Managing Malaria in the Pediatric Intensive Care Unit

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ABSTRACT

Malaria in children is associated with high mortality and morbidity. High index of suspicion is required for diagnosis. Clinical assessment should be supplemented by laboratory investigations including peripheral blood smear examination and rapid diagnostic tests. Common associated life-threatening problems include coma, seizures, raised intracranial pressure (ICP), shock, respiratory failure, acute kidney injury, anemia and fluid and electrolyte abnormalities. Aggressive supportive care in pediatric emergency and pediatric intensive care unit includes control of airway, breathing and circulation; maintaining adequate intravascular volume; management of raised ICP and status epilepticus; and close monitoring for early detection of complications. Artesunate combination therapy should be administered promptly. Clinical evaluation, laboratory workup, specific antimicrobial therapy, supportive treatment and management of associated complications should go hand in hand in a protocolized way for better outcome.

Key words: Malaria, Child, PICU, Artesunate

Introduction

Malaria is a protozoan disease that continues to affect millions of lives around the world every year causing significant morbidity and mortality. Though developed countries have virtually eliminated the disease, most of the developing world including India still grapples with
this deadly infection. Consequently, the world has witnessed varying phases of treatment regimes and control programs to tackle malaria over time. Malaria affects all age groups and presents with multisystem manifestations. It is one of the important tropical infections in the ‘tropical fever’ conundrum, easily treatable, if recognized early and managed appropriately. Children with severe malaria often present with various complications that require admission to pediatric intensive care unit (PICU) for monitoring, treatment of complications, and organ support. Severe malaria commonly present as serious medical emergencies. Early, aggressive, and appropriate intensive care is required to prevent morbidity and mortality. This review focuses on management of malaria from the perspective of an intensivist.

**Epidemiology**

Latest WHO estimates reveal that there were 212 million cases of malaria with 429,000 deaths in 2015 alone, with the African region bearing the brunt of the disease with 90% of these cases and 92% of deaths. More than 2/3rd of deaths occurred in under-5 children in high transmission areas. Though under-5 malaria death rate fell by 29% between 2010 and 2015, it is an important killer in this age group, claiming one child every 2 minutes. South-East Asia, the Middle East and Latin America are also significantly affected. India accounts for 70% of the burden of the South East Asian Region of WHO. Within India, about 91% of malaria cases and 99% of malarial deaths occur in the high disease burden states which are the Northeastern (NE) states, Andhra Pradesh, Chhattisgarh, Gujarat, Jharkhand, Karnataka, Madhya Pradesh, Maharashtra, Odisha, Rajasthan and West Bengal. It is an important cause of admission to PICU, frequently progressing to multiorgan dysfunction syndrome (MODS) and having a high mortality. Severe malaria once believed to be mainly caused by *Plasmodium falciparum* has been increasingly attributed equally to *P. vivax* over the past few decades. In a Brazilian study on *P. vivax*-associated admissions to PICU, male sex, age <5 years, parasitemia >500/mm³ and presence of acute or chronic co-morbidity were independently associated with PICU admission.

**Biology and transmission dynamics**

There are 5 species of the genus *Plasmodium* which cause malaria in human beings: *P. falciparum, P. vivax, P. ovale, P. malariae,* and in parts of Southeast Asia, *P. knowlesi.* Malaria is transmitted to humans by bite of infected female Anopheles mosquito. Other modes of transmission include transfusion of infected blood, use of contaminated needles and transplacentally from an infected mother to fetus. *Plasmodium* undergoes an asexual cycle called schizogony in man (vertebrate host) and a sexual cycle called sporogony in the vector, anopheles (invertebrate host). Incubation period varies from 9-40 days, being shortest for *P. falciparum* and longest for *P. malariae.* Knowledge of the life cycle (Figure 1) is essential in understanding the phases of illness and natural course.

The clinical presentation of malaria is closely related to the dynamic relationships between the causative agent (*Plasmodium* species), vector (Anopheles mosquito) and host (man) characteristics in a area (Figure 2). The pattern and intensity of transmission of the parasite is determined by density, longevity, biting habits and efficiency of mosquito vector and in turn determines the background level of acquired protective immunity in the host and the clinical picture.

