

# Severe Malaria in Africa

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**Abstract** Malaria is responsible for about 1 – 2 million deaths annually in Africa. These deaths occur mainly in children aged six months to 5 years and result almost entirely from the severe malaria. In most African setting, severe malaria is mostly a disease of childhood, however, in situation of unstable transmission, adults can also be subjected to severe malaria. Criteria for malaria severity were recently revised by WHO. They include clinical (impair consciousness, generalized convulsions, respiratory distress, renal failure, acute pulmonary oedema — etc), and biological (severe anaemia, hypoglycaemia, acidosis —etc) criteria. The clinical/biological manifestations may be different in children and in adults. The standard treatment for severe malaria in most African countries is quinine given by intravenous infusion. Intra-muscular injections of artemether or arteether, two artemisinin derivatives have shown to be appropriate alternative to quinine. Studies conducted in Cameroon, showed that presenting signs and symptoms of severe malaria varied from one study to another, but were not different from the ones reported in the literature; Quinine appeared to be very efficacious in the treatment of severe malaria in Cameroon. Artemether and arteether were as effective as quinine and are promising alternatives to quinine in case of allergy to the later.

**Introduction** Malaria is still the most frequent and the most lethal endemic diseases in developing countries. According to the World Health Organization (WHO), malaria is responsible for about 1 – 2 million deaths annually in Africa. These deaths occur mainly in children aged six months to 5 years and result almost entirely from the severe form of *P falciparum* malaria. In addition, recent estimates of the global burden of malaria showed increasing levels of malaria morbidity and mortality, probably due to the widespread resistance of *Plasmodium falciparum* to conventional antimalarials.

**Presentation of severe malaria** In most African setting, severe malaria is predominantly a disease of childhood. However, in situations of unstable transmission (Sahelian part of Africa, urban areas—), adults can also be subjected to severe malaria. The criteria for malaria severity were revised by WHO in 2000 and include:

- Clinical criteria: impaired consciousness (Glasgow  $\leq$  9 for adults or Blantyre  $\leq$  2 for children), generalized convulsion, prostration (extreme weakness), metabolic acidosis with signs of respiratory distress, renal failure (diuresis  $<$ 15 ml /kg /day for children or  $<$  400ml/24hrs for adults), acute pulmonary oedema, circulatory collapse (systolic blood pressure  $\leq$  80mm Hg with peripheral signs of circulatory failure), abnormal bleeding (retinal hemorrhages—), jaundice, and macroscopic haemoglobinuria.
- Biological criteria: severe anaemia (haematocrit  $<$  15% or haemoglobin

**Table 1:** Comparison of frequency of signs/symptoms of severe malaria between children and adults (WHO 2001)

<b>Signs or symptoms</b>	<b>children</b>	<b>Adults</b>
Convulsions	+++	++
Resolution of coma	1-2 days	2-4 days
Neurological sequelae	>10 %	< 5 %
Jaundice	rare	++
Hypoglycaemia	+++	+
Pulmonary oedema	Rare	+
Renal failure	+	++
Respiratory distress	++	+
Abnormal bleeding	rare	+++

< 5g/dl for children / haematocrit < 20% or haemoglobin < 7g/dl for adults), hypoglycaemia (blood sugar < 2.2 mmol/L or < 40mg/dl), acidosis (bicarbonates < 15 mmol/L; Ph < 7.35), hyperlactataemia (plasmatic lactate > 5mmol/L), hyperparasitaemia (parasitaemia 4% in non immune subjects), renal failure (creatinemia > 265 umol/l or 3mg/dl).

The clinical/biological manifestations may be different in children and in adults. In children, the most frequent and lethal forms of *P. falciparum* infection are cerebral malaria and severe anaemia. In adults, cerebral malaria, renal failure and jaundice represent the severe forms of malaria (table1).

Adverse prognostic risk factors in severe malaria in African children include deep coma, multiple and prolonged convulsions, age below 3 years, metabolic acidosis and severe anaemia. However, these vary from one study to another. Cerebral malaria is the most lethal form of malaria with mortality ranging from 10% to 50% in studies reported in the literature. We conducted a study in children with cerebral malaria in Yaounde to compare the efficacy and safety of arteether versus quinine from 1996 to 1998. The mortality rate was 27.45% and 15.68% in the quinine and arteether groups respectively;

### **Management of severe malaria**

The standard treatment for severe malaria in most African countries is quinine given by intravenous infusion. However, quinine has some disadvantages including the frequent appearance of sterile abscesses and sciatic nerve injuries associated with IM injections, the need for multiple daily doses, the induction of hypoglycaemia, cardiac arrhythmia, and black water fever. Intra-muscular injections of artemether or arteether, two artemisinin derivatives have shown to be appropriate alternative to quinine (Fargier et al 1999, Murphy et al 1996, Moyou et al 2001). Studies are going on to evaluate the efficacy and safety of rectal and injectable artesunate for the treatment of severe malaria in Africa (Barnes et al 2004; Nealon et al 2002). Preliminary results are promising. These artemisinin derivatives are safe, well tolerated and their use is easy. Therefore, they are promising alternative drugs for the treatment of severe malaria in zones where quinine efficacy is reduced, in case of allergy to quinine, and in rural areas where monitoring facilities are most often absent.

Supporting treatment to correct or to prevent the adverse risk factors should be associated to the specific antimalarial drug treatment when needed.

## **Severe Malaria in Cameroon**

### *1 - Presentation of the disease:*

Three studies on severe malaria were conducted in Cameroon: the first study took place in the paediatric department of the Yaounde Central Hospital from July to December 1990 (Tchokoteu et al 1994). Thirty six (36) children were included. Signs and symptoms at admission included: coma in all the patients, convulsion in 91.7%, hypoglycaemia in 2.8%. The children were treated with quinine salt. 5.6% of them died and among the survivors, 16.7 had neurological sequelae.

The second study was carried out in the intensive care department of the Yaounde Central Hospital between June 1993 and June 1994 (Fargier et al 1999). Ninety (90) adults and adolescents were enrolled. In addition to the impairment of consciousness, the following signs of severe malaria were noted at presentation: renal failure (1%), hypoglycaemