9 Management of Severe Malaria and Severe Dengue in Resource-Limited Settings

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9.1 Introduction

Sepsis in resource-limited settings will often have different etiologies to those in Western settings, including severe malaria, severe dengue, viral hemorrhagic fevers, melioidosis, typhus, and leptospirosis. The Surviving Sepsis Campaign (SSC) guidelines [1] are mainly based on evidence from studies on bacterial sepsis. These guidelines are widely applicable, but there are also exceptions. We here focus on disease-specific recommendations for the management of severe falciparum malaria and severe dengue. An international team with extensive practical experience in resource-limited intensive care units (ICUs) identified key questions concerning the SSC's management recommendations on these diseases. Pertinent evidence from resource-limited settings was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tools.

Severe falciparum malaria is a multiorgan disease caused by *Plasmodium falciparum* transmitted by *Anopheles* mosquitoes. The highest transmission and disease burden is in sub-Saharan Africa, where severe malaria is largely a pediatric disease, as older children and adults become partly immune. In Asia and South America, all age groups may be affected. Independent of age, the presenting symptoms with the strongest prognostic significance are coma (cerebral malaria), metabolic (lactic) acidosis, and renal dysfunction. Acute respiratory distress syndrome is a common and often fatal complication in adult patients with severe malaria. Hypotension occurs infrequently (~12% of cases), and should raise a suspicion of concomitant bacterial sepsis. One of the main pathophysiologic differences of severe falciparum malaria compared to bacterial sepsis is microcirculatory impairment caused by sequestration of parasite-infected erythrocytes, red cell rigidity, and red cell clumping.

Severe dengue is caused by dengue virus transmitted by *Aedes* mosquitoes. Approximately 1–5% of patients will develop severe manifestations. The defining feature is a vasculopathy with increased capillary permeability, causing plasma leakage, reduced intravascular volume, and if severe life-threatening hypovolemic shock [2]. This "critical phase" typically starts during the period of defervescence and lasts for approximately 48 h. Bleeding complications and organ involvement of the brain, liver, kidney, and heart may be additional features and occur more frequently in adult cases [3]. Recommendations and suggestions are summarized in Table 9.1.

9.2 Fluid Management in Severe Malaria

Severe malaria is an old disease, and historically, the guidance for fluid management has been to "keep them dry." This approach was subsequently challenged when it was recognized that severe malaria is a severe sepsis syndrome with signs of tissue hypoperfusion and thus might benefit from fluid bolus therapy. The SSC guidelines recommend in patients with sepsis-induced tissue hypoperfusion and suspicion of hypovolemia an initial fluid challenge of minimal 30 mL/kg of crystalloids, to be completed within 3 h, of which a portion may be albumin equivalent;

Table 9.1 Recommendations and suggestions for the management of patients with severe malaria and severe dengue in resource-limited settings (with grading)

Fluid management of severe malaria	We recommend not to use fluid bolus therapy in normotensive patients with severe falciparum malaria (1A). We suggest that patients receive maintenance isotonic crystalloid fluid therapy (2–4 mL/kg/h), which may subsequently be reduced to 1 mL/kg/h in patients receiving additional fluids, e.g., through enteral tube feeding (2D). We suggest that in patients with hypotensive shock, fluid bolus therapy (30 mL/kg) with isotonic crystalloids be commenced (ungraded) and, if available, early initiation of vasopressor medication (ungraded)
Timing of enteral feeding in cerebral malaria	We suggest initiating enteral feeding in non-intubated adult patients with cerebral malaria after 60 h, in order to limit the possibility of aspiration pneumonia (2B). There are insufficient data to make this recommendation for children with cerebral malaria
Permissive hypercapnia in ventilated cerebral malaria	We suggest not to use a strategy of permissive hypercapnia to achieve ventilation with low tidal volumes in patients with cerebral malaria, because of the high incidence of brain swelling in these patients (ungraded)
Fluid management in severe dengue	We recommend that fluid resuscitation in severe dengue is executed promptly and guided by pulse pressure, capillary refill time, hematocrit, and urine output according to WHO guidelines and that fluid therapy should be restricted as soon as the critical phase of the disease is over to avoid pulmonary edema (1C). We recommend that rapid administration of large fluid boluses should be avoided, unless the patient is hypotensive (1D). We recommend that in dengue patients with compensated shock, colloid fluids are not used (1A)
Use of corticosteroids in severe dengue	We recommend not to use corticosteroids in the treatment of severe dengue (1B)
Use of prophylactic platelet transfusion in severe dengue	We recommend not to use prophylactic platelet transfusion for thrombocytopenia in the absence of active bleeding complications or other risk factors (uncontrolled arterial hypertension, recent stroke, head trauma or surgery, continuation of an anticoagulant treatment, existing hemorrhagic diathesis) (1B)

this applies to patients with hypotension or a plasma lactate ≥4 mmol/L [1]. It was shown by various techniques that both children and adults with severe falciparum malaria are intravascular dehydrated [4–6] although this was debated by some [7]. Small trials in African children with severe malaria suggested a benefit from fluid bolus therapy, in particular with albumin [8–11], as recently reviewed [12]. However, a subsequent large trial on fluid bolus therapy in 3138 African children with severe infections and compensated shock, of which 57% had falciparum malaria, showed overall a 40% increase in mortality with fluid bolus therapy (20 mL/kg or 40 mL/kg with either saline or albumin). In the 1793 children with severe *P. falciparum* malaria, mortality in the bolus groups was 51% higher (RR 1.51 [1.17–1.95]) than without fluid bolus therapy [13]. In the same study, febrile patients with hypotensive ("decompensated") shock were randomized between 20 and 40 mL/kg fluid bolus therapy with either saline or albumin; 69% of the children (9 of 13) in the albumin bolus group and 56% (9 of 16) in the saline-bolus group died ($P = 0.45$). In Asian studies in adult severe malaria, rapid fluid resuscitation did not improve metabolic

acidosis [14, 15], and transpulmonary thermodilution-guided rapid fluid resuscitation resulted in pulmonary edema in 8/28 (29%) patients [15]. One observational study showed no deterioration in renal function or plasma lactate with maintenance fluid therapy between 1.3 and 2.2 mL/kg/h [16]. A recent systematic review concluded that fluid bolus therapy with either crystalloid or albumen is not beneficial in severe falciparum malaria [17].

We *recommend* not to use fluid bolus therapy in normotensive patients with severe falciparum malaria (1A). We *suggest* not to use colloid therapy, including albumin 5% (2C). In normotensive patients, we *suggest* initial crystalloid fluid therapy of 2–4 mL/kg/h (2D). In patients receiving enteral fluids, e.g., through enteral tube feeding, we suggest that this can be reduced to 1 mL/kg/h (2D). This is slightly more conservative than the recommendation in the management guidelines for severe malaria issued by the World Health Organization, recommending 3–5 mL/kg/h [18]. There are no data on the benefit of balanced fluids over normal saline. We suggest fluid bolus therapy (30 mL/kg) with an isotonic crystalline in patients with hypotensive shock and, if available, early start of vasopressive medication (ungraded). Hypotensive shock in a patient with severe malaria could indicate concomitant bacterial sepsis, and be evaluated and treated accordingly.

9.3 Timing of Enteral Nasogastric Tube Feeding in Cerebral Malaria

The SSC guidelines suggest administering oral or enteral (if necessary) feeds, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 h after a diagnosis of severe sepsis/septic shock (grade 2C) [1]. Early enteral feeding is thought to preserve gut integrity and function, maintain bile secretion and secretory IgA, maintain gut-associated lymphoid tissue (GALT) resulting in reduced translocation, improve splanchnic blood flow, and act prophylactically against stress ulceration. In patients with severe malaria, malnutrition is common, as is concomitant invasive bacterial infection [19]. Therefore, the recommendation for early start of enteral feeding seems valid for patients with severe malaria, including intubated patients with cerebral malaria. However, in resource-limited settings, endotracheal intubation of comatose patient is often not practiced, and there might be an increased risk of aspiration pneumonia.

We could identify one randomized clinical trial on the timing of enteral feeding in patients with cerebral malaria [20]. This trial in (mainly) adult Bangladeshi patients with cerebral malaria who were not on mechanical ventilation, and thus had an unprotected airway, showed that early (<60 h) enteral feeding was associated with aspiration pneumonia in 9/27 (33%) versus 0/29 with late start after 60 h ($p = 0.001$). This despite proper positioning of patients, and pre-feed inspection of gastric retention. No difference in the incidence of hypoglycemia was observed.

We *suggest* starting enteral feeding in non-intubated adult patients with cerebral malaria after 60 h (2B). There are insufficient data on pediatric patients with cerebral malaria from African settings.

9.4 Mechanical Ventilation in Patients with Severe Malaria and Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS), or pulmonary malaria, is a feared complication of severe falciparum malaria and can also complicate the course of vivax malaria [21]. The incidence of ARDS in adult patients with severe malaria is estimated 5 to 25% and up to 29% in pregnant women; ARDS is thought to be rare in pediatric severe malaria [22]. To protect the lung from the damaging effects of mechanical ventilation, the SSC recommends targeting a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced acute respiratory distress syndrome (ARDS), that plateau pressures be measured in patients with ARDS and that the initial upper limit goal for plateau pressures in a passively inflated lung be <30 cm H_2O [1]. There are no randomized clinical trials to evaluate this recommendation specifically for ARDS in the context of severe malaria. However, given the large benefit of this ventilation strategy in patients with other causes of ARDS, this recommendation should also be valid in severe malaria. The SSC guidelines also suggest that to facilitate the use of a lung protective ventilatory strategy, permissive hypercapnia can be used. It should be noted that availability of blood gas or end-tidal CO_2 monitoring is limited in resource-limited settings, compromising its safe implementation.

