Fluid therapy for severe malaria

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Abstract

Fluid therapy is an important supportive measure for patients with severe malaria. Patients usually have preserved cardiac index, vascular resistance and blood pressure and a limited degree of hypovolaemia due to dehydration. Cell hypoxia, reduced kidney function and acidosis result from microcirculatory compromise and malarial anaemia reducing tissue oxygenation, not hypovolemia. Hence, aggressive fluid loading does not correct acid-base status, enhance kidney function or improve patient outcomes, and risks complication like pulmonary oedema. Individualised conservative fluid managments is recommended in severe malaria. Physical examination and physiological indices have limited reliability in guiding fluid therapy. Invasive measures may be more accurate but are often unavailable in endemic areas and non-invasive measures such as ultrasound remain relatively unexplored. Research into reliable methods to determine fluid status and response that are applicable in low-rsource settings is a priority. This reviews outlines current knowledge on fluid management in severe malaria and highlights research needed to optimize fluid therapy and hence improve survival in severe malaria.

Key words: fluid resuscitation; *Plasmodium falciparum*; review; severe malaria; supportive therapy

Introduction

Malaria is caused by protozoan parasites in the genus *Plasmodium*. *Plasmodium falciparum* most frequently causes severe malaria that presents with life-threatening end-organ damage and caused an estimated 409.000 malaria deaths worldwide in 2019. This burden is unacceptably high, and key targets of the World Health Organizations' global malaria strategy to reduce disease incidence and death rates have not been met.[1] To reduce mortality, patients should be promptly treated with parenteral artesunate and receive supportive care including adequate fluid management.[2]

Intravenous fluid therapy dates from the early 19th century, when it was described to 'reanimate the dead´ when given to fluid-depleted cholera patients with hypovolemic shock.[3] As recent experience with fluid resuscitation stems largely from the treatment of sepsis and ideas from sepsis research are often applied to studies on fluid management in malaria, fluid therapy in sepsis is summarised here. Fluids became a cornerstone of the supportive treatment in sepsis when Rivers and colleagues published their landmark trial in 2001.[4] It showed how early goal-directed therapy (including fluids) to reach haemodynamic targets increased the survival of sepsis patients. This outcome supported the theory that bolus fluids augment circulatory volume, potentially increasing cardiac output and organ perfusion. Fluid boluses (approx. 30 mL/kg within the first 1-3 hours) are therefore recommended in the international Surviving Sepsis Guidelines, and fluid loading is common practice in haemodynamically unstable patients with sepsis.[5,6] However, the value of fluid therapy in sepsis following strict protocolised resuscitation has been challenged in recent multi-centre trials. Moreover, the optimal method to estimate circulatory volume and cardiac preload to guide fluid resuscitation in sepsis is debated.[7,8,9,10]

The ideal fluid volume administered to a specific patient provides sufficient cardiac preload to optimise cardiac output, without excessively raising intravascular hydrostatic pressure. The

latter would encourage fluids to accumulate in the interstitial space, impairing oxygenation and organ function and potentially increasing mortality risk.[5,7,10,11] Besides preload, cardiac and systemic vascular compliance influence cardiac output (Figure 1). Both are regularly compromised in sepsis, as the peripheral vasodilatation initiated by host immune responses exacerbates hypotension and sepsis-induced cardiac dysfunction may be present.[11,12] A fluid bolus in a patient with uncompromised cardiac function likely increases cardiac output, meaning the patient is 'fluid responsive', while the same treatment in a patient with impaired ventricular function may not improve haemodynamic status.[7]

In low-resource settings, physical examination and physiologic variables (e.g. blood pressure and capillary refill) frequently guide fluid titration. Also, lactate is used as a marker of tissue hypoxia and therefore utilised to guide fluid therapy. Invasive measures applied in intensive care settings include central venous pressure (CVP) measurement as a surrogate for intravascular volume. However, current sepsis research does not support CVP as being consistently reliable in judging intravascular volume. Its use is not recommended in sepsis guidelines. More accurate methods to estimate preload are transpulmonary thermodilution and pulmonary artery occlusion pressure (PAoP), used in sepsis patients to measure total blood volume in cardiac chambers (global end-diastolic volume or GEDVI) and left ventricular end-diastolic pressure, respectively. Non-invasive techniques include echocardiography to compute stroke volume and ultrasound of the inferior vena cava (IVC) diameter and its collapsibility during respiration. These techniques perform better as predictors of patients' response to fluids when measurements are ´dynamic´, meaning they are carried out in real-time during passive leg-raise test or after a first fluid bolus.[5,7,13,14,15,16,17]

Severe malaria has its own distinct pathophysiology that influences intravascular volume, haemodynamic indices and the response of patients to fluid therapy. This review summarises current knowledge on fluid therapy in severe malaria to allow informed decisions when

prescribing fluids. Areas of future research that may advance fluid management in severe malaria are highlighted.

Fluid status of patients with severe malaria

In uncomplicated falciparum malaria, fluid status is hardly a matter of primary concern. In severe malaria understanding the haemodynamic state helps shape the optimal resuscitation strategy.[18] The manifestations of severe malaria differ in adults and children. Children with severe malaria frequently have impaired consciousness, convulsions, severe anaemia, hypoglycaemia and lactic acidosis. Adults more commonly suffer from malaria-associated acute kidney and lung injury.[19,20] These age groups are discussed separately in this article, with most studies performed in southeast Asian adults and African children (Supplement 1).

Adults

Multiple observational studies have measured GEDVI in adults presenting with severe malaria, using transpulmonary thermodilution. They concluded mean GEDVI decreases to 473-650 mL/m^2 (680 to 800mL/m^2 is considered normal) in most patients.[21,22,23,24,25] Consistent with this, Kingston and colleagues found IVC inspiratory diameters to be smaller and IVC collapsibility greater in severe malaria compared to healthy individuals.[26] This decrease in preload is likely due to fluid losses caused by fever, vomiting, diarrhoea and diminished fluid intake with impaired consciousness.[22,24,27] However, cardiac output is usually preserved, or even increased as heart rate increases and stroke volume is maintained despite a reduction in left ventricular filling time.[21,22,26,28] Similarly, systemic vascular resistance was reportedly lower in severe malaria patients compared to healthy controls, but higher compared to septic patients.[29] Macrovascular indices such as mean arterial pressure (MAP), systolic blood pressure (SBP), CVP and PAoP were thus found to be within normal range in most

included patients.[13,21,23,24,26,28] So although preload appears to be moderately decreased, peripheral vascular resistance and cardiac function are largely preserved in severe malaria, enabling the majority of patients to maintain adequate blood pressure.

A drop in blood pressure indicating macro-circulatory shock is seen in a minority of adults with severe malaria. The frequency of this ´algid malaria´ syndrome, varies across included studies. Hypotension (generally defined as SBP < 80) was present on admission in only 2% of Indian and Bangladeshi adults with severe malaria but in 20-25% of patients in India, Vietnam and Senegal.[24,28,30,31,32], with low participant numbers (N~30) in these studies, increasing uncertainty for these estimates. Concomitant bacterial sepsis is suggested as a cause of hypotension in severe malaria, although blood culture results are scarce in resource-poor settings. In imported severe malaria, a meta-analysis found 8% of adults had a community acquired bacterial co-infection, (n = 66; range 0-13%)(Michael Marks et al. 2014). Prevalence rates of any bacterial co-infection, including hospital acquired infections, are reported to be as high as 20% (M. E. Marks et al. 2013)(Bruneel et al. 2003)(Corne et al. 2004)(Bruneel et al. 2010). Rate of concurrent bacteraemia varied from 3% or less (Ishioka et al. 2019)(Michael Marks et al. 2014)(Phu et al. 2020) to >10% (J. Hanson et al. 2021). The quality of microbiological cultures, antibiotic use prior to enrollment and patient-inherent and environmental factors contribute to uncertainties in estimating rates of bacterial co-infetion, highlighting the need for prospective studies (J. Hanson et al. 2021). It should be recognised that bacterial co-infections, including non-invasive nosocomial infections, may need antibiotic treatment but do not necessarily cause a sepsis syndrome requiring fluid therapy. As clinical features of severe malaria and sepsis overlap, more detailed studies to define the contribution of bacteriaemia and sepsis to severe malaria syndromes are needed.

Regarding microvascular function, a study measuring capillary permeability by estimating albumin/creatinine ratios and transcapillary escape of radiolabelled albumin in Thai patients

reported increased capillary permeability in the most severely ill patients, suggesting vascular integrity may be impaired in a subset of severe malaria patients.[38] Finally, while most adult patients have unimpaired myocardial function, two studies observed hypokinesia with reduced left ventricular ejection fraction on echocardiography in a minority (~11%) of cases, possibly contributing to macro-circulatory shock.[32,39]

Children

The results of observational studies in children with severe malaria are consistent with those of adults. Nguah and colleagues describe how GEDVI in Ghanaian children with severe malaria (N = 183) was slightly reduced and echocardiographic cardiac index increased.[40] Yacoub and colleagues also found a higher IVC collapsibility index, indicating hypovolaemia.[41] When total body water was directly measured using stable isotope dilution techniques and results then used to calibrate bioelectrical impedance measurements in Gabonese children with severe malaria, patients were only minimally water-depleted, consistent with mild dehydration.[42,43] Intravascular volume depletion was also not a feature of severe malaria when directly assessed using chromium-53 labelled red blood cells in children with malaria in Gabon.[44]

Most studies reported preserved cardiac function in children with severe malaria.[45,46,47] although Yacoub and colleagues (N = 30) observed mildly decreased myocardial performance, especially in acidotic patients.[41] Myocardial dysfunction in children with severe malaria is also described in case reports and often been attributed to acidosis and hypoglycaemia. It therefore seems an exception rather than a rule.[48] Bacterial co-infection was reportedly low in Kenyan children (1-3%)(K. Maitland et al. 2005 RCT volume)(Kathryn Maitland et al. 2005 pre-trans)(S. O. Akech et al. 2010) A systematic review, including 25 studies across 11 African countries, reported a mean prevalence of invasive bacterial co-

infection in children with severe malaria of 6.4%, with substantial inter-study variability. Of note, in health settings without intensive care, bolus fluid administration is not recommended in children with bacterial infection unless hypotension is present (Weiss 2020).

Based on these findings, adults and children with severe malaria mostly present with mild to moderate hypovolemia and preserved macro-circulatory parameters, because cardiac function and peripheral vascular resistance are generally maintained. A minority of patients presents with hypotension and these symptoms may not be explained by bacterial co-infection alone.

Optimising fluid status in patients with severe malaria

Besides understanding the general haemodynamic status in severe malaria, it is important for clinicians to know what specific signs should trigger fluid resuscitation, how fluid volume should be titrated, and what resuscitation endpoints should be used. This section summarises how macro-circulatory indices change when fluids are administered to patients with severe malaria, how these influence markers of end-organ perfusion, and what adverse effects and patient outcomes can be expected.

Macro-circulatory indices

Physical signs and physiological parameters are often used to guide fluid therapy. The latest WHO malaria treatment guidelines recommend careful evaluation of jugular venous pressure (JVP), peripheral perfusion, skin turgor and urine output to guide fluid management.[2] Other physical signs of hypoperfusion used to determine fluid status and response include BP, heart rate, arterial oxygen saturation, capillary refill, temperature of the extremities and moisture of mucous membranes.

Adults

Hanson and colleagues investigated the use of physical examination to predict volume status and response in adults with severe malaria, using transpulmonary thermodilution indices as comparators. They found JVP and dry mucous membranes had a positive predictive value of <50% for fluid responsiveness. GEDVI was actually higher in patients with decreased tissue turgor, while poor capillary refill correlated with GEDVI but was only present in 7% of patients. Anuria on admission was unrelated to GEDVI. MAP correlated with intravascular volume but was preserved in patients even before resuscitation and did not adequately predict volume responsiveness.[13] The same study reported how tachycardia, one of the indices that might prompt fluid infusion in critically ill patients, failed to predict fluid responsiveness. Tachycardia was also unrelated to IVC diameter in adults with malaria, whilst it was positively correlated with fever.[26]

Children

In children, several studies showed tachycardia was proportional to the fall in haemoglobin level and therefore may be better related to the degree of anaemia rather than hypovolemia.[40,45] Jarvis and colleagues also reported how a large proportion (61%) of children with severe malaria presented with clinical features suggesting dehydration and shock (*e.g.* tachycardia, prolonged refill time), while bioimpedance analysis found no volume depletion, suggesting these clinical signs can be easily misinterpreted.[43] Titrating fluids using physical examination has been undertaken in the multicentre ´FEAST´ trial conducted by Maitland and colleagues. This trial included children with severe febrile illness and physical signs of impaired perfusion (prolonged capillary refill, cold extremities, weak radial pulse volume or severe tachycardia), including a subgroup of children with malaria (N=1790). A significant increase in mortality was observed in the children with malaria receiving bolus

fluids (20-40mL/kg) (RR 1.51 CI 1.17 – 1.95). Critics argued the inclusion criteria of the trial were too broad, with children presenting with only one physical sign of impaired perfusion (*e.g.*, tachycardia) receiving bolus fluids, while the more strict WHO criteria for shock (cold hands, capillary refill > 3 seconds and weak and fast pulse) should have been used (Southall and Samuels 2011). The authors argued excess mortality by bolus fluids was seen in all subgroups of children, independent of the severity of their underlying disease and including those fulfilling the WHO definition of shock (N = 56).(Kiguli and Akech 2017) Following publication of the FEAST trial, WHO advises not to use bolus fluids in children with infection and compensated shock, including those with severe malaria, but continued to recommend bolus therapy in patients fulfilling the WHO criteria for shock as the FEAST trial was insufficiently powered to prove harm of bolus fluids in this subgroup of patients.(World Health Organization (WHO) 2014)(WHO 2013).

In short, physical signs of hypoperfusion should be interpreted with caution, as they appear to be inadequate in assessing intravascular volume in children and adults with severe malaria, and unsafe in guiding fluid bolus therapy in children with malaria. This also raises the question whether the presence of hypotension justifies aggressive fluid resuscitation in severe malaria.

CVP, PAoP and thermodilution are invasive measures that can be used in ICU setting to assess changes in the macro-circulation in patients with malaria. The problem is that ICU facilities are often not available in low-resource, rural settings where malaria is prevalent, and that placing a central venous catheter enhances the risk of infection and bleeding.[21]

Children

In an early observational study by Maitland and colleagues, children with severe malaria (N = 53) were administered 10-40 mL/kg of normal saline or albumin solution in the first hour of admission to optimise the CVP to between 5 to 8 cm H_2O, resulting in improved CVP and physical signs of perfusion and reduced mortality compared to historic controls.[56] No other studies on invasive hemodynamic measures, their reliability and their effect on mortality in children with severe malaria have been identified.

Adults

When comparing CVP recordings with volumetric measures derived from transpulmonary thermodilution in adults with severe malaria, CVP did not correlate with GEDVI, cardiac index, or likelihood of being fluid-responsive. It also failed to signal over-hydration and its adverse effects.[21] In 2013, Hanson and colleagues used transpulmonary thermodilution to determine cardiac index and extravascular lung water as a sign of fluid overload in order to guide fluid therapy in patients with severe malaria (N = 28). As most patients had low GEDVI on admission, they received a median fluid load of 3230mL isotonic saline in the first six hours of admission. After liberal fluid loading, GEDVI increased in most patients but remained low, while markers of fluid overload became apparent; 77% of patients developed extravascular lung water, eight developed clinical pulmonary oedema and half of the patients had marked generalised oedema. The study concluded liberal fluid loading, even when guided by transpulmonary thermodilution, was ineffective and unsafe.[22] Other observational studies in adults reported similar findings. Rapid volume expansion improved macro-circulatory parameters such as CVP, PAoP and cardiac output, but did not improve mortality and did not prevent deleterious adverse effects such as pulmonary oedema from developing.[23,28] When using thermodilution to guide fluid replacement administered at a maintenance rate, or when using a simple weight-based algorithm to determine the amount of maintenance fluids needed

(mean 3.3mL/kg per 6 hours in Ishioka *et al.*), no increase in adverse effects such as the development of hypovolaemic shock or kidney failure were observed. Also, mortality was lower compared to historic controls who received fluids based on clinical judgement.[24,27] Notably, the studies mentioned in this section showing resuscitation with bolus fluids may not be beneficial included a small number of severe malaria patients presenting with hypotension. This may indicate that a more prudent fluid strategy is preferable even in 'algid malaria'.