Transmission can be ‘stable’ or ‘unstable’. When it is constant, frequent and occurs all through the year, it is called stable transmission. When it is low, erratic or focal it is called unstable transmission. Geographical areas are classified into high and low transmission areas. An area with >1 case/1000 population is a high transmission area and that with 0-1
case/thousand population is a low transmission area. Sub-Saharan Africa, where transmission is stable, entomological inoculation rate (number of infectious bites/year) is high and *P. falciparum* predominates is a high transmission area. High transmission areas have higher morbidity and mortality in early childhood and asymptomatic infections in older age groups. Most of Asia has low and seasonal transmission with roughly equal prevalence of *P. falciparum* and *P. vivax* malaria and a lower entomological inoculation rate and is thus a low transmission area. Protective immunity is not acquired and symptomatic disease can occur at any age. Changes in environmental, economic or social conditions (heavy rains after drought, large population movements) and breakdown in malaria control programs can precipitate epidemics. In India, 22% of the population lives in high transmission areas (parts of the North Eastern states, Odisha and Rajasthan), 67% in low transmission areas and 11% in malaria free areas.

![Figure 1: Life cycle of the malarial parasite and its relation to phases of illness.](image)

**Clinical features**

**Uncomplicated malaria**

Illness begins with a prodrome of nonspecific symptoms of fatigue, headache, arthralgia, myalgia, abdominal and chest pain mimicking a viral illness that may last for 2-3 days. This is followed by fever, which is the cardinal symptom of malaria. The classic malarial paroxysm consists of fever with chills and rigors occurring at periodic intervals (24 hours for *P. falciparum*, 48 hours for *P. vivax* and *P. ovale* and 72 hours for *P. malariae*) with abdominal
pain, nausea, vomiting, diarrhea, back pain, pallor and jaundice. These classic paroxysms, though eloquently described, are uncommon in children and periodicity is least apparent with *P. falciparum*. Splenomegaly, hepatomegaly and pallor are important examination findings. No specific set of signs and symptoms reliably differentiates malaria from other tropical infections.

The clinical diagnosis of uncomplicated malaria is based on the following WHO recommendations: *in low risk areas* - history of exposure to malaria, fever in last 3 days with no features of severe disease; *in high risk areas*, history of fever in last 1 day, or in children, presence of palmar pallor (Hb < 8 g/dl). Prompt and appropriate antimalarial therapy at this stage when there is no organ dysfunction can ensure a rapid and complete recovery. If not, the increasing parasite burden may lead to organ dysfunction which may become potentially life threatening (*severe malaria*).

**Severe malaria**

Severe malaria is defined as the presence of ≥1 complications (Table 1) and *P. falciparum* or *P. vivax* parasitemia and absence of an identified alternative cause. The definition is same for *P. vivax* and *P. falciparum* malaria but no parasite density thresholds are described for *P. vivax*. About 1% of symptomatic infections complicate into severe malaria. The severity of malaria, like the clinical presentation, also depends on characteristics of the agent-vector-host triad (Figure 2). Severe malaria, attributed mainly to *P. falciparum* has been increasingly seen to be caused by *P. vivax* leading one to suspect if ‘benign tertian malaria’ is benign. Multiple studies have shown that *P. vivax* is as capable as *P. falciparum* to cause virtually any complication that defines severe malaria and has similar mortality rates. Atypical presentations ranging from viral hepatitis-like presentation, acute abdomen, gastrointestinal bleed, generalized edema, hyperglycemia to rarely, subacute intestinal obstruction, hemiplegia, severe headache and ptosis can be seen.

