Neurological score	975	1·92	-0·088, 3·93	0·061	975	0·19	-1·82, 2·20	0·85	0·092
Cardiovascular score	982	-0·55	1·33, -2·44	0·56	981	-0·038	1·85, -1·92	0·97	0·59
8 hours									
Respiratory score	937	0·16	-2.00, 2·33	0·88	943	3.0	0·83, 5·16	0·0068	0·011
Neurological score	954	0·93	-0·94, 2·80	0·33	956	-0·29	1·58, -2·16	0·77	0·21
Cardiovascular score	960	-0·40	1·47, -2·28	0·67	962	0·61	-1·27, 2·48	0·53	0·29
Lactate mmol/L	895	-0.075	-0.32, 0.17	0.55	921	-0.16	-0.41, 0.081	0.19	0.48
Haemoglobin g/dL (untransfused)	949	-0.30	-0.45, -0.15	<0.0001	967	-0.49	-0.64, -0.34	<0.0001	0.012
Haemoglobin g/dL (transfused)	973	-0.34	-0.60, -0.079	0.0097	976	-0.12	-0.38, 0.14	0.37	0.095
24 hours									
Chloride mmol/L	265	2.1	1.15, 3.06	<0.0001	284	1.41	0.45, 2.37	0.0040	0.16
Bicarbonate mmol/L	270	-1.06	-1.65, -0.47	0.00057	294	-0.87	-1.46, -0.28	0.0039	0.53
Base excess mEq/L	271	-1.52	-2.27, -0.77	0.00010	294	-1.31	-2.05, -0.56	0.00065	0.579

Effect size is the mean change in the variable attributable to bolus. Positive effect size indicates increase in parameter, negative effect size indicates decrease, as compared with no bolus control.

Web extra Table 4. Association between changes in variables and risk of death in clusters within FEAST.

Group	n	OR	95% CI	p
Respiratory score				
FEAST	3037	1·09	1·07,1·11	<0·0001
Cluster 1	1967	1.00	0·90,1·11	0·98
Cluster 2	717	1·07	1,1·14	0·040
Cluster 3	353	1·03	1,1·06	0·020
Neurology score				
FEAST	3096	1·26	1·21,1·31	<0·0001
Cluster 1	1955	1·41	1·26,1·57	<0·0001
Cluster 2	772	1·30	1·2,1·41	<0·0001
Cluster 3	369	1·06	1·01,1·12	0·020
Cardiovascular score				
FEAST	3110	1·09	1·05,1·14	<0·0001
Cluster 1	1963	0·97	0·88,1·08	0·60
Cluster 2	777	1·05	0·98,1·12	0·16
Cluster 3	370	1·03	0·96,1·11	0·43
Haemoglobin (g/dL)				
FEAST	3082	0·88	0·85,0·91	<0·0001
Cluster 1	1929	1.00	0·91,1·1	0·97
Cluster 2	780	1·11	1·01,1·22	0·030
Cluster 3	373	0·91	0·85,0·98	0·008
Lactate (mmol/L)				
FEAST	3009	1·23	1·2,1·26	<0·0001
Cluster 1	1888	1·30	1·08,1·57	0·0060
Cluster 2	768	1·15	1·08,1·22	<0·0001
Cluster 3	353	1·15	1·09,1·22	<0·0001

OR, odds ratio for death for each ten-unit increase in the physiological scores and each unit increase in haemoglobin and lactate in FEAST overall and in clusters

Web extra Table 5. Changes in physiological scores and blood parameters associated with fluid bolus in FEAST Cluster 1.

Time (Hours)	n	Effect size	95% CI	p
Respiratory score				
1	1934	2·67	0·35, 4·99	0·020
4	1935	1·54	-0·50, 3·57	0·14
12	1916	0·87	-0·93, 2·67	0·34
Neurology score				
1	1926	3·42	1·38, 5·46	0·0010
4	1927	1·49	-0·47, 3·44	0· 13
12	1906	-0·14	-1·92, 1·64	0·87
Cardiovascular score				
1	1937	-1·72	-3·57, 0·14	0·070
4	1933	0·55	-1·37, 2·47	0·57
12	1915	0·66	1·24, 2·57	0·50
Haemoglobin (g/dL)				
8	1837	-0·35	-0·49-0·20	<0·0001
24	1818	-0·19	0·34, -0·035	0·020
Lactate (mmol/L)				
8	1806	-0·16	-0·39, 0·064	0· 15
24	1776	-0·070	-0·30, 0·16	0·50
Base excess (mEql/L)				
24	590	-1·34	-2·03, -0·64	0·0002
Bicarbonate (mmol/L)				
24	592	-0·90	-1·44, -0·36	0·0012
Chloride (mmol/L)				
24	575	1·99	0·46, 3·52	0·0010

*Effect size is the mean change in the variable attributable to bolus. Positive effect size indicates increase in parameter, negative effect size indicates decrease, as compared with no bolus control.

Web extra Table 6. Changes in physiological scores and blood parameters associated with fluid bolus in FEAST Cluster 2.

Time (Hours)	n	Effect size	95% CI	p
Respiratory score				
1	676	5·11	-0·37, 10·6	0·06
4	655	3·8	0·038, 7·6	0·040
12	634	1·1	-2·79, 5·02	0·50
Neurology score				
1	730	4·32	0·41, 8·22	0·030
4	698	1·19	-2·48, 4·86	0· 15
12	676	0·57	-3·01, 4·16	0·70
Cardiac score				
1	737	-1·75	-5·24, 1·75	0·32
4	706	-0·65	-4·08, 2·78	0·71
12	683	-0·33	-3·87, 3·21	0·85
Haemoglobin (g/dL)				
8	646	-0·16	-0·45, 0·13	0·27
24	628	-0·091	-0·38, 0·2	0·54
Lactate (mmol/L)				
8	654	-0·041	-0·58, 0·50	0· 88
24	616	0·030	-0·42, 0·48	0·90
Base excess (mEql/L)				
24	182	-1·34	-3·46, -0·021	0·050
Bicarbonate (mmol/L)				
24	180	-1·74	-2·62, 0·082	0·070
Chloride (mmol/L)				
24	180	2·87	0·73, 5·02	0·0090

*Effect size is the mean change in the variable attributable to bolus. Positive effect size indicates increase in parameter, negative effect size indicates decrease, as compared with no bolus control.

Web extra Table 7. Changes in physiological scores and blood parameters associated with fluid bolus in FEAST Cluster 3.

Time (Hours)	n	Effect size	95% CI	p
Respiratory score				
1	315	3·44	-10·9, 17·8	0· 63
4	294	3·69	-7·65, 15	0· 52
12	288	7·13	-3·86, 18·1	0·20
Neurology score				
1	336	-5·19	-12·9, 2·55	0·19
4	308	-1·32	-8·46, 5·83	0· 71
12	299	2·98	-3·79, 9·76	0·38
Cardiac score				
1	336	-4·84	-10·2, 0·56	0·08
4	309	-4·23	-10·1, 1·6	0·15
12	299	-2·06	-7·8, 3·68	0·48
Haemoglobin (g/dL)				
8	288	-0·52	-0·92, -0·12	0·010
24	277	-0·59	-1·02, -0·16	0·008
Lactate (mmol/L)				
8	277	0·0022	-0·75, 0·76	0· 99
24	265	0·30	-0·40, 1.00	0·40
Base excess (mEql/L)				
24	85	-1·09	-3·68, 1·5	0·41
Bicarbonate (mmol/L)				
24	86	-0·69	-2·69, 1·32	0·50
Chloride (mmol/L)				
24	85	-3·04	-5·94, -0·15	0·040

*Effect size is the mean change in the variable attributable to bolus. Positive effect size indicates increase in parameter, negative effect size indicates decrease, as compared with no bolus control.

Web extra Table 8. Studies evaluating the effects of unbalanced salt solutions on blood acid-base balance and chloride

Paper	Author	Year	Fluid volume	Study Type/Detail	Bicarbonate	Base Excess	Chloride
Balanced Crystalloids Versus Saline for Perioperative Intravenous Fluid Administration in Children Undergoing Neurosurgery: A Randomized Clinical Trial[23]	Lima et al.	2019	"4-2-1 rule"	RCT: 53 paediatric patients having neurosurgery randomised to saline or balanced crystalloid.		post-preop change in BE: −4.4 [IQR −5.0; −2.3] in saline group vs. −0.4 [−2.7; 1.3] mmol/L in balanced group; P < 0.001	post-preop change in chloride: 6 [IQR 3.5; 8.5] mmol/L in saline group compared with 0 [−1.0; 3.0] mmol/L in balanced group; P < 0.001
Balanced Crystalloids versus Saline in Critically Ill Adults[24]	Semler et al.	2018	Median volume saline given 1020mls	Cluster-randomized, multiple-crossover trial of 15,802 adult ICU patients. Randomised to saline or balanced crystalloid.	Lowest level between enrolment and day 30, median [IQR]: Balanced group 21.0 mmol/L [18.0 – 23.0] vs 20.0 in saline group [17.0 – 22.0]. p <0.001 Bicarb < 20 mmol/L between enrolment and day 30, No. (%): balanced group 2793 (35.2) vs 3307 (42.1) in saline group. p<0.001		Highest level between enrolment and day 30, median [IQR]. Balanced group 108 mmol/L [105 – 111] vs saline group 109 [105 – 112]. P<0.001 Cl >110 mmol/L between enrolment and day 30, No. (%) 1945 (24.5) in balanced group vs 2796 (35.6) in saline group. P<0.001
Balanced Crystalloids versus Saline in Noncritically Ill Adults[25]	Self et al.	2018	Median volume in ED 1079 mls	Multiple crossover trial of 13,347 adults requiring hospital but not ICU admission	Lowest bicarb <20mmol/L: 1668 (24.9%) in balanced group vs 1859 (28%) in saline group. P<0.01		Highest chloride >110 mmol/L: 1020 (15.2%) in balanced group vs 1280 (19.3%) in saline group. P<0.01
Normal saline versus a balanced crystalloid for goal-directed perioperative fluid therapy in major abdominal surgery: a double-blind randomized[26]	Pfortmueller et al.	2018	2 ml/kg ideal body weight/hr (increased if viscera exposed)	RCT of adults undergoing major abdominal surgery		Median minimum base excess was lower in the saline group than the balanced group: -6.0 (-12 to 4) vs 0.0 (-5 to 3) mmol/L P<0.0001	Intra-operative change in chloride 7 mmol/L (2-16) in saline group compared to 2mmol/L (0-9) in the balanced group p<0.0001
A randomized trial of Plasma-Lyte A and 0.9 % sodium chloride in acute paediatric gastroenteritis[27]	Allen et al.	2016	No standard regime	RCT of children with moderate to severe dehydration.	Mean change in bicarb 1.6 mEq/L in balanced group vs 0mEq/L in saline group (p=0.004)		Balanced group: baseline Cl 103.03 mmol/L +/- 4.74 to 104.49 +/- 3.18 at 4 hours. Saline group 103.53 +/- 4.19 to 108.51 +/- 4.87. P<0.001

Effects of Fluid Resuscitation With 0.9% Saline Versus a Balanced Electrolyte Solution on Acute Kidney Injury in a Rat Model of Sepsis[28]	Zhou et al.	2014	10 mL/kg in the first hour and 5 mL/kg in the next 3 hr	Controlled laboratory experiment of 60 adult rats		In saline group, BE changed following resuscitation (2 vs 5 mmol/L; $p < 0.05$)	Saline group: chloride increased (109 vs 102 mmol/L; $p < 0.05$), Balanced fluid group: no hyperchloremia (102 vs 101 mmol/L; $p > 0.05$)
Saline Versus Plasma-Lyte A in Initial Resuscitation of Trauma Patients[29]	Young et al.	2014	No standard regime	RCT of adult trauma patients. Plasmalyte vs 0.9% saline	Change in bicarbonate in saline group at 24 hours 22 ± 4 mEgl/L compared to 26 ± 3 in balanced group.	Change in BE in saline group at 24 hours 4.4 ± 3.9 mmol/L compared to 7.5 ± 4.7 in balanced group	At 24 hours saline group 111 +/- 8 mEq/L vs 104 +/- 4 in plasma-lyte group. Difference of -7 (95% CI -10 - -3).
A novel balanced isotonic sodium solution vs normal saline during major surgery in children up to 36 months: a multicentre RCT[30]	Disma et al.	2014	4 ml/kg/h for the first 10 kg, 2 ml/kg/h from 11 to 20 kg and 1 ml/kg/h for every kg more than 20 kg	RCT: 240 paediatric patients undergoing major surgery. Balanced crystalloid plus 1% glucose vs saline + 1% glucose		Median change balanced solution -0.95 vs -1.7 in saline group (p=0.019)	Median change 4 mEq/L in the saline group compared to 2 in balanced group (p= 0.0001)
Comparisons of normal saline and lactated Ringer's resuscitation on hemodynamics, metabolic responses, and coagulation in pigs after severe hemorrhagic shock.[31]	Martini et al.	2013	To match MAP achieved in a pig resus with 3*bled volume of RL	Randomised trial of 20 pigs. Induced haemorrhage following by resuscitation with Ringer's lactate (RL) or normal saline (NS)	Bicabronate drop in RL and NS group. Bicarbonate remained lower in NS group compared to RL group at 3 and 6 hours (P<0.05)	Base excess drop in RL and NS group and remained lower in NS group compared to RL group at 3 and 6 hours (P<0.05)	Hyperchloraemia for 6 h after NS resuscitation (102 mM +/-3 at baseline to 123 +/- 3 at 6 hours),. Not seen after RL resuscitation (101 mM +/- 2 at baseline to 97 +/-3 at 6 hrs).
Balanced versus chloride-rich solutions for fluid resuscitation in brain-injured patients: a randomised double-blind pilot study.[32]	Roquilly et al.	2013	30ml/kg/day	RCT: 42 patients with severe traumatic brain injury randomised to isotonic balanced solutions or isotonic sodium chloride solutions		Saline group: Median (IQR) BE at baseline -1.7 (-3.9 - -0.3) to -2.4 (-3.7 - -0.9) at 6 hrs vs balanced group -2.6 (-3.5 - -0.1) to -0.3 (-1.3 - 1) at 6 hrs (p=0.004)	Higher incidence of hyperchloremic acidosis in the saline than balanced fluid group ($P = 0.01$). Mean difference in chloride between the saline and balanced group of 4.8 mmol/L (1.9 to 7.6); $P = 0.002$
A Randomized, Controlled, Double-Blind Crossover Study on the Effects of 2L Infusions of 0.9% Saline and Plasma-Lyte 148 on Renal Blood Flow Velocity and Renal	Chowdhury et al.	2012	2L over 1 hour	12 healthy adult males			Chloride peaked at 109mol/L in saline group. Remained high for duration of study. Levels remained normal in plasmalyte group (p<0.0001)

Cortical Tissue Perfusion in Healthy Volunteers.[33]							
The biochemical effects of restricting chloride-rich fluids in intensive care.[34]	Yunos et al.	2011	No standard fluid prescriptio n	Prospective, open-label, before-and-after study. Significant reduction in use of chloride rich fluids between control (828 patients) and intervention (816 patients) periods.	Time weighted mean (SD) pre-intervention 25.3 mmol/L (4.0) and 26.4 (4.1) after (P<0.001).	Pre-intervention (no limitation on chloride rich fluids) 9.1% had a base excess <-5mEq/L compared to 6% following intervention (P<0.001). Time weighted mean (SD) pre-intervention 0.5 mmol/L (4.5) and 1.8 (4.7) after (P<0.001).	Severe hyperchloraemia (>114mmol/L) reduced from 6.2% pre-intervention to 2.3% following intervention (P<0.001). Time weighted mean (SD) pre-intervention 104.9 mmol/L (4.9) and 102.5 (4.6) after (P<0.001).
Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis.[35]	Mahler et al.	2010	20ml/kg bolus then DKA protocol rates	RCT of the resuscitation of adults with DKA. Normal saline vs plasma-lyte A	Mean post-resuscitation bicarb 17 mmol/L (95% CI 15-18) in saline group vs 20 (18-21) in plasmalyte group. P=0.02		Mean post-resuscitation chloride 111 mmol/L (95% CI 110-112) in saline group vs 105 (103-108) in plasmalyte group. P<0.001
Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: A randomized, three-way crossover study in healthy volunteers.[36]	Lobo et al.	2010	1L over 1 hr	Randomized, three-way crossover study of 10 healthy adult males.	Reduction in bicarbonate after infusion but non-significant chance between saline and voluven or gelofusin.		Persistent hyperchloremia more marked after 0.9% saline and Voluven than Gelofusine. Saline vs gelofusin p=0.08
Lactated Ringer's is Superior to Normal Saline in the Resuscitation of Uncontrolled Hemorrhagic Shock.[37]	Todd et al.	2007	Fluids to target MBP 256.3 +/- 145.4 mL/kg of fluid	Randomised study of 20 adult swine		Final BE in saline group -4.6 +/- 7.9 mmol/L compared to 7.2 +/- 4.2 in RL group (p<0.01)	Final chloride in saline group 119 +/- 5.6 mEq/L compared to 105 +/- 2.9 in RL group (p<0.0001)
(Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study.[38]	Reid et al.	2003	2L infusion over an hours	Double-blind crossover study of 9 healthy adult males	Saline group: Mean 26.7 mmol/L to 25.6 at one hour; Hartmann's group 26.9 to 27.1 mmol/L (p=0.008)		Saline group: Mean 103 mmol/L to 108 at one hour; Hartmann's group 103 to 104 mmol/L (p<0.001)
The Effects of Balanced Versus Saline-Based Hetastarch and Crystalloid Solutions on	Wilkes et al.	2001	500ml bolus then 7ml/kg/hr	Randomised trial of 47 adult patients.	Pre to post op change in balanced group: 25.8 +/- 3.3 to 24.7 +/- 3. Pre to post op change in saline	Pre to post op change in balanced group: 0.7 +/- 2.7 to -0.2 +/- 2.6. Pre to post op change in	Pre to post op change in balanced group: 104.9 +/- 3.2 to 108.2 +/1 3.4. Pre to post op change in

Acid-Base and Electrolyte Status and Gastric Mucosal Perfusion in Elderly Surgical Patients.[39]					group: 25.7 +/- 2.6 to 21.8 +/- 3.2 ($p<0.0073$)	saline group: 1.7 +/- 2.3 to -3.8 +/- 2.9 ($p=0.0001$)	saline group: 104.2 +/- 3.5 to 114 +/- 4.9 ($p=0.0001$)
Rapid Saline Infusion Produces Hyperchloremic Acidosis in Patients Undergoing Gynecologic Surgery.[40]	Scheingraber et al.	1999	30ml/kg/hr	Randomised trial: 24 women received saline or ringer's lactate (RL). Comparison between 0 and 120 mins	Calculated using Henderson—Hasselbach. In saline group change from 23.5 mM +/- 2.2 to 18.4 +/- 2. In RL group 23.3 +/- 2.0 to 23.0 +/- 1.1	Mean change of -6.3 mM in saline group. 'No major change' in RL group.	Change from a mean of 104 to-115 mM in saline group and a mean of 104 – 106 mM in RL group.
A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement.[41]	McFarlane et al.	1994	15ml/kg/hr during surgery	Randomised trial of 30 patients undergoing major surgery.	Difference between mean pre and post op values in saline group: -4 mmol/L +/- 2.0; Plasmalyte group -0.7 +/- 1.0 ($p<0.01$)	Difference between mean pre and post op values in saline group: -5 +/- 2.1; Plasmalyte group -1.2 +/- 1.1 ($p<0.01$)	Difference between mean pre and post op values in saline group: 6.9 mmol/L +/- 2.03; Plasmalyte group 0.6 +/- 1.2 ($p<0.01$)

RCT, Randomised controlled trial; RL, Ringer's lactate; op, operative. Blank cells indicate that the parameter was not assessed.

Web extra Table 9. Cox proportional hazard regression models for time of death.

Covariate	Coefficient	p
Model using values at baseline with composite physiological scores		
Bolus – literature derived estimates	0·50	0·011
Neurological score	0·015	<0·0001
Respiratory score	0·0019	0·075
Base excess	-0·024	0·34
Bicarbonate	-0·097	0·0065
Chloride	0·019	0·095
Haemoglobin	-0·015	0·62
Cardiovascular score	0·00093	0·77
Model using values at 1 hour with composite physiological scores (covariate sets 1 & 2)		
Bolus – data derived estimates	0·17	0·42
Bolus – literature derived estimates	-0·37	0·15
Neurological score	0·026	<0·0001
Respiratory score	0·0082	<0·0001
Base excess	-0·029	0·25
Bicarbonate	-0·067	0·068
Chloride	0·016	0·25
Haemoglobin	0·020	0·50
Cardiovascular score	-0·00086	0·79
Model using values at 1 hour with component physiological variables (covariate sets 3 & 4)		
Bolus – data derived estimates	0·22	0·30
Bolus – literature derived estimates	-0·33	0·20
Heart rate - down	0·039	<0·0001
Base excess	-0·027	0·28
AVPU	0·75	<0·0001
O_2 saturation	-0·041	<0·0001
SBP - up	0·021	<0·0001
Bicarbonate	-0·066	0·066
SBP - down	0·026	0·092
Chloride	0·018	0·18
Respiratory rate - up	0·0066	0·25
Haemoglobin	0·034	0·27
Heart rate - up	-0·0025	0·59
Capillary refill time	0·019	0·88

Cox-proportional hazards regression coefficients and p-values for association with time of death in a multivariate model with all listed covariates included. Coefficients and p-values for all covariates in sets1 and 2, except bolus, are identical. Similarly for covariate sets 3 and 4.

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Annex II

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Mortality after Fluid Bolus in African Children with Severe Infection

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ABSTRACT

BACKGROUND

The role of fluid resuscitation in the treatment of children with shock and life-threatening infections who live in resource-limited settings is not established.

METHODS

We randomly assigned children with severe febrile illness and impaired perfusion to receive boluses of 20 to 40 ml of 5% albumin solution (albumin-bolus group) or 0.9% saline solution (saline-bolus group) per kilogram of body weight or no bolus (control group) at the time of admission to a hospital in Uganda, Kenya, or Tanzania (stratum A); children with severe hypotension were randomly assigned to one of the bolus groups only (stratum B). All children received appropriate antimicrobial treatment, intravenous maintenance fluids, and supportive care, according to guidelines. Children with malnutrition or gastroenteritis were excluded. The primary end point was 48-hour mortality; secondary end points included pulmonary edema, increased intracranial pressure, and mortality or neurologic sequelae at 4 weeks.

RESULTS

The data and safety monitoring committee recommended halting recruitment after 3141 of the projected 3600 children in stratum A were enrolled. Malaria status (57% overall) and clinical severity were similar across groups. The 48-hour mortality was 10.6% (111 of 1050 children), 10.5% (110 of 1047 children), and 7.3% (76 of 1044 children) in the albumin-bolus, saline-bolus, and control groups, respectively (relative risk for saline bolus vs. control, 1.44; 95% confidence interval [CI], 1.09 to 1.90; P=0.01; relative risk for albumin bolus vs. saline bolus, 1.01; 95% CI, 0.78 to 1.29; P=0.96; and relative risk for any bolus vs. control, 1.45; 95% CI, 1.13 to 1.86; P=0.003). The 4-week mortality was 12.2%, 12.0%, and 8.7% in the three groups, respectively (P=0.004 for the comparison of bolus with control). Neurologic sequelae occurred in 2.2%, 1.9%, and 2.0% of the children in the respective groups (P=0.92), and pulmonary edema or increased intracranial pressure occurred in 2.6%, 2.2%, and 1.7% (P=0.17), respectively. In stratum B, 69% of the children (9 of 13) in the albumin-bolus group and 56% (9 of 16) in the saline-bolus group died (P=0.45). The results were consistent across centers and across subgroups according to the severity of shock and status with respect to malaria, coma, sepsis, acidosis, and severe anemia.