Micro-circulatory indices

In severe malaria, lactate is a strong predictor of disease severity and mortality.[28,57,58] Importantly, elevated lactate in adults and children with severe malaria does not seem to be the result of tissue hypoxia caused by profound hypovolaemia. Observational studies in adults show that when macro-circulatory indices improve with fluid loading, this does not result in a significant change in acid-base status.[22,23,28] Similarly, treating adults with maintenance fluids only did not lead to a significant rise in lactate.[24,27] Maitland *et al.* found that in children with severe malaria receiving bolus fluids, lactate levels remained just as high as those in children receiving maintenance fluids only.[49] Also, when measuring the volume status of Gabonese children, the fluid volumes in different compartments were not related to hyperlactataemia or other markers of disease severity.[42,44]

Elevated lactate in severe malaria is reflective of increased anaerobic glycolysis in hypoxic cells. Agbenyega and colleagues showed glucose and lactate kinetics in children with severe malaria positively correlated, suggesting glucose in severe malaria is predominantly consumed through anaerobic pathways. This is likely the consequence of microcirculatory impairment.[59] Parasite-infected red blood cells bind endothelial receptors and other erythrocytes in processes called sequestration and rosetting, respectively. This leads to microcirculatory congestion causing hypoxia, acidosis and organ dysfunction. Multiple

studies showed this link as microvascular sequestration visualised by orthogonal polarized spectroscopy (a microscope that allows viewing the microcirculation in mucosal surfaces in vivo) correlated with lactate level in adults with severe malaria.[22,60,61] This relationship persisted after liberal fluid loading, as fluids had no effect on sequestration and its sequelae.[22] Correspondingly, hyperlactataemia occurs less frequent in patients infected with *Plasmodium* species that are unable to sequester, and RNA sequencing has shown an association between lactate levels and the expression of *P. falciparum* genes important for cytoadherence.[62]

Several other pathophysiological mechanisms contribute to increased anaerobic glycolysis and hence lactate production. In anaemic patients, the capacity for oxygen delivery is reduced, leading to tissue ischaemia and hypoxia.[62,59] Low haemoglobin levels are therefore associated with elevated lactate in children and adults with severe malaria.[24,44,45] Fever and seizures in ill patients can further contribute to increased metabolic rates and hence anaerobic glycolysis, and the intraerythrocytic malaria parasite itself anaerobically consumes glucose and produces lactate. Thiamine deficiency may be an underrecognised cause PMID: 10028983. Finally, ketoacidosis in hypoglycaemia can contribute to decreased pH levels and increased lactate production.[19,62,63,64] Impaired lactate clearance due to malarial kidney disease and impaired hepatic function may worsen acidosis.[19,59,62,65,66] Based on these findings, volume status has no clear correlation with lactate and should not be used as an indicator for fluid loading in adults and children with severe malaria.

Decreased kidney function due to malaria is mostly seen in adults and evidence is therefore only available in this age group. Four observational studies in adults reported that anuria on admission was not linked to volume status, liberal fluid loading did not reverse anuria and in most cases did not improve kidney function.[13,22,23,28] Likewise, treating with only maintenance fluids caused no significant change in renal function in adults with severe malaria.[24,27]

Malarial kidney disease is likely the result of sequestration in the glomerular and tubulo-interstitial vessels, as well as cell-free haemoglobin and inflammatory changes damaging the kidney, rather than of decreased kidney perfusion.[24,67] Anuria and other signs of reduced kidney function, which are often interpreted as signs of hypovolemia prompting fluid resuscitation in the critically ill, are therefore not suited to guide fluid therapy in adults with severe malaria.

Adverse effects of fluid therapy

Pulmonary oedema is the most-feared complication of fluid loading in critically ill malaria patients, especially in low resource settings where mechanical respiratory support is often lacking. Respiratory distress unrelated to fluid status (caused by acidosis, concomitant pneumonia or severe malarial anaemia) is prevalent in children, while pulmonary oedema is more common in adults. Pulmonary oedema in severe malaria, which can result in acute respiratory distress syndrome (ARDS), results from inflammatory mediated increased capillary permeability leading to alveolar damage. Potential causes of this process include sequestration in the pulmonary microcirculation as well as the host inflammatory response to the parasite.[68,69]

Several observational studies in adults investigated whether liberal fluid loading could cause pulmonary oedema. They generally reported no direct link between the amount of fluids administered or the macro-circulatory parameters on admissions and the risk of developing pulmonary oedema.[22,28] For example, Hanson *et al.* reported 70% of patients with pulmonary oedema appeared hypovolaemic as determined by macro-circulatory measurements.[22] However, bolus fluids are likely to exacerbate pulmonary oedema. In adults included in studies with protocolized liberal fluid resuscitation, around 30% developed clinical pulmonary

oedema and a larger percentage (77% in Hanson and colleagues' study) showed an increase in extravascular lung water as measured by thermodilution.[13,22,23] This also underlines pulmonary oedema and impaired oxygenation may be present even when physical signs (chest crackles on auscultation, decreased oxygen saturation on pulse oximetry) are not observable. Indeed the study of Hanson *et al.*, on the value of physical examination in malaria mentioned only half of the cases of pulmonary oedema were identified on physical examination.[13] Also, it remains a challenge that there are no clear biomarkers that can be used to predict which patients will develop pulmonary oedema.[68,69] It was noticed, however, that patients who developed this complication generally had more severe disease with higher plasma lactate, less urine output and more peripheral oedema.[22,23] This indicates a cautious fluid strategy may be warranted in these patients. None of the adults being treated with maintenance fluids only developed clinical pulmonary oedema,[24,27] suggesting fluid loading potentially exacerbates pulmonary oedema, especially in severely ill adults. As it is difficult to predict which patients will develop this complication, a conservative fluid strategy seems advisable.