![Figure 2: Factors affecting the clinical presentation of malaria](image-url)
Table 1: Features of severe P. falciparum malaria

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. Impaired consciousness</td>
<td>Glasgow Coma Score &lt; 11 in adults or Blantyre Coma Score &lt; 3 in children</td>
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<tr>
<td>2. Prostration</td>
<td>Generalized weakness - unable to sit, stand or walk without assistance</td>
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<tr>
<td>3. Multiple convulsions</td>
<td>More than two episodes within 24 hours</td>
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<tr>
<td>4. Shock</td>
<td>Compensated shock: Capillary refill ≥ 3 seconds, but no hypotension. Decompensated shock: Systolic BP &lt; 70 mm Hg in children or &lt; 80 mm Hg in adults, with evidence of impaired perfusion.</td>
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<tr>
<td>5. Acidosis</td>
<td>Base deficit of &gt;8 mEq/L or a plasma bicarbonate level of &lt;15 mmol/L or venous plasma lactate ≥5 mmol/L, manifesting clinically as rapid, deep, labored breathing</td>
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<tr>
<td>6. Hypoglycemia</td>
<td>Blood or plasma glucose &lt;2.2 mmol/L (40 mg/dl)</td>
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<tr>
<td>7. Pulmonary edema</td>
<td>Radiologically confirmed or SpO2 &lt;98% on room air with a respiratory rate &gt;30/minute</td>
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<tr>
<td>8. Severe malarial anemia</td>
<td>Hb ≤ 5 g/dl or hematocrit ≤15% in children &lt;12 y of age, Hb ≤ 7 g/dl or hematocrit ≤20% in adults with parasite count &gt;10,000/μL</td>
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<tr>
<td>9. Significant bleeding</td>
<td>Recurrent or prolonged bleeding from nose, gums or venepuncture sites; hematemesis or melena</td>
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<tr>
<td>10. Jaundice</td>
<td>Plasma or serum bilirubin &gt;50 μmol/L (&gt;3 mg/dl) with parasite count &gt;100,000/μL</td>
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<tr>
<td>11. Renal impairment</td>
<td>Plasma/serum creatinine &gt;265 μmol/L (&gt;3 mg/dl) or blood urea &gt;20 mmol/L</td>
</tr>
<tr>
<td>12. Hyperparasitemia</td>
<td>P. falciparum parasitemia &gt;10%</td>
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</table>

Complications and organ system involvement

Cerebral malaria:

It is defined as coma lasting at least 1 hour after termination of a seizure or correction of hypoglycemia with asexual forms of P. falciparum in blood with no other cause to explain the coma. Cerebral malaria is a medical emergency which is rapidly reversible with few sequelae if diagnosed and managed on time. Prompt diagnosis demands an accurate peripheral blood film (PBF) assessment with reliable exclusion of other causes. Incidental parasitemia in endemic areas may pose a problem interfering with the specificity of the diagnosis by PBF. In a post mortem study of cerebral malaria in Malawi, 24% of patients had other causes. Mechanisms of brain injury in cerebral malaria include parasite sequestration causing hypoxia-ischemia; cytokines, chemokines and excitotoxicity; and endothelial activation, apoptosis, blood-brain barrier dysfunction, and intracranial hypertension.
Encephalopathy is the cardinal feature of severe malaria, and besides being caused by Cerebral malaria *per se* and and co-infections like viral encephalitis, it is often caused by easy to recognize and treat etiology such as hypoglycemia, seizures (postictal or non-convulsive status epilepticus), electrolyte imbalances (hypo or hypernatremia) or metabolic acidosis. These patients regain consciousness within a few hours after resuscitation and outcome depends on timing of treatment. If encephalopathy is due to a prolonged post-ictal state, patients usually regain consciousness within 6 hours and have a good neurological recovery. On the other hand, if it is due to a covert status epilepticus, the neuro-cognitive outcome will be variable. If coma lasts more than 24-48 hours, it is commonly associated with raised intracranial pressure (ICP) and has a worse neurological outcome.