There are no randomized clinical trials on the use of permissive hypercapnia in mechanically ventilated patients with severe falciparum malaria. However, in cerebral malaria, brain swelling is common, caused by an increase in intracerebral blood volume including the sequestered parasitized red blood cell mass, vasogenic edema, and cytotoxic edema, and is more prominent in pediatric cases [23–26]. Because hypercapnia will further increase intracranial pressure, we *suggest* against the use of permissive hypercapnia to achieve the goal of low tidal volume ventilation in patients with cerebral malaria, as cerebral malaria is associated with brain swelling and variably increased intracranial pressure (ungraded).

9.5 Fluid Management in Severe Dengue

Severe dengue can be defined as a sepsis syndrome. Yet, important aspects of the pathophysiology of the circulatory changes are distinct from bacterial sepsis. Dengue shock syndrome is characterized by a vasculopathy during the critical phase of the disease, with a plasma leak and hemoconcentration, causing important intravascular volume depletion [3]. This initially leads to a compensated shock with signs of tissue hypoperfusion and a decreased pulse pressure with preserved systolic blood pressure. This can be followed by life-threatening hypotensive shock. Hemorrhage, in particular from the gastrointestinal tract, and more rarely myocarditis, can contribute to circulatory shock. The onset is usually more gradual than with bacterial sepsis. Management of patients with severe dengue relies largely on careful monitoring, including early recognition of vascular leakage and proper fluid replacement, combined with prompt but carefully guided volume resuscitation for

patients who develop dengue shock syndrome. The SSC guidelines advocate fluid bolus therapy for patients with sepsis-induced tissue hypoperfusion and suspicion of hypovolemia [1], which might not be appropriate for patients with severe dengue and compensated shock. In addition, because of the prominent plasma leak, the use of colloids might be beneficial in dengue with hypotensive shock, as opposed to its use in patients with bacterial sepsis. The WHO guidelines for the management of patients with severe dengue distinguish patients with compensated shock from those with decompensated (hypotensive) shock [2, 27]. In compensated shock, recommended initial fluid therapy is with isotonic crystalloid solutions at 5–10 mL/kg over 1 h, which can be tapered every few hours if the patient improves guided by the pulse pressure, capillary refill time, hematocrit, and urine output. Prudential fluid therapy is important throughout the disease, but in particular fluid administration should be restricted as soon as the critical phase of the disease is over to avoid pulmonary edema. In the same guidelines, it is recommended in patients with hypotensive shock, to resuscitate with crystalloid or colloid solution at 20 mL/kg as a bolus given over 15 min.

No randomized clinical trials to support the WHO fluid resuscitation recommendations could be identified. Fluid bolus therapy, and liberal fluid management more in general, was a risk factor for respiratory distress in a large prospective observational study in Latin American and Asian patients with dengue [28]. A large prospective observational study in 1719 Vietnamese children with laboratory-confirmed dengue shock syndrome practiced an initial fluid regimen of Ringer's lactate solution at 25 mL/kg over 2 h, with colloid solutions reserved for children presenting with decompensated shock [29]. The observed case fatality rate with this approach was 8/1719 children (0.5%).

We *recommend* to follow the current WHO guidelines on fluid management in severe dengue/dengue shock syndrome (1C). We *recommend* that rapid (<30 min) administration of large (>15 mL/kg) fluid boluses should be avoided, unless the patient is hypotensive (1D).

There are several randomized clinical trials comparing crystalloid with colloid fluid management for the treatment of patients with severe dengue and compensated shock. In a Vietnamese trial, 383 children with moderately severe dengue shock syndrome were randomized to fluid therapy with either Ringer's lactate, 6% dextrose, or 6% hydroxyethyl starch in a 1:1:1 ratio [30]. The need for rescue resuscitation with a colloid or the proportion of children with shock recurrence (which carries a worse prognosis) was similar between treatment arms. An additional two other randomized trials did not show better outcome parameters with (more expensive) colloids over crystalloid fluids [31, 32]. A quasi-randomized study from the Philippines with alternate allocation of starch versus crystalloid fluids also did not show an additional benefit of colloid therapy [33].