In RCTs conducted in children with severe malaria and signs of decreased tissue perfusion, no increase of clinical pulmonary oedema was observed when bolus fluids were administered.[50,53] In the FEAST trial, no physical signs of pulmonary oedema were seen after bolus fluids were administered. As mentioned, monitoring for this complication solely based on physical examination may have been sub-optimal. One of the re-analyses of the FEAST trial data suggests respiratory deterioration may have contributed to the increase in fatal outcomes in the subgroup of children receiving bolus fluids. This reanalysis by Levin and colleagues compared sequential data on haemodynamics, vital signs and metabolic changes in the study arms using new composite scores for respiratory, cardiovascular and neurological function. It concluded cardiovascular function (comprising heart rate, blood pressure, and

capillary refill time) improved. Respiratory function, neurological status, pH and haemoglobin levels in non-transfused patients deteriorated and together may have caused excess mortality in the bolus fluid groups.(Levin et al. 2019)[55,70,71]

Several theories on the cause of excess mortality in the children receiving bolus fluids in the FEAST trial were shared after the trial results were published. Haemodilution in children with anaemia, reperfusion injury or worsening of neurological sequelae, including cerebral oedema, may have played a role. However, there no primary evidence is available to support these theories.[53,55,56,72] The first FEAST re-analysis showed higher mortality in more severely ill children receiving fluid resuscitation, as their mortality rate declined more slowly over time. This led to the theory reperfusion injury caused a surge in cytokines impacting negatively on myocardial performance, leading to cardiovascular collapse in children with more advanced shock receiving bolus fluids.(K Maitland et al. 2013)(George et al. 2019) This conclusion was criticised, as it was built around cardiovascular arrest being a sign of deteriorating cardiac function, while cessation of cardiac activity as a terminal clinical event can result from different pathologies.(Levin, Cunnington, and Hoggart 2019)

Hyperchloraemic acidosis caused by the infusion of chloride-rich fluids was also suggested as a cause of increased mortality.[71] The same theory is mentioned in studies in adults, were Hanson and colleagues measured a slight decrease in lactate after fluid loading but a fall in pH and a rise in chloride levels and base deficit.[22] Likewise, other observational studies reported base deficit and bicarbonate worsened after fluid loading.[23,28] Hence, fluid loading in severe malaria may hold the potential harm of worsening acidosis. Also, normal saline has been reported to aggravate kidney injury in critically ill patients receiving large amounts of fluids when compared to balanced crystalloid solutions containing less chloride (*e.g.*, Ringer's lactate). Saline and Ringer's lactate have not been compared in patients with severe malaria

specifically and as stated above, fluid loading in severe malaria neither improved nor diminished kidney function. Human albumin solutions were believed to have additional beneficial physiological effects such as preventing oedema by drawing more volume into the intravascular space through the oncotic gradient and have been tested in children with severe malaria. While early pilot studies showed somewhat promising results with improved outcomes in children receiving albumin bolus fluids compared to children receiving normal saline [49], this benefit was not observed in the larger FEAST trial and in systematic reviews. Its use is therefore not recommended.[55,72,73]

Blood transfusion to correct Hb levels in severe malarial anaemia is recommended by WHO (WHO 2015). Assessing the risk of volume overload with blood transfusion and if it outweighs the benefit of correcting anaemia has only been addressed in children with severe malaria. In African children with severe anaemia (Hb <6g/dl), of whom more than half tested positive for malaria, transfusion volumes of upto 30ml/kg infused over 3-4 hours did not cause signs of pulmonary oedema or fluid overload. Also, different transfusion volumes (either 20 or 30ml/kg) did not significantly influence mortality (Olupot-Olupot et al. 2014)(K. Maitland et al. 2019). Similarly, no significant difference in survival and adverse events was found in severely anemic transfused or non-transfused children fulfilling WHO criteria of severe malaria (Meremikwu and Smith 1999). A recent multicentre observational study reported only children with very severe malarial anaemia (Hb <4g/dL) or with severe anaemia and signs associated with high mortality (including impaired consciousness and elevated lactate) receiving a blood transfusion had a clear survival benefit (Ackerman et al. 2020). In concludion, whole blood given according to current transfusion guidelines (and thus with significantly lower rate and volume compared to bolus fluids), does not cause overhydration. While the impact of blood transfusion on mortality is controversial and further investigation required, benefit may outweigh harm in severely ill or severely anaemic children with

malaria. Importantly, clinicians should take into account the need for transfusion and its rate and volume when optimising fluid status in patients with severe malaria.

The evidence summarised above suggests the optimal way of determining fluid status and response in adults and children with severe malaria is to be determined and includes careful consideration in each individual patient. Even when macrovascular parameters are compromised on presentation and improve with fluid loading, this does not necessarily translate into improved tissue perfusion because other pathological processes such as sequestration of infected red blood cells in the capillary vessels and malarial anaemia contribute to hypoxia, and are not altered by bolus fluids. A conservative fluid strategy using maintenance fluids only is generally found to be safe. Contrary to this, liberal fluid loading, even when guided by transpulmonary thermodilution, potentially leads to adverse effects such as tissue oedema and increased mortality in severe malaria in adults. A summary of these findings compared to sepsis as indication indication for fluid loading is given in Figure 2.

Discussion

When the FEAST trial showed increased mortality in children with malaria and decreased tissue perfusion receiving bolus fluids the question as to whether a large interventional phase III trial with mortality as primary endpoint without first further investigating the safety of bolus fluids was debated.(Tim Planche 2005) The ethical dilemma posed by the reported harm of bolus fluids led to an impasse, with no additional large RCTs on fluid resuscitation in adults and children with severe malaria being undertaken. Systematic reviews on fluid therapy in severe malaria only include RCTs and therefore draw heavily on the disputed FEAST trial results.(Hodgson and Angus 2016) The strength of this review is that it incorporates a wide range of evidence, including expert opinion and observational studies. These provide

important insights in how the pathophysiology of malaria influences volume status, fluid response and the variables used to titrate fluid therapy. However, the majority of observational (N=30) studies included a small number of participants (~30) making it difficult to observe differences in fluid needs resulting from patient characteristics, thus limiting the generalisability of the results.

Several limitations of the available evidence impacting the results presented in this review should be considered. RCTs on fluid therapy in severe malaria are conducted in African children, while observational studies mainly include adult severe malaria patients living in southeast Asia. Many patient-inherent factors (e.g. nutritional status, immunity, disease trajectory, bacterial co-infection, co-morbidities) and environmental aspects (*e.g.,* available health services, endemicity of malaria) may impact on fluid status response and rehydration response, and therefore also impact on the generalisability of research findings. Also, this review focuses on *P. falciparum* infection as the main pathogen causing severe malaria. Asian studies frequently included a small proportion of patients with *P. vivax*, *P. knowlesi*, or mixed infections. As *Plasmodium* species other than *P. falciparum* have their own distinct pathophysiology, this may influence findings. Population-based differences in haemodynamic state and fluid needs remain unclear, as studies on imported malaria conducted among severe malaria patients from different backgrounds mainly focus on assessing risk factors of ICU admission and mortality. Prevalence of hypotensive shock on admission and details on haemodynamics are generally not reported.[31,35,36,52,68,75,76,77,78,79,80,81] What is presented as beneficial in this review may not apply to all patient populations.

The interventions in the included studies are heterogenous. RCTs on fluid therapy in severe malaria usually include patients at the moment of admission and report on the effect of bolus

fluid therapy in the initial resuscitation phase, mainly initiated based on physical examination and physiological parameters. Observational studies often include patients when they are transported to ICU, meaning the initial fluid resuscitation provided in the emergency room might differ from patient to patient. Their outcomes therefore relate to the role of fluid therapy in further stabilising severe malaria patients in ICU while using invasive cardiovascular monitoring. These differences in intervention and health-care settings should be taken into account.

Conclusion

Adults and children with severe malaria generally have mild-to-moderate hypovolaemia due to a varying degree of fluid losses and reduced fluid intake. However, their macro-circulatory parameters, including their blood pressure, are usually within normal range as their cardiac function and peripheral vascular resistance are preserved. Only a small proportion of patients presents with hypotensive shock and it remains obscure why this more sepsis-like profile develops in a subset of patients. Larger observational studies in a variety of patients reporting on patient specific factors such as bacterial co-infection, disease trajectory and other comorbidities could help to gain more insight into this phenomenon.

Hypovolaemia does not appear to be a relevant contributor to elevated lactate in adults and children with severe malaria. Instead, it is mainly the result of microcirculatory blockage caused by sequestration of infected erythrocytes. Hence, fluids may improve macrocirculatory parameters, but do not necessarily alleviate hypoxia at the cellular level. Liberal fluid loading may exacerbate pulmonary oedema in adults with severe malaria and is shown to increase mortality in children with malaria and signs of decreased tissue perfusion. Rapid administration of bolus fluids in patients with severe malaria is therefore generally contra-indicated, consistent with WHO guidelines(WHO 2015). A conservative fluid strategy is

found to be safe and effective in adult patients in observational studies. Maintenance fluids only did not increase acidosis or kidney dysfunction and led to a lower mortality rate in adults with severe malaria. It therefore seems preferable to rehydrate severe malaria patients with fluids at maintenance rate. Further research on the safety and benefit of conservative fluid therapy, especially in children, is warranted. Additionally, it should be investigated whether specific patient characteristics, such as the presence of hypotension, should prompt a more liberal fluid strategy. Other supportive therapies (*e.g.* dichloroacetate to increase aerobic utilisation of lactate in mitochondria and glucose in hypoglycaemia) should be considered by clinicians, but as their main goal is not to optimise fluid status they are beyond the scope of this review.[2,59]

There is no single fluid prescription appropriate for all patients with severe malaria. A minority of patients will present with hypotension, the level of hypovolaemia may differ per patient and some patients may have concomitant bacterial sepsis. This makes it imperative to assess volume status and fluids response on an individual patient basis. There is no consensus on the constellation of variables to guide liberal fluid resuscitation in severe malaria. Physical examination and physiological parameters are unreliable in predicting fluid status and response in adults and children with severe malaria. An early study showed promise of CVP guided fluid loading in children, but this measure has proven unreliable in adult patients and in critically ill patients in general. PAoP and thermodilution may be more accurate, but failed to prevent overhydration when used to guide liberal fluid loading in adults with severe malaria. Fluid loading based on thermodilution measurements only seemed safe when regulating conservative fluid therapy. The use of non-invasive measurements including IVC ultrasound and echocardiography to guide fluid therapy, which could be used at bedside in rural settings to assess real-time changes in haemodynamics, and to examine organs including the lungs for pulmonary oedema, remain relatively unexplored.[14,82,83,84,85] Trials integrating

non-invasive diagnostic measures into resuscitation strategies for patients with severe malaria are currently ongoing in Bangladesh.[86,87,88] A summary of the caveats and recommendations for clinicians and researchers regarding fluid management in patients with severe malaria is provided in Table 1 and Figure 2. It would be valuable to further investigate the sensitivity and specificity of diagnostic measures such as IVC ultrasound in predicting fluid status and response in patients with severe malaria to establish whether this individualised, haemodynamically guided approach with clear resuscitation endpoints will improve patient outcome.

Contributors

LCK - data collection, data interpretation and analysis, visualisation, lead in writing of the original draft and writing review & editing.

TH - conceptualisation, data interpretation and analysis, visualisation, contribtuiton to writing of the original draft and writing review and editing.

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Declaration of interests

None of the authors has a conflict of interest to declare.

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Panel Legends

Panel 1. Search strategy and study selection

Table Legends

Table 1. Summary of caveats and recommendations

Figure Legends

Figure 1. Fluid status and response in severe malaria as compared to septic shock

Figure 2. Summary of most important findings on measuring fluid status and response, general haemodynamic status and fluid strategy in severe malaria.

Supplementary Material Legends

Panel 1. Search strategy and selection criteria

References for this review were identified through searches of Medline, Embase, PubMed, Cochrane and TRIP. Search terms related to malaria and relevant diagnostic or therapeutic measures, such as 'malaria' or 'Plasmodium falciparum' combined with for example 'hypotension', 'fluid resuscitation', 'fluid bolus*', 'echocardiography' and 'ultrasound'. The search was last updated on the 7th of April 2021. Studies of all publication dates and study design, written in English or French were included, if they specifically reported on fluid therapy as therapeutic interventions or diagnostic measures used to determine fluid status or response in severe malaria. Additionally, references of the studies retrieved were examined to identify additional relevant studies, and guidelines on malaria treatment where consulted.

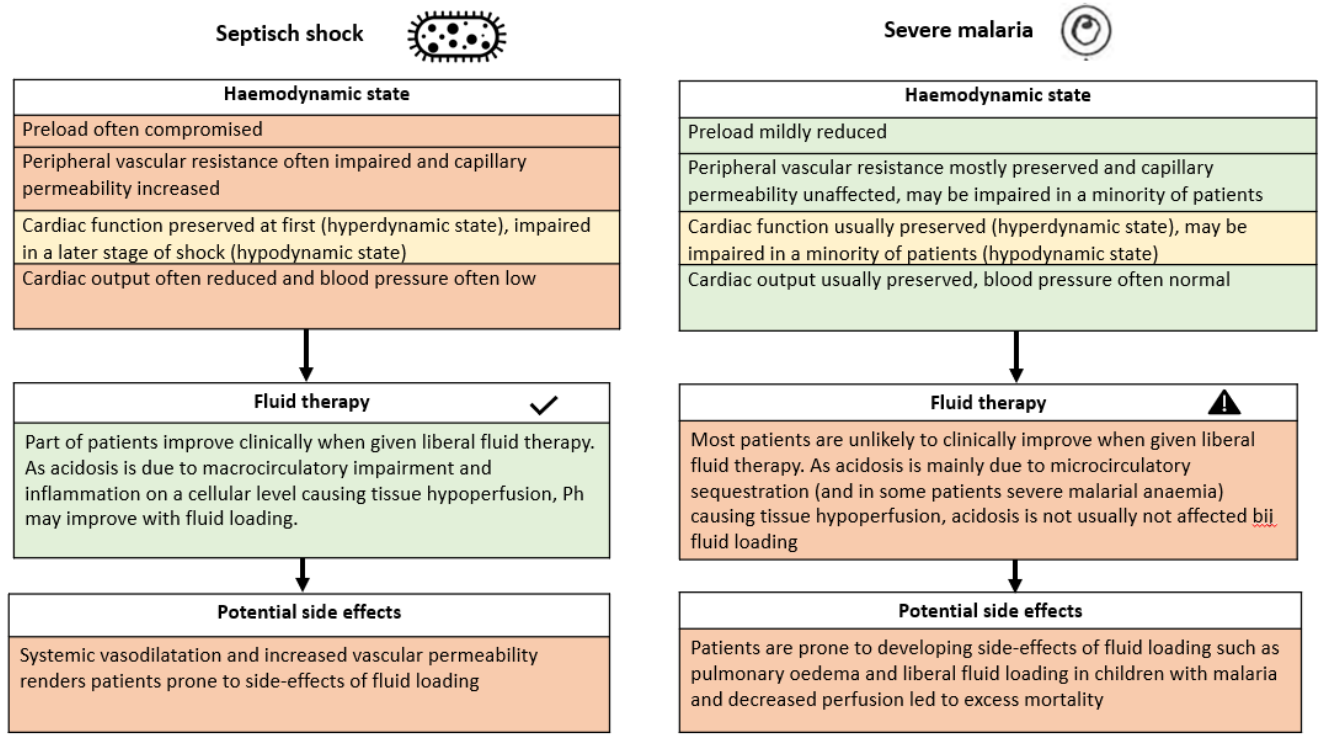
Table 1. Summary of caveats and recommendations

Assessment of fluid status and response	
⊘ **Caveats**	✓ **Recommendations**
Macrocirculation - haemodynamics - **Physical examination seems unreliable in predicting fluid status and response in adults and children with severe malaria.** - **CVP is likely unreliable in predicting fluid status and response in adults with severe malaria.** - **PAoP and transpulmonary thermodilution seem to measure fluid status and response more reliably in adults with severe malaria, but their use fails to prevent overhydration and does not improve patient outcome when applying them to guide liberal fluid loading.** **Microcirculation - tissue perfusion** - **Elevated lactate is mainly the result of sequestration of erythrocytes in the microvasculature and malarial anaemia in adults and children with severe malaria, and not the result of hypovolemia. Lactate level and pH should therefore not be used to guide fluid therapy** **Monitoring side effects** - **Physical examination is shown to have limited reliability in identifying pulmonary oedema.** - **Thermodilution can be used to measure extravascular lung water, but its use failed to prevent pulmonary oedema from developing in adult patients.**	Observational studies in a variety of patients reporting on patient specific factors (bacterial co-infection, disease trajectory, comorbidities) may help us to understand what patients develop a septic-like disease profile including hypotension. Further investigation to find out what methods can be applied to move towards a more individualized approach in fluid loading is needed, focussing on non-invasive measures such as bed-side IVC ultrasound, and reliable resuscitation indicators and end-points.
General fluid resuscitation strategy	
Liberal fluid resuscitation - **Bolus fluids are proven to increase mortality in children with malaria and physical signs of impaired perfusion.** - **Liberal fluid resuscitation in adults did not decrease acidosis**	A conservative fluid strategy using maintenance fluids only was found to be safe in adults with severe malaria as it did not increase kidney damage or acidosis. It led to a decrease in mortality compared to historic controls. Additional observational studies to assess the safety of a conservative fluid strategy in different settings and different subset of

	and did not improve kidney function, while it does potentially exacerbate pulmonary oedema and hyperchloremic acidosis.	patients (including those with hypotension and including children) would be helpful.