Studies have shown that up to 80% of patients with cerebral malaria are admitted with seizures and seizures recur in 60% during admission. There may be raised ICP or brainstem signs (abnormalities in posture, pupil size and reaction, ocular movements or abnormal respiratory patterns). Retinopathy is seen in 2/3rd of children with clinically defined cerebral malaria.\(^{23,24}\) It has 3 components: retinal whitening, vessel changes, and retinal hemorrhages. It is most readily appreciated in fully dilated pupils with thorough direct ophthalmoscopic examination and may be the only clinical feature to differentiate malarial and non-malarial coma. It has both diagnostic and prognostic significance as mortality is highest in children with papilledema and retinopathy, compared to those with retinopathy alone and those with normal fundus.\(^{25,26}\) Retinal signs resolve over 1 to 4 weeks without sequelae.\(^{25}\)

The commonest neurological sequelae in survivors of cerebral malaria are cognitive sequelae in 14-25% of children. Predictors for the development of these sequelae include hypoglycemia, seizures, depth and duration of coma and hyporeflexia. Other sequelae described include speech and language impairment (11.8%), epilepsy (10%) and behavior and neuropsychiatric disorders.\(^{22}\)

### Cardiovascular complications

A wide range of cardiovascular complications have been reported, including subclinical electrocardiographic changes, raised cardiac markers, shock and fatal myocarditis.\(^{27-29}\) Shock can be due to hypovolemia, microvascular changes or myocardial dysfunction. Though absolute or relative hypovolemia is always a component of every child with shock, it is important to remember that changes at a microvascular level (like sequestration, endothelial dysfunction and changes in blood rheology) are more important in children with severe malaria and shock;\(^{30}\) hypovolemia is relatively mild and not commensurate with degree of end organ damage.\(^{31}\)

Myocardial dysfunction is known in severe malaria.\(^{32}\) Increased pulmonary pressures and myocardial wall stress that has been documented in severe malaria supposedly occur from the pathophysiologic cascade from intravascular hemolysis, NO depletion and consequent cardiopulmonary effects.\(^{33}\) A prospective study in Ghanaian children with severe malaria showed increased cardiac index (CI) on day 0 compared to day 42 correlated negatively with hemoglobin but not with impaired tissue perfusion parameters or metabolic acidosis.\(^{34}\) Parasite levels had a significant influence on metabolic acidosis but not on CI. Changes in cardiac function, hemoglobin levels and metabolic acidosis were most prominent in children below 2 years. There are several case reports of peripheral gangrene in both *P. vivax* and *P. falciparum* malaria.

### Pulmonary complications

Pulmonary complications presenting with respiratory distress are seen in up to 40% of children with severe *P. falciparum* malaria.\(^{35}\) Causes ascribed include respiratory compensation
of metabolic acidosis, noncardiogenic pulmonary edema, concomitant pneumonia and severe anemia. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are important complications in severe *P. falciparum* malaria as well as in *P. vivax* and *P. ovale* malaria. ARDS can develop either at initial presentation or after initiation of treatment when the parasitemia is falling and the patient is improving. Increased alveolar capillary permeability resulting in intravascular fluid loss into the lungs appears to be the key pathophysiologic mechanism. *P. falciparum* malaria with severe metabolic acidosis or acute pulmonary edema is known to present with a clinical picture of ‘pneumonia’, hence a high index of suspicion in endemic areas is essential.

**Hyperparasitemia**

Definition of hyperparasitemia is controversial, with lower cutoffs being suggested over the years. The WHO defined hyperparasitemia as a parasite index of >2% in low transmission areas and >5% in high transmission areas. As symptoms have been seen to develop with lower parasite indices, studies have suggested cutoffs as low as 0.5% to define hyperparasitemia. A higher parasite load accelerates the pathological process, increases the risk of severe malaria, organ failure, and antimalarial drug resistance.

**Hypoglycemia**

Hypoglycemia (blood sugar <2.2 mmol/l or <40 mg/dl) is a defining feature of severe malaria and the most frequent metabolic complication. It indicates a poor prognosis, predominantly when accompanied by acidemia (pH <7.3) or hyperlactatemia (lactate >5 mmol/l) and is an independent risk factor for mortality. A random blood sugar estimation using a point-of-care glucose device is mandatory at admission in all children with suspected malaria for timely recognition and prevention.

**Acute kidney injury (AKI)**

Malaria is an important cause of AKI in the PICU. It has been seen mostly with *P. falciparum* though *P. vivax* is increasingly noted to cause renal impairment. It is less common in younger children as compared to non-immune adults and older children with *P. falciparum* malaria. Several hypotheses have been proposed including mechanical obstruction by infected erythrocytes, immune mediated glomerular and tubular pathology, fluid loss due to multiple mechanisms and alterations in the renal microcirculation. Disseminated intravascular coagulation (DIC), jaundice and parasite density (≥3+) were found to be significant factors contributing to mortality in children with AKI.

**Anemia**

Definitions for anemia in malaria are given in Table 1. Mechanisms leading to anemia include direct and indirect destruction of parasitized and non-parasitized RBC, immune-complex mediated hemolysis, suppression of erythropoiesis, dyserythropoiesis, and significant bleeding. Pre-existing micronutrient deficiency prevalent in malaria endemic areas also contributes to the anemia.

**Diagnosis**

Timely diagnosis and management of malaria is a continuing challenge. Differentiating malaria from several other infections in malaria endemic areas which present at the same time of the year and initiating initial, empirical management in such critically ill children in crowded emergency rooms is a huge challenge. Overlapping clinical presentations adds to difficulties in arriving at specific diagnoses. The ISCCM guidelines on management of tropical fevers classify the clinical presentations of tropical fever into 5 categories viz. undifferentiated fever, fever with rash/thrombocytopenia, fever with ARDS, febrile encephalopathy, and fever with multiorgan
dysfunction. Malaria with its protean manifestations figures among the common causes in each of these categories. Hence a diagnosis of malaria based on clinical features alone can lead to overtreatment. All suspected cases of malaria should undergo either a parasitological test (light microscopy) or rapid diagnostic test (RDT) to confirm the diagnosis.

**Light microscopy**

Light microscopic examination of a PBF is considered the gold standard test. Thick smears are more sensitive for detecting the presence of malaria parasites, while thin smears are useful for detecting the species. Sensitivity is about 75% for a single thick blood film; it is lower in those with immunity, non-falciparum malaria, partially treated malaria or low-level parasitemia. Smears are positive if about 50-100 parasites/ml are present, though experienced technicians may be able to detect even 5 parasites/ml. Blood should be used as soon as possible to minimize morphological changes in the parasites.

**Rapid diagnostic tests**

The advent of RDTs has dramatically improved patient management in the emergency room (ER). RDTs are lateral flow immunochromatographic antigen-detection tests, which rely on the capture of dye-labeled antibodies to produce a visible band on a strip of nitro-cellulose. With malaria RDTs, the dye-labeled antibody first binds to a parasite antigen, and the resultant complex is captured on the strip by a band of bound antibody, forming a visible test line (T). The control line (C) gives information on the integrity of the antibody-dye conjugate. Parasite antigens used here are pHRP2 (*P. falciparum* histidine rich protein 2, specific for *P. falciparum*), pLDH (Plasmodium lactate dehydrogenase - species specific LDH for *P. falciparum* and *P. vivax*, and a pan malarial LDH), and pAldolase (pan malarial antigen). As we encounter both *P. falciparum* and non-falciparum infections, combination RDTs that detect all species and can distinguish *P. falciparum* from non-falciparum are preferred.

Advantages of RDTs are they are quick, easy, relatively inexpensive and reliable (overall 80-95% sensitivity and 85% specificity). Disadvantages are they do not provide information about parasite density and continue to be positive 2-3 weeks after disappearance of the parasite. Hence, they are not useful to detect a recrudescence or monitor resolution. Also, RDTs perform better at high parasite concentrations and are variable with a low parasitemia. Evidence says that algorithms incorporating RDTs can substantially reduce antimarial prescribing if health workers adhere to test results. Negative RDTs are equally important to improve overall health outcomes in febrile children. A recent systematic review revealed that the two RDTs performed satisfactorily for the diagnosis of *P. falciparum*, but the pLDH tests had higher specificity, whereas the pHRP2 tests had better sensitivity. A combination of both antigens might be a more reliable approach for the diagnosis of malaria.

**Polymerase chain reaction**

Polymerase chain reaction (PCR) is the most reliable method for detecting parasites (97% sensitivity and 100% specificity) and is especially helpful in low-level infections with a limit of detection of 0.5-5 parasites/μL. They are, however, more expensive, prone to contamination, and require sophisticated equipment and hence primarily used in research.