We *recommend* that in dengue patients with compensated shock, colloids are not used for initial resuscitation (1A). There is insufficient evidence to recommend fluid choice in severe dengue with hypotensive shock, but there is discussion among experts whether there is a role for colloids in severe dengue patients with hypotension, given the prominent role of capillary leak it its pathogenesis. Since current evidence strongly suggests that all hydroxyethyl starches (HES) increase the risk of

acute kidney injury and renal replacement therapy [34], we *suggest* not to use HES for fluid resuscitation in patients with severe dengue (ungraded).

9.6 Use of Corticosteroids in Severe Dengue

Both humoral and cellular immune responses are thought to be implicated in the pathogenesis of vasculopathy, which is central in the pathogenesis of dengue shock syndrome [35]. The risk for developing severe disease is increased in secondary heterotypic infections, in which antibody-dependent enhancement (ADE) of infection and cross-reactive memory T cells are thought to play a role. These insights have led to the use of immunomodulatory therapy with corticosteroids in severe dengue infection.

A Cochrane review on patients with dengue shock syndrome identified four randomized or quasi-randomized trials comparing corticosteroids with no corticosteroids or placebo involving 284 participants with dengue shock syndrome [36]. Corticosteroids did not reduce the number of deaths (RR 0.68, 95% CI 0.42–1.11; 284 participants, 4 trials), the need for blood transfusion (RR 1.08, 0.52–2.24; 89 participants, 2 trials), or the number of serious complications (convulsions and pulmonary hemorrhage, 1 trial). The evidence was rated low quality as most studies were underpowered or lacked stringent randomization or allocation concealment. Corticosteroids were administered after the onset of shock. A more recent Vietnamese randomized trial in 225 children with dengue fever evaluated early oral prednisolone therapy (2 mg/kg versus 0.5 mg/kg versus placebo for 3 days) [37]. The use of oral prednisolone was not associated with prolongation of viremia and was considered safe. However, no reduction in the development of dengue shock syndrome or other complications was observed with early prednisolone therapy, although the trial was not sufficiently powered to assess efficacy. An additional analysis of the same trial focusing on immunological endpoints did not show an important attenuation of the host immune response with prednisolone treatment [38]. An additional Cochrane review of trials on the early use of corticosteroids in patients with dengue fever identified four studies (including the study discussed above), enrolling a total of 664 children and adults, showing no benefit of corticosteroids regarding mortality or dengue complications, although the evidence was considered low to very low quality [39].

With the current level of evidence, the use of corticosteroids is not recommended in the treatment of severe dengue (1B).

9.7 Preventive Platelet Transfusion in Patients with Severe Dengue

Bleeding is a feared complication of severe dengue infection. Thrombocytopenia with a thrombocytopathy is invariably present in patients with severe dengue infection. However, vasculopathy is a central and important additional contributor to the bleeding risk [3]. Prophylactic transfusion of platelets is a common practice in

dengue-endemic countries [40]. Platelet transfusion is not without risks, since it can cause allergic reactions and transmission of blood-borne pathogens.

An open-label randomized study in 87 patients with dengue and a platelet count below 30,000/μL did not show decreased incidence of severe bleeding with prophylactic platelet transfusion [41]. A non-randomized Singaporean study in 256 dengue patients with thrombocytopenia <20,000/μL, of whom 188 were given prophylactic platelet transfusion, also did not show decreased bleeding episodes in the treatment group [42]. An observational study from Martinique during a dengue outbreak evaluated a conservative strategy to prophylactic platelet transfusion (only if platelets count <5000/μL, or in case of additional risk factors). A poor correlation between thrombocytopenia and the occurrence of severe bleeding during admission was observed, and the followed conservative transfusion strategy was considered safe [43]. The WHO guidelines do not recommend prophylactic platelet transfusion in severe dengue. The results of the Adult Dengue Platelet Study (ADEPT, ClinicalTrials.gov: NCT01030211), a prospective randomized open-label trial to examine the safety and efficacy of prophylactic platelet transfusion in Singaporean adults with severe dengue-related thrombocytopenia (platelet count below 20,000/μL but no bleeding), are pending. In resource-limited settings, the availability of safe pathogens vs. screened blood products can be limited, and platelet transfusion can have important cost implications, supporting restrictive use of platelet transfusion.

We do *not recommend* platelet transfusion for thrombocytopenia in the absence of active bleeding complications or other risk factors such as the use of anticoagulants, existing hemorrhagic diathesis, uncontrolled arterial hypertension, recent stroke, head trauma or surgery (1C). In case of bleeding complications, we *suggest* transfusion of fresh-frozen plasma (or cryoprecipitate) and platelet concentrate (ungraded).

9.8 Conclusions

Although most recommendations in the SSC guidelines are also applicable for the management of severe malaria and severe dengue, there are some important exceptions, in particular regarding fluid management.

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