Figure 1. Fluid status and response in severe malaria as compared to septic shock

	Hypovolemic shock	Septic shock	Severe malaria
Blood pressure	Often low	Often low	Often normal
Preload	Often compromised	Often compromised	Moderately reduced
Peripheral vascular resistance and capillary permeability	Mostly uncompromised	Often impaired	Mostly preserved, may be impaired in a minority of patients
Cardiac function	Usually preserved, unless in late stage of shock	Preserved at first (hyperdynamic state), impaired in a later stage of shock (hypodynamic state)	Usually preserved (hyperdynamic state), may be impaired in a minority of patients (hypodynamic state)
Cause of acidosis	Mostly due to macrocirculatory impairment causing tissue hypoperfusion	Mostly due to macrocirculatory impairment and inflammation on a cellular level causing tissue hypoperfusion	Mostly due to microcirculatory sequestration (and in some patients - severe malarial anaemia) causing tissue hypoperfusion
General response to liberal fluid resuscitation	Likely to clinically improve when given liberal fluid therapy	Part of patients improve clinically when given liberal fluid therapy	Most patients are unlikely to clinically improve when given liberal fluid therapy
Potential side-effects of fluid therapy	A minority of patients may develop side-effects of fluid loading when given excessive fluids	Systemic vasodilatation and increased vascular permeability renders patients prone to side-effects of fluid loading	Increased vascular permeability makes patients prone to developing side-effects of fluid loading such as pulmonary oedema and liberal fluid loading in children with malaria and decreased perfusion led to excess mortality



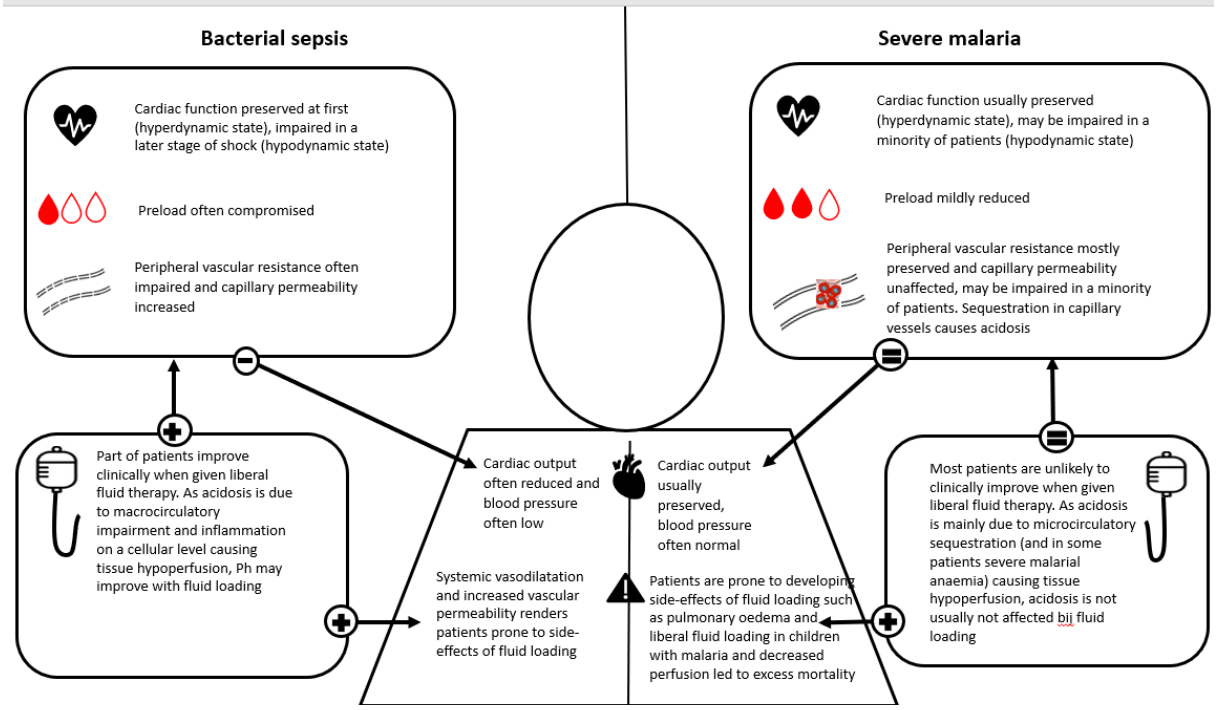

Bacterial sepsis
Cardiac function preserved at first (hyperdynamic state), impaired in a later stage of shock (hypodynamic state)
Preload often compromised
Peripheral vascular resistance often impaired and capillary permeability increased
Severe malaria
Cardiac function usually preserved (hyperdynamic state), may be impaired in a minority of patients (hypodynamic state)
Preload mildly reduced
Peripheral vascular resistance mostly preserved and capillary permeability unaffected, may be impaired in a minority of patients. Sequestration in capillary vessels causes acidosis
Part of patients improve clinically when given liberal fluid therapy. As acidosis is due to macrocirculatory impairment and inflammation on a cellular level causing tissue hypoperfusion, Ph may improve with fluid loading
Cardiac output often reduced and blood pressure often low
Systemic vasodilatation and increased vascular permeability renders patients prone to side-effects of fluid loading
Cardiac output usually preserved, blood pressure often normal
Patients are prone to developing side-effects of fluid loading such as pulmonary oedema and liberal fluid loading in children with malaria and decreased perfusion led to excess mortality
Most patients are unlikely to clinically improve when given liberal fluid therapy. As acidosis is mainly due to microcirculatory sequestration (and in some patients severe malarial anaemia) causing tissue hypoperfusion, acidosis is not usually not affected bij fluid loading

Figure 2. Summary of most important findings on measuring fluid status and response, general haemodynamic status and fluid strategy in severe malaria