**Management**

The main objectives of treatment of severe malaria are to prevent death, disabilities and recrudescent infection. Management comprises clinical assessment of the patient, specific antimalarial treatment, and supportive care. Here we discuss the specific treatment using antimalarial drugs as well as supportive care of critically ill children with severe malaria in PICU.
Specific treatment: Antimalarial drugs

Management of uncomplicated malaria mainly involves administration of antimalarial drug/s and symptomatic treatment (Table 2). Management of severe malaria is a medical emergency as it can lead to death within hours. Achieving therapeutic concentrations of a highly effective antimalarial drug as soon as possible is the main goal. The core principles of antimalarial usage are early initiation, rational use, appropriate combination therapy, and appropriate weight based dosing.

Two important groups of antimalarial drugs are available today- artemisinin derivatives (artesunate, artemether), and cinchona alkaloids (quine, quinidine, chloroquine). A Cochrane systematic review in 2012 incorporating evidence from 8 randomized controlled trials (1664 adults, 5765 children) concluded that use of artesunate reduced mortality by 40% in adults and 25% in children. A small increase in neurological sequelae was observed, which were however self-limited and no difference was notable by day 28. Artemisinin derivatives are more effective, simpler, and safer than the cinchona alkaloids. Overall, artesunate is more effective than artemether which is more effective than quinine. For pre-referral administration, intramuscular (IM) artesunate is more effective than rectal artesunate which is more effective than IM artemether, followed by IM quinine in children <6 years. In children > 6 years, rectal artesunate is not recommended, otherwise the same comparison holds true.52

The combination drugs available in artemisinin combination therapy (ACT) are artesunate+sulfadoxine-pyrimethamine, artesunate+amodiaquine, artemether+lumefantrine, dihydroartemisinin+piperazine, Artesunate+mefloquine (avoided in cerebral malaria), and artesunate+doxycycline or clindamycin.13 The dose of artesunate is 3 mg/kg/day for children weighing <20 kgs and 2.4 mg/kg/day for larger children. Younger children require a higher dose due to larger volume of distribution. Route of ACT must be parenteral for atleast 24 hours and later, once patient starts taking orally, can be converted to oral to complete a 3-day course.

<table>
<thead>
<tr>
<th></th>
<th>Uncomplicated</th>
<th>Severe</th>
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<tbody>
<tr>
<td><strong>P. vivax</strong></td>
<td>Areas with chloroquine susceptibility: chloroquine or ACT</td>
<td>ACT +Primaquine</td>
</tr>
<tr>
<td></td>
<td>Areas with chloroquine resistance: ACT</td>
<td></td>
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<tr>
<td></td>
<td>Primaquine: 0.25-0.5 mg/kg/d for 14d</td>
<td></td>
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<tr>
<td></td>
<td>Except in &lt;6months and known G6PD deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G6PD deficiency: 0.75 mg/kg/week for 8 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G6PD status unknown and unavailable: individualize</td>
<td></td>
</tr>
<tr>
<td><strong>P. falciparum</strong></td>
<td>ACT+single dose of primaquine in low transmission areas (0.25 mg/kg)</td>
<td>ACT+single dose of primaquine in low transmission areas (0.25 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>No G6PD testing required</td>
<td>No G6PD testing required</td>
</tr>
<tr>
<td><strong>Mixed</strong></td>
<td>ACT+Primaquine (as for P. vivax)</td>
<td>ACT+Primaquine (as for P. vivax)</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>As for uncomplicated P. falciparum</td>
<td>As for complicated P. falciparum</td>
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Chloroquine resistance in *P. vivax*: current scenario

Artesunate plus sulfadoxine-pyrimethamine remains a safe and effective for uncomplicated *P. falciparum* malaria. Chloroquine remains a safe and an effective for uncomplicated *P. vivax* malaria. The epicentres of chloroquine-resistance are the eastern provinces of Indonesia and in the past 5 years, convincing evidence has been reported from South America and some Asian countries. Reports from the Indian subcontinent (India, Afghanistan, and Pakistan) are mostly reassuring.53

Intensive care issues

As in any critically ill child, irrespective of the underlying diagnosis, initial assessment and stabilization are paramount to ensure a good outcome. Stabilization starts with assessment and management of airway, breathing, and circulation.