CONCLUSIONS

Fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion in these resource-limited settings in Africa. (Funded by the Medical Research Council, United Kingdom; FEAST Current Controlled Trials number, ISRCTN69856593.)

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Rapid, early fluid resuscitation in patients with shock, a therapy that is aimed at the correction of hemodynamic abnormalities, is one component of goal-driven emergency care guidelines. This approach is widely endorsed by pediatric life-support training programs, which recommend the administration of up to 60 ml of isotonic fluid per kilogram of body weight within 15 minutes after the diagnosis of shock.[1] Children who do not have an adequate response to fluid resuscitation require intensive care for inotropic and ventilatory support.[1] Substantial improvements in the outcomes of pediatric septic shock have been attributed to this approach.[2,3] Nevertheless, evidence regarding the criteria for intervention and the volume and type of fluid is lacking.[4,5]

In hospitals with poor resources in sub-Saharan Africa, in which intensive care facilities are rarely available, child-survival programs have largely ignored the role of triage and emergency care,[6] despite evidence of their cost-effectiveness.[7,8] Malaria, sepsis, and other infectious conditions cause major health burdens for children in sub-Saharan Africa[9,10] and are associated with high early mortality.[11] Hypovolemic shock (a term incorporating all degrees of impaired perfusion) is common and increases mortality substantially.[12-15] However, World Health Organization guidelines[16] recommend reserving the practice of fluid resuscitation for children with advanced shock (characterized by a delayed capillary refill time of more than 3 seconds, weak and fast pulse, and cold extremities); consequently, it is not widely practiced. Most children in hospitals in sub-Saharan Africa receive no specific fluid management apart from blood transfusion for severe anemia[17] or maintenance fluids.

The Fluid Expansion as Supportive Therapy (FEAST) study was designed to investigate the practice of early resuscitation with a saline bolus as compared with no bolus (control) and with an albumin bolus as compared with a saline bolus.

METHODS

DESIGN AND TREATMENT PROTOCOL

We conducted this two-stratum, multicenter, open, randomized, controlled study in six clinical centers in Kenya (one center), Tanzania (one center), and Uganda (four centers). In stratum A, we enrolled children without severe hypotension; children with severe hypotension (systolic blood pressure of <50 mm Hg in children younger than 12 months of age, <60 mm Hg in children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of age) were enrolled in stratum B. In stratum A, eligible children were randomly assigned, in a 1:1:1 ratio, to rapid volume expansion over the course of 1 hour with 20 ml of intravenous 0.9% saline solution per kilogram (saline-bolus group), 20 ml of 5% human-albumin solution per kilogram (albumin-bolus group), or no bolus (control group). Children in stratum B were randomly assigned to receive 40 ml of albumin bolus or saline bolus per kilogram. In both strata, the saline-bolus and albumin-bolus groups, but not the control group, received an additional 20 ml of bolus solution per kilogram at 1 hour if impaired perfusion (see below) persisted. If severe hypotension developed, the child was treated with 40-ml boluses of study fluid per kilogram (saline in the case of the control group); no crossover between bolus groups was permitted. Bolus volumes and rates were conservative relative to U.S. and European guidelines[1] because we were concerned about the potential risk of pulmonary edema developing in children who were being treated in settings that lacked intensive care facilities. The initial boluses were increased to 40 ml per kilogram (60 ml per kilogram in stratum B) after a protocol amendment in June 2010. The study protocol and a detailed description of study methods are available with the full text of this article at NEJM.org.

STUDY OVERSIGHT

The ethics committees at Imperial College, London, Makerere University, Uganda, Medical Research Institute, Kenya, and National Medical Research Institute, Tanzania, approved the protocol. In cases in which prior written consent from parents or guardians could not be obtained, provision was made for oral assent from a legal surrogate, followed by delayed written informed consent as soon as practicable.

An independent data and safety monitoring committee reviewed the interim analyses from the study twice a year. The Haybittle–Peto criterion[18] was the statistical guide that the committee used in considering a recommendation to stop or modify the trial. At the fifth interim review

of data on January 12, 2011, with data available from 2995 children, the independent data and safety monitoring committee recommended stopping enrollment owing to safety concerns in the saline-bolus and albumin-bolus groups and because it was very unlikely that superiority of the bolus strategy over the control strategy would be shown.

ROLE OF THE FUNDING SOURCES

The study was funded by the Medical Research Council, United Kingdom; Baxter Healthcare donated the 5% albumin and 0.9% saline solutions. Neither of those bodies, nor Imperial College, London, which held the legal responsibility for the trial, had any role in the design of the study, the collection, analysis, or interpretation of the data, or the writing of the manuscript. The corresponding author had full access to all trial data and assumes final responsibility for the decision to submit the manuscript for publication.

STUDY POPULATION

Children were eligible for inclusion in the study if they were between 60 days and 12 years of age and presented with a severe febrile illness complicated by impaired consciousness (prostration or coma), respiratory distress (increased work of breathing), or both, and with impaired perfusion, as evidenced by one or more of the following: a capillary refill time of 3 or more seconds, lower-limb temperature gradient,[19] weak radial-pulse volume, or severe tachycardia (>180 beats per minute in children younger than 12 months of age, >160 beats per minute in children 1 to 5 years of age, or >140 beats per minute in children older than 5 years of age) (Fig. 1). Exclusion criteria were severe malnutrition, gastroenteritis, noninfectious causes of shock (e.g., trauma, surgery, or burns), and conditions for which volume expansion is contraindicated.

END POINTS

The primary end point was mortality at 48 hours after randomization. Secondary end points were mortality at 4 weeks, neurologic sequelae at 4 and 24 weeks, episodes of hypotensive shock within 48 hours after randomization, and adverse events potentially related to fluid resuscitation (pulmonary edema, increased intracranial pressure, and severe allergic reaction). An end-point review committee, whose members were unaware of the treatment assignments, reviewed all deaths, neurologic sequelae, and adverse events.

RANDOMIZATION

Randomization was performed in permuted blocks of random sizes and was stratified according to clinical center. The trial statistician at the Medical Research Council Clinical Trials Unit, London, generated and kept all the randomization schedules. The schedule for each center contained a list of trial numbers and the randomly assigned intervention. Trial numbers were kept inside opaque, sealed envelopes, which were numbered consecutively and opened in numerical order by a study clinician.

STUDY PROCEDURES

Children were treated on general pediatric wards; assisted ventilation other than short-term bag-and-mask support was unavailable. Training in triage and emergency pediatric life support was given to participating providers throughout the trial to optimize case recognition, supportive management, and adherence to the protocol. Basic infrastructural support was provided for emergency care and for the monitoring of patients' oxygen saturation and blood pressure, which was measured with the use of an automated blood-pressure monitor. Children received intravenous maintenance fluids (2.5 to 4.0 ml per kilogram per hour); antibiotics; antimalarial, antipyretic, and anticonvulsant drugs; treatment for hypoglycemia (if the blood glucose was <2.5 mmol per liter [45 mg per deciliter]); and transfusion with 20 ml of whole blood per kilogram over the course of 4 hours if the hemoglobin level was less than 5 g per deciliter, according to national guidelines.

A structured clinical case-report form was completed at admission and at 1, 4, 8, 24, and 48 hours. Hypovolemia, neurologic and cardiorespiratory status, and adverse events — particularly suspected pulmonary edema, increased intracranial pressure, and allergic reaction — were recorded. Adverse events were reported to the Clinical Trials Facility in Kilifi, Kenya, within 2 days and were verified against source documents by visiting monitors. At 4 weeks, assessments of neurologic sequelae were performed, and these were reviewed by an independent clinician, who was unaware of the treatment as-

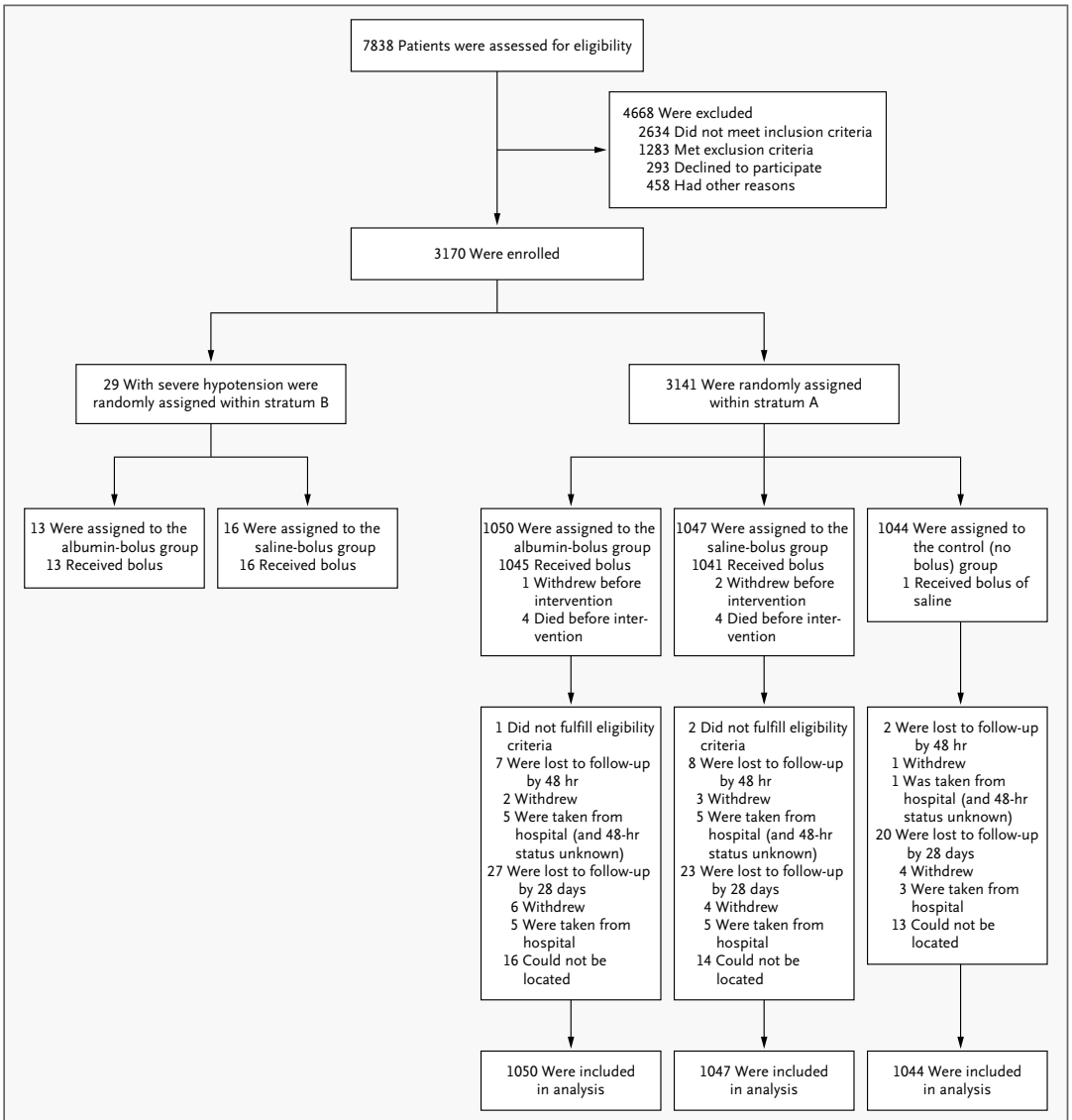

Figure 1. Screening, Randomization, and Follow-up.

Of the 4668 children excluded after initial assessment for eligibility, 2634 with severe illness did not meet the inclusion criteria because they did not have at least one of the following: impaired perfusion, impaired consciousness, fever, or respiratory distress. A total of 1283 children met exclusion criteria because they had evidence of severe acute malnutrition, defined as visible severe wasting or kwashiorkor (254 children); gastroenteritis (792); chronic renal failure, pulmonary edema, or other conditions in which volume expansion is contraindicated (90); or noninfectious causes of severe illness (68); or because they had already received isotonic volume resuscitation (79). In addition, 458 children were not enrolled in the trial because they were unable to return for follow-up assessments (111 children), were enrolled in a different study (65), had been previously enrolled in the FEAST trial (17), or died before enrollment (11); because no fluid or blood or trial packs were available (47); or because of other reasons (181). The reason for noneligibility was missing in the case of 26 children. During the intervention period, among children in stratum A, 1 child in the albumin-bolus group did not fulfill the eligibility criteria because the child had no fever or history of fever, and 2 children in the saline-bolus group did not fulfill the eligibility criteria, one because the child had severe hypotension and the other because the child did not have impaired perfusion.

signments. Children with neurologic sequelae at 4 weeks were reassessed at 24 weeks.

STATISTICAL ANALYSIS

The protocol specified two primary comparisons (saline bolus vs. control, and albumin bolus vs. saline bolus) with respect to the risk of death from any cause by 48 hours. In stratum A, the initial sample size of 2800 assumed a risk of death of 15% in the control group[12]; however, through a protocol amendment in June 2010, the sample size was increased to 3600 because the risk of death in the combined groups was lower than anticipated. We estimated that with a sample size of 3600 children, the study would have 80% power to detect a 33% relative reduction in mortality with a saline bolus as compared with the control group and a 40% reduction with an albumin bolus as compared with a saline bolus, assuming a risk of death of 11% in the control group, at a two-sided alpha level of 0.05, adjusted for two comparisons with the use of a nominal alpha of 0.025.

All the analyses were performed according to the intention-to-treat principle, and all the statistical tests were two-sided. The three treatment groups were compared with respect to the primary end point (48-hour mortality) with the use of the chi-square test, and the relative difference among the groups was estimated by a calculation of the relative risk (the ratio of the proportion of children who died by 48 hours), adjusted for stratification according to clinical center and randomization date (before or after the protocol amendment) with the use of a Mantel–Haenszel type of adjustment.[20] Kaplan–Meier plots show the time to death according to treatment group during the first 48 hours. The few children whose vital status was unknown (because of withdrawal of consent or loss to follow-up) were assumed to be alive at the end of the study. The same methods were used for the prespecified secondary comparisons, including pairwise comparisons of the risk of death or neurologic sequelae by 4 weeks and comparisons of bolus therapy (combined albumin bolus and saline bolus) with control (no bolus) with respect to the risk of death at 48 hours and the risk of neurologic sequelae or death by 4 weeks. Comparisons among the three groups with respect to the primary end point were also summarized for predefined subgroups according to coma status, positive or negative status for malaria, presence or absence of severe anemia (hemoglobin level <5 g per deciliter vs. ≥5 g per deciliter), age, sex, base deficit (≥8 mmol per liter vs. <8 mmol per liter), lactate level (≥5 mmol per liter vs. <5 mmol per liter), and date of randomization (before or after the protocol amendment).

RESULTS

STUDY PATIENTS

In stratum A, 3141 children were randomly assigned from January 13, 2009, through January 13, 2011 — 1050 to the albumin-bolus group, 1047 to the saline-bolus group, and 1044 to the control group. Three children who did not meet the eligibility criteria were included in all the analyses (Fig. 1). The baseline characteristics of the children were similar across the groups (Table 1). The median age was 24 months (interquartile range, 13 to 38); 62% had prostration, 15% were comatose, and 83% had respiratory distress. The majority of children (52%) had more than one feature of impaired perfusion, most commonly severe tachycardia and cold extremities. Moderate-to-severe acidosis was present in 51% of the children (1070 of 2079) and severe lactic acidosis (lactate ≥5 mmol per liter) in 39% (1159 of 2981). The mean (±SD) hemoglobin level was 7.1±3.2 g per deciliter, and the glucose was 6.9±3.9 mmol per liter (124±70 mg per deciliter). Malaria was confirmed in 57% of the children (1793 of 3123), and 4% (106 of 2483) were positive for human immunodeficiency virus infection. Only 17 children (0.5%) were lost to follow-up for the primary end point — 7 in the albumin-bolus group, 8 in the saline-bolus group, and 2 in the control group. Vital status at 4 weeks was ascertained in 97% (1023 of 1050), 98% (1024 of 1047), and 98% (1024 of 1044) of the children in the three groups, respectively. A total of 29 children were enrolled in stratum B. The median systolic blood pressure was 57 mm Hg (interquartile range, 51 to 59) (Table 1 in the Supplementary Appendix, available at NEJM.org); no children in stratum B were lost to follow-up. In both strata, working diagnoses were reported by a clinician at 48 hours (Table 2 in the Supplementary Appendix).

ADMINISTERED FLUIDS

A total of 99.5% of the children in the albumin-bolus group (1045 of 1050 children) and 99.4% of the children in the saline-bolus group (1041 of 1047) received the treatment to which they had been randomly assigned (Fig. 1). One child in the

control group received a saline bolus in the first hour (owing to hypotension). The median volumes of all fluids (including blood) received during the first and second hours were 20.0 ml per kilogram (interquartile range, 20.0 to 20.0) and 4.5 ml per kilogram (interquartile range, 1.7 to 16.2), respectively, in the albumin-bolus group; 20.0 ml per kilogram (interquartile range, 20.0 to 20.0) and 5.0 ml per kilogram (interquartile range, 1.7 to 16.0), respectively, in the saline-bolus group; and 1.2 ml per kilogram (interquartile range, 0 to 2.5) and 2.9 ml per kilogram (interquartile range, 0.2 to 4.2), respectively, in the control group. Over the course of 8 hours, the median cumulative volume of fluid received was 40.0 ml per kilogram (interquartile range, 30.0 to 50.0) in the albumin-bolus group, 40.0 ml per kilogram (interquartile range, 30.4 to 50.0) in the saline-bolus group, and 10.1 ml per kilogram (interquartile range, 10.0 to 25.9) in the control group. A total of 1408 children received blood transfusions — 472 (45%) in the albumin-bolus

Table 1. Baseline Characteristics of the Children.*

Variable	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Total (N=3141)
Demographic and anthropometric characteristics				
Age — mo				
Median	23	23	25	24
Interquartile range	14–37	13–37	14–40	13–38
Female sex — no. (%)	474 (45)	480 (46)	498 (48)	1452 (46)
Mid-upper-arm circumference ≤11.5 cm — no./total no. (%)	21/982 (2)	24/974 (2)	25/1003 (2)	70/2959 (2)
Findings at presentation				
Axillary temperature >39°C — no. (%)	243 (23)	236 (23)	264 (25)	743 (24)
Hypothermia (temperature <36°C) — no. (%)	59 (6)	64 (6)	66 (6)	189 (6)
Respiratory distress — no./total no. (%)	874/1048 (83)	854/1045 (82)	857/1037 (83)	2585/3130 (83)
Respiratory rate — breaths/min	58±15	58±15	57±15	58±15
Oxygen saturation <90% — no. (%)†	249/1015 (25)	253/1008 (25)	257/1015 (25)	759/3038 (25)
Bradycardia (<80 beats/min) — no. (%)	13 (1)	7 (1)	10 (1)	30 (1)
Severe tachycardia — no. (%)	736 (70)	721 (69)	738 (71)	2195 (70)
Weak radial pulse — no. (%)	210 (20)	238 (23)	206 (20)	654 (21)
Capillary refill time — no. (%)				
≥2 sec	712 (68)	720 (69)	673 (64)	2105 (67)
≥3 sec	263 (25)	299 (29)	257 (25)	819 (26)
Positive temperature gradient — no. (%)‡	620 (59)	629 (60)	610 (58)	1859 (59)
Systolic blood pressure — mm Hg				
Median	92	93	92	93
Interquartile range	85–101	85–101	86–101	85–101
Moderate hypotension — no./total no. (%)§	66/1030 (6)	69/1036 (7)	57/1034 (6)	192/3100 (6)
Dehydration — no. (%)¶	78 (7)	95 (9)	58 (6)	231 (7)
Severe pallor manifested in lips, gums, or inner eyelids — no. (%)	523 (50)	546 (52)	520 (50)	1589 (51)
Prostration — no./total no. (%)‖	655/1048 (62)	667/1046 (64)	619/1044 (59)	1941/3138 (62)
Coma — no. (%)**	156 (15)	161 (15)	140 (13)	457 (15)
Convulsions during this illness — no./total no. (%)	414/1047 (40)	387/1045 (37)	371/1039 (36)	1172/3131 (37)
Hemoglobinuria (dark urine) — no. (%)	122 (12)	123 (12)	144 (14)	389 (12)
Jaundice visible to clinician — no. (%)	336 (32)	336 (32)	330 (32)	1002 (32)

Table 1. (Continued.)

Variable	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Total (N=3141)
Laboratory assessments††				
Positive for malaria parasitemia — no./total no. (%)‡‡	590/1044 (57)	612/1042 (59)	591/1037 (57)	1793/3123 (57)
Hemoglobin — no./total no. (%)				
<5 g/dl	323/1024 (32)	332/1015 (33)	332/1015 (33)	987/3054 (32)
>10 g/dl	231/1024 (23)	230/1015 (23)	244/1015 (24)	705/3054 (23)
Glucose — no./total no. (%)				
<2.5 mmol/liter (45 mg/dl)	43/990 (4)	46/991 (5)	42/989 (4)	131/2970 (4)
<3.0 mmol/liter (54 mg/dl)	67/990 (7)	61/991 (6)	59/989 (6)	187/2970 (6)
Lactate ≥5 mmol/liter — no./total no. (%)	357/1000 (36)	407/989 (41)	395/992 (40)	1159/2981(39)
Base deficit ≥8 mmol/liter — no./total no. (%)	380/710 (54)	360/689 (52)	330/680 (49)	1070/2079 (51)
Severe acidemia (pH <7.2) — no./total no. (%)	71/712 (10)	73/694 (11)	65/685 (9)	209/2091 (10)
Hyperkalemia (potassium >6.5 mmol/liter) — no./total no. (%)	67/686 (10)	68/687 (10)	65/670 (10)	200/2043 (10)
Positive for HIV antibody — no./total no. (%)	37/817 (5)	28/827 (3)	41/839 (5)	106/2483 (4)
Positive blood culture — no. of positive cultures/total no. of cultures (%)	38/347 (11)	52/360 (14)	36/363 (10)	126/1070 (12)
Positive cerebrospinal fluid culture — no. of positive cultures/total no. of cultures (%)	2/94 (2)	4/102 (4)	4/96 (4)	10/292 (3)

* Plus–minus values are mean ±SD. HIV denotes human immunodeficiency virus.
† Oxygen saturation and pulse rate were recorded by a pulse oximeter.
‡ The temperature gradient was assessed by running the back of hand from the toe to the knee; a positive temperature gradient was defined as a notable temperature change from cold (dorsum of foot) to warm (knee).
§ Moderate hypotension was defined as a systolic blood pressure of 50 to 75 mm Hg in children younger than 12 months of age, 60 to 75 mm Hg in children 12 months to 5 years of age, and 70 to 85 mm Hg in children older than 5 years of age, as measured with the use of an automated blood-pressure monitor.
¶ Dehydration was identified by the presence of sunken eyes or decreased skin turgor.
‖ Prostration was defined as the inability of a child older than 8 months of age to sit upright or the inability of a child 8 months of age or younger to breast-feed.
** Coma was defined as the inability to localize a painful stimulus.
†† Venous blood samples were obtained at admission for immediate analyses of pH level and potassium level with the use of a handheld blood analyzer (i-STAT, Abbott Laboratories); measurement of hemoglobin (HemoCue), blood glucose, and lactate levels; and HIV antibody testing. Denominators vary because data for some children were not available. Blood smears to test for malaria parasites were prepared for immediate reading and subsequent quality control. Blood cultures at admission were obtained at certain centers only.
‡‡ The parasite that was identified was *Plasmodium falciparum* in every case except four: three in which *P. vivax* was identified and one in which *P. ovale* was identified.

group, 487 (47%) in the saline-bolus group, and 449 (43%) in the control group. Transfusion was initiated marginally earlier in the control group, but by 2 hours the proportion of children who received transfusions and the volumes of blood received were similar across all groups (Fig. 1 and Table 3 in the Supplementary Appendix).

END POINTS

By 48 hours, 111 of the children in the albumin-bolus group (10.6%), 110 children in the saline-bolus group (10.5%), and 76 children in the control group (7.3%) had died. The relative risk of death with a saline bolus versus no bolus was 1.44 (95% confidence interval [CI], 1.09 to 1.90; P=0.01); the relative risk of death with an albumin bolus versus a saline bolus was 1.00 (95% CI, 0.78 to 1.29; P=0.96); and the relative risk of death with bolus therapy (combined albumin bolus and saline bolus) versus no bolus was 1.45 (95% CI, 1.13 to 1.86; P=0.003) (Table 2); the absolute difference in risk was 3.3 percentage points (95% CI, 1.2 to 5.3). There was no evidence of heterogeneity according to center (Fig. 2 in the Supplementary Appendix) or date of randomization before or after the protocol amendment (Fig. 2). In stratum B, 9 of 13 children in the albumin-bolus group (69%) and 9 of 16 in the saline-bolus group (56%) died (relative risk with albumin bolus, 1.23; 95% CI, 0.70 to 2.16; P=0.45).

Table 2. Death and Other Adverse Event End Points at 48 Hours and 4 Weeks.

End Point	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Saline Bolus vs. No Bolus		Albumin Bolus vs. No Bolus		Albumin Bolus vs. Saline Bolus		Albumin and Saline Boluses vs. No Bolus	
				Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
		no. (%)									
48 Hours											
Death — no. (%)	111 (10.6)	110 (10.5)	76 (7.3)	1.44 (1.09–1.90)	0.01	1.45 (1.10–1.92)	0.008	1.00 (0.78–1.29)	0.96	1.45 (1.13–1.86)	0.003
Pulmonary edema — no. (%)	14 (1.3)	6 (0.6)	6 (0.6)								
Increased intracranial pressure — no. (%)	16 (1.5)	18 (1.7)	11 (1.1)								
Severe hypotension — no. (%)*	1 (0.1)	2 (0.2)	3 (0.3)								
Allergic reaction — no. (%)	3 (0.3)	4 (0.4)	2 (0.2)								
Pulmonary edema, increased intracranial pressure, or both — no. (%)†	27 (2.6)	23 (2.2)	17 (1.6)	1.34 (0.72–2.51)	0.34	1.57 (0.87–2.88)	0.10	1.17 (0.68–2.03)	0.49	1.46 (0.85–2.53)	0.17
4 Weeks											
Death — no. (%)	128 (12.2)	126 (12.0)	91 (8.7)	1.38 (1.07–1.78)	0.01	1.40 (1.08–1.80)	0.01	1.01 (0.80–1.28)	0.91	1.39 (1.11–1.74)	0.004
Neurologic sequelae — no./total no. (%)‡	22/990 (2.2)	19/996 (1.9)	20/997 (2.0)	0.95 (0.51–1.77)	0.87	1.10 (0.61–2.01)	0.74	1.16 (0.63–2.14)	0.62	1.03 (0.61–1.75)	0.92
Neurologic sequelae or death — no./total no. (%)‡	150/990 (15.2)	145/996 (14.6)	111/997 (11.1)	1.31 (1.04–1.65)	0.02	1.36 (1.08–1.71)	0.008	1.04 (0.84–1.28)	0.71	1.33 (1.09–1.64)	0.005

* Severe hypotension was defined as a systolic blood pressure of less than 50 mm Hg in children younger than 12 months of age, less than 60 mm Hg in children 1 to 5 years of age, and less than 70 mm Hg in children older than 5 years of age, plus one or more features of impaired perfusion.
† Four children — three in the albumin-bolus group and one in the saline-bolus group — had both increased intracranial pressure and pulmonary edema.
‡ A total of 60 children in the albumin-bolus group, 51 in the saline-bolus group, and 47 in the control group did not have a neurologic assessment at 4 weeks.

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The risk of death 1 hour after randomization was similar in the three groups (1.2% in the albumin-bolus group, 1.1% in the saline-bolus group, and 1.3% in the control group). Beyond 1 hour, there was a persistent trend to higher mortality in the bolus groups as compared with the control group (Fig. 2A). Most deaths occurred before 24 hours (259 deaths, 87%). Only a small number of deaths occurred after 48 hours, and there was no evidence that children in the control group had excess delayed mortality (Fig. 2B). The excess mortality associated with the bolus groups as compared with the control group was consistent across all prespecified subgroups (Fig. 3), and there was no evidence supporting a benefit from bolus fluid infusion in any subgroup. At 4 weeks, neurologic sequelae were noted in 22 children (2.2%) in the albumin-bolus group, 19 (1.9%) in the saline-bolus group, and 20 (2.0%) in the control group ($P=0.92$ for bolus vs. control) (Table 2). The 24-week follow-up assessment is ongoing.

Suspected pulmonary edema occurred in 26 children (14 in the albumin-bolus group, 6 in the saline-bolus group, and 6 in the control group) and increased intracranial pressure in 45 children (16 in the albumin-bolus group, 18 in the saline-bolus group, and 11 in the control group) ($P=0.17$ for the comparison of bolus with control with respect to combined pulmonary edema and increased intracranial pressure) (Table 2). Details of the review of deaths and targeted adverse events by the end-point review committee are provided in Tables 4A and 4B in the Supplementary Appendix.

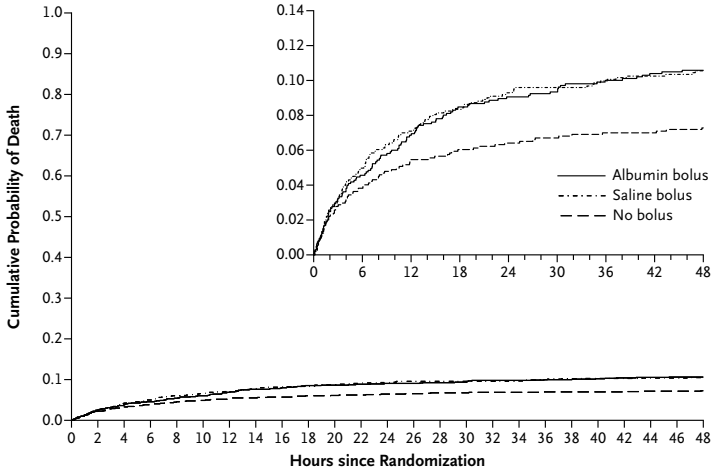
DISCUSSION

We evaluated the effect of resuscitation with bolus fluids in children who presented to the hospital with severe febrile illness and impaired perfusion, in order to generate practical data for resource-poor settings in sub-Saharan Africa in which malaria is endemic. Bolus-fluid resuscitation with either albumin or saline, as compared with control, increased the absolute risk of death at 48 hours by 3.3 percentage points and the risk of death, neurologic sequelae, or both at 4 weeks by nearly 4 percentage points. There was no evidence of a difference in either primary or secondary end points between the albumin-bolus and saline-bolus groups. Most deaths (87%) occurred before 24 hours; however, the predicted severe adverse effects of fluid overload (pulmonary edema or increased intracranial pressure) developed in few children. Our findings appear to be robust owing to the large number of children enrolled, the multinational nature of the sample, the small loss to follow-up, the concealment of treatment assignments, and the high rate of adherence to the assigned treatment. The results do not support the routine use of bolus resuscitation in severely ill febrile children with impaired perfusion in African hospitals and also raise questions about its use in other settings.

Our large, controlled trial of fluid resuscitation applied an international standard of practice (bolus-fluid resuscitation) and compared it with the local standard of care (no bolus-fluid resuscitation). It was conducted in typical African hospitals, which have no intensive care facilities. The inclusion criteria were broad, but children with gastroenteritis, severe malnutrition, or noninfectious causes of shock were excluded, so results cannot be extrapolated to those groups. Few children were recruited to stratum B, which was reserved for children with severe hypotension, in whom randomization to a control group was considered to be unethical, and mortality was high in both bolus groups in that stratum.

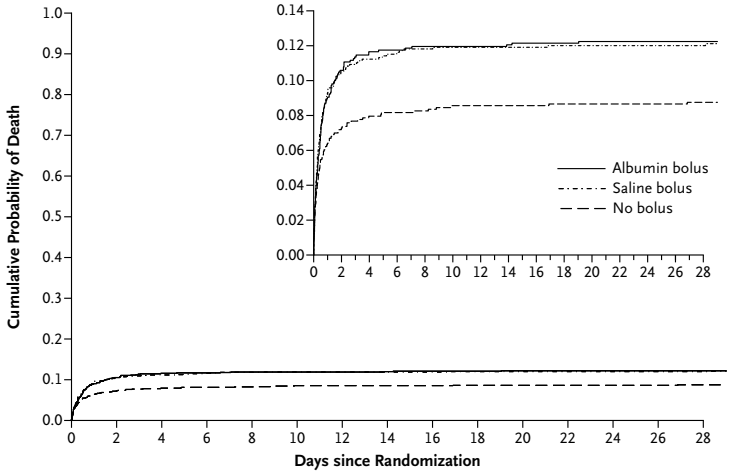
Clinical differentiation of major causes of severe illness in sub-Saharan Africa — in particular, severe malaria, sepsis, pneumonia, and meningitis — is not possible at the time of admission to the hospital.[21,22] However, recommendations regarding fluid resuscitation differ substantially among these conditions,[16] and the practice of fluid resuscitation remains highly controversial in children with severe malaria.[23-25] By including in our study children with these critical illnesses, our trial offered an efficient means of providing practical information for hospitals that have few diagnostic facilities. Mortality was lower than expected and than previously reported.[12,14,22] Consistent with other studies,[22,26] mortality was lower in children with severe malaria than in the subgroup without malaria, but there was no evidence that the increase in 48-hour mortality associated with boluses differed between the two subgroups. Although fluid boluses adversely affected the outcome, important survival gains, across all the groups, may have resulted from training and implementation of triage, basic life-support measures, and regular observation.

A Mortality at 48 Hours



	Hr 1			Hr 2			Hr 3			Hr 4			Hr 5–8			Hr 9–24			Hr 24–48		
	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus
No. at Risk	1050	1047	1044	1037	1033	1030	1024	1018	1021	1016	1010	1015	1010	1001	1011	992	980	996	954	945	975
Died	13	12	14	13	15	9	8	7	6	6	9	4	17	20	14	38	34	20	16	13	9
%	1.2	1.1	1.3	1.3	1.5	0.9	0.8	0.7	0.6	0.6	0.9	0.4	1.7	2.0	1.4	3.8	3.5	2.0	1.7	1.4	0.9

B Mortality at 4 Weeks



	Day 1			Day 2			Day 3–7			Day 8–14			Day 15–21			Day 21–28		
	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus
No. at Risk	1050	1047	1044	954	945	975	914	917	947	901	909	940	899	902	933	897	901	934
Died	95	97	67	16	13	9	11	7	7	2	6	2	2	1	4	2	1	1
%	9.0	9.3	6.4	1.7	1.4	0.9	1.2	0.8	0.7	0.2	0.7	0.2	0.2	0.1	0.4	0.2	0.1	0.2

Figure 2. Kaplan–Meier Curves for Mortality.
Kaplan–Meier curves show the rate of death in the three study groups over the course of 48 hours from randomization (Panel A) and over the course of 4 weeks from randomization (Panel B).

We could not identify any subgroup in which fluid resuscitation was beneficial; this is remarkable given that many of the baseline characteristics of the children in this study are considered to be important criteria for bolus-fluid therapy, including moderate hypotension and severe metabolic acidosis.[27] All the children received maintenance fluids and the standard of care recommended by national guidelines. The receipt, and the timing of the receipt, of blood, quinine, and antibiotics were similar across groups; only bolus-fluid resuscitation differed between the intervention and control groups. The apparent lack of effect on early mortality (<1 hour), followed by an increasing negative effect over time, without amelioration of neurologic events, suggests a consistent adverse effect of bolus resuscitation with both saline and albumin. It has been thought that albumin has physiological benefits over saline, a hypothesis that was supported by the results of small trials involving children with severe malaria[28-30] and a recent analysis of the sepsis subgroup[31,32] of the adult Saline versus Albumin Fluid Evaluation trial (SAFE; Current Controlled Trials number, ISRCTN76588266). However, we observed no detectable differences between the bolus groups, providing evidence against a beneficial effect of albumin over saline. The excess mortality with fluid resuscitation was consistent across all subgroups, irrespective of physiological derangement or underlying microbial pathogen, also raising fundamental questions about our understanding of the pathophysiology of critical illness.

We had predicted that complications of fluid

Subgroup	Bolus	No Bolus	Relative Risk (95% CI)
	no. of events/total no.		
Malaria			
Positive	110/1202	34/591	1.59 (1.10–2.31)
Negative	108/884	38/446	1.43 (1.01–2.04)
Subtotal (I^2=0.0%, P=0.69)	218/2086	72/1037	1.51 (1.17–1.95)
Coma			
Yes	78/317	33/140	1.04 (0.73–1.49)
No	143/1777	43/904	1.69 (1.21–2.36)
Subtotal (I^2=74.3%, P=0.05)	221/2094	76/1044	1.40 (1.10–1.79)
Hemoglobin			
<5 g/dl	101/655	30/332	1.71 (1.16–2.51)
≥5 g/dl	114/1384	43/683	1.31 (0.93–1.84)
Subtotal (I^2=2.9%, P=0.31)	215/2039	73/1015	1.47 (1.14–1.90)
Base deficit			
≥8 mmol/liter	128/740	34/330	1.68 (1.18–2.39)
<8 mmol/liter	20/659	10/350	1.06 (0.50–2.24)
Subtotal (I^2=14.8%, P=0.28)	148/1399	44/680	1.54 (1.12–2.13)
Lactate			
≥5 mmol/liter	157/764	59/395	1.38 (1.05–1.81)
<5 mmol/liter	49/1225	11/597	2.17 (1.14–4.14)
Subtotal (I^2=39.2%, P=0.20)	206/1989	70/992	1.50 (1.17–1.93)
Date of randomization			
Before amendment	172/1691	62/844	1.38 (1.05–1.83)
After amendment	49/406	14/200	1.72 (0.98–3.05)
Subtotal (I^2=0.0%, P=0.50)	221/2097	76/1044	1.45 (1.13–1.86)

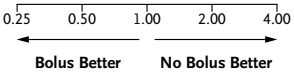


Figure 3. Mortality at 48 hours in Prespecified Subgroups.
The sizes of the boxes are proportional to the Mantel–Haenszel weights. The I^2 statistic indicates the percentage of total variation that was due to heterogeneity.

overload would develop in some children and incorporated mandatory clinical reviews to monitor for pulmonary edema and increased intracranial pressure. All reported adverse events were reviewed by the end-point review committee, whose members were unaware of the treatment assignments; in addition the committee reviewed the records of all deaths for evidence of the presence of pulmonary edema or increased intracranial pressure. Few events were identified by this process, and there was no evidence of differences among the groups; most deaths appeared to be attributable to the severity of the underlying condition. The question therefore arises as to the reasons for the excess mortality among children receiving boluses. Our a priori hypothesis was that the benefit of bolus interventions would be greatest for the group that was at the highest risk, which included the children with the most severe hemodynamic and metabolic derangement. However, although the degree of shock has been shown to be prognostic for an adverse outcome,[12,14] our results suggest that it may not be a surrogate on the causal pathway for the effect of bolus resuscitation on survival. One could speculate that the vasoconstrictor response in shock confers protection by reducing perfusion to nonvital tissues and that rapid reversal with fluid resuscitation is deleterious. Alternatively, the adverse consequences of fluid boluses (even at low volumes) might act through other mechanisms such as reperfusion injury, subclinical effects on pulmonary compliance, myocardial function, or intracranial pressure.[33]

In conclusion, the results of this study challenge the importance of bolus resuscitation as a lifesaving intervention in resource-limited settings for children with shock who do not have hypotension and raise questions regarding fluid-resuscitation guidelines in other settings as well.

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