Airway and breathing:

Tachypnea may be due to pulmonary complications, shock or just ‘silent’ tachypnea (acidotic breathing) due to acidosis, and severe anemia. Children with tachypnea, pallor, or shock should be promptly started on oxygen through nasal prongs or face mask. Indications for endotracheal intubation and ventilation in children with severe malaria are Glasgow Coma scale score < 8, status epilepticus, ALI/ARDS, shock, pulmonary edema, and myocardial dysfunction.

Circulation:

Assessment and optimization of volume status is one of the foremost priorities in children with severe malaria. It is well known that no single parameter from clinical examination, central venous pressure, echocardiography to advanced thermodilution techniques can reliably assess volume status irrespective of the underlying disease. Fluid resuscitation in critically ill children has been an intense debate. The landmark ‘FEAST trial’ on more than 3000 African children suffering from severe febrile illness (more than half of whom had malaria) showed that fluid boluses significantly increased 48 hour mortality irrespective of type of fluid.54 Cardiovascular collapse rather than fluid overload appeared to contribute most to excess deaths with rapid fluid resuscitation.55

Thus, in the absence of uniform recommendations, pediatric intensivists need to remember following points in this regard. Each child must be assessed individually with a combination of clinical, bedside, and laboratory parameters. Crystalloids are the fluids of choice as evidence is lacking for colloids/balanced salt solutions. Fluid boluses should be given with extreme caution only if there is hypotension. Presence of acute kidney injury or severe acidosis unresponsive to fluids is an indication for renal replacement therapy. Urgent blood transfusion is important if hemoglobin is <7 gm%. Children presenting with high grade fever and hemodynamic instability should receive intravenous broad-spectrum antibiotics as coexistent bacterial sepsis is always a consideration.13

Management of cerebral edema:

Management of cerebral edema remains largely supportive. Therapeutic measures include stabilization of airway, breathing, and circulation; neutral neck position, head end elevation by 30°, adequate sedation and analgesia, minimal stimulation, and seizure control; and maintenance of euthermia and euglycemia. Short-term hyperventilation to achieve PCO2 ~30 mm Hg using bag ventilation can be done if signs of impending herniation are present. A Cochrane systematic
review to study the role of mannitol in children with cerebral malaria found only one randomized trial and concluded that short of further trials mannitol cannot be recommended as a general adjunct for treating cerebral malaria. Once the child is shifted to PICU, invasive ICP monitoring would be valuable option in guiding therapy. Studies have shown that pediatric intensivists can safely and successfully perform burr holes at bedside for establishing ICP monitoring.

Adequate control of seizure and status epilepticus is essential and use of antiepileptic drugs is like other diseases. A detailed approach to treatment of SE can be found elsewhere. A single IM dose of phenobarbitone at 20 mg/kg increased mortality; hence it should not be given without respiratory support. There is no role for prophylactic anticonvulsants.

**Hyperparasitemia and role of exchange transfusion:**

Exchange transfusion (ET) rapidly reduces the parasitic index (PI) and expected to cause survival benefit. Whether it is more effective when compared to chemotherapy alone resulting in any survival benefit is not clear. Evidence in children is scarce. The WHO guidelines thus do not make any recommendation regarding exchange transfusion. In a few studies that demonstrated the benefits of ET in children with hyperparasitemia, volume used has been variable, from a partial ET at 40 ml/kg to double volume ET at 160 ml/kg. On an average around 4/5th of preexchange PI was reduced by ET irrespective of the preexchange PI. Reduction in PI did not depend on percentage of blood volume exchanged or the chemotherapeutic agent used (quinine or artisunate). All the children survived intact without and sequelae and required around 5-10 days to get a discharge. Adverse events reported during the procedure include hypocalcemia, oozing from lines, and bradycardia. The procedure, being labor-intensive method may be used in complicated malaria with hyperparasitemia or multiorgan dysfuction which fail to respond to chemotherapy alone, preferably in an intensive care setting.

**Treatment and prevention of hypoglycemia:**

Rapid recognition and correction of hypoglycemia is extremely important. A bolus (5 ml/kg) of 10% dextrose solution should be given by a rapid intravenous push. RBS should be rechecked after 30 minutes. It is important to give 10% dextrose in normal saline or Ringer’s lactate for maintenance infusion to prevent hypoglycemia. Routine blood glucose measurement, frequent monitoring, and early recognition are mandatory.

**Acute kidney injury:**

Loop diuretics can convert an oliguric renal failure to non-oliguric renal failure without affecting outcome of the disease though the conversion reduces the risk of volume overload. There is little evidence on beneficial effect of vasoactive drugs. Nephrotoxic drugs such as ACE inhibitors, NSAIDs, aminoglycosides, cephalosporins should be avoided. Early institution of renal RRT is beneficial. More than half of patients with malaria in different series required RRT. Early RRT is often indicated to take care of hypercatabolic state. Although peritoneal dialysis may be less effective because of the complicating circulatory disturbances, practically it may be the only available dialysis modality in children. Beneficial effects of continuous peritoneal dialysis have been observed in patients of malarial AKI. A comparative study to evaluate efficacy of hemofiltration versus peritoneal dialysis showed significant lower mortality with hemofiltration (15 vs. 47%). Rate of resolution of acidosis and decline in the serum creatinine concentration with hemofiltration were more than twice than with peritoneal dialysis. RRT was required for a significantly shorter period with hemofiltration. In adults with AKI (of all causes) indicated intermittent hemodialysis and continuous RRT appear
to lead to similar clinical outcomes in ARF patients. Majority of antimalarial drugs are metabolized in liver and excreted through kidneys. What happens to their metabolism and excretion when both the organs are involved needs to be clearly understood for effective management and prevention of adverse drug reactions.

**Pulmonary complications:**
Timely intubation and mechanical ventilation, hemodynamic stabilization, and optimizing fluid balance along with chemotherapy are the cornerstones of management. Coexistent bacterial sepsis is frequently present in patients with malarial ARDS though an obvious focus may not be evident, necessitating broad spectrum antibiotics. As mortality is high, timely intervention in PICU is life saving.

**Anemia:**
All children with hemoglobin <7 gm% should be urgently transfused.

**Outcome of severe malaria**
A study on Gambian children showed that cold peripheries, deep coma, hypoglycemia, elevated admission urea levels and multiple convulsions were the strongest predictors of mortality. In a large prospective study on 1682 Indian children with confirmed malaria, 374 subjects had severe malaria. Case fatality rate was 12%. Multiple regression analysis showed that respiratory distress, coma, multiple organ dysfunctions, and hyperparasitemia were the major predictors of death. Another large study on 1320 patients with complicated malaria, 22% of them children had an overall case fatality rate of 4.3%, being significantly higher in children (12.3%) compared to adults (2%). Major causes of death were cerebral malaria (45.6%), malaria with a respiratory infection (19.3%) and anemia (10.5%). Another study from South India on 922 adults showed that 21.8% had more than 7 days of hospitalization, 8.6% required intensive care, and 1.2% died. More than 3 days history of fever, leukocytosis, severe thrombocytopenia, and renal failure were predictors of prolonged hospitalization and/or intensive care.

**Conclusion**
Severe malaria is associated with high mortality and morbidity in children. Management of severe malaria is a medical emergency which requires high index suspicion, rapid diagnosis, and aggressive management. The diagnosis should be prompt and investigations should include peripheral blood smear and rapid diagnostic tests depending upon availability and expertise. Antimalarial drugs should be administered promptly according to the weight of child. Artesunate combination therapy is recommended in malaria. Supportive treatment is of utmost importance and includes control of airway, breathing and circulation; management of cerebral edema, raised ICP and status epilepticus, anemia, and acute kidney injury; maintaining adequate intravascular volume; and vigilant monitoring of cardiovascular, respiratory, renal, neurological system, and fluid and electrolyte status to detect complications and their treatment.

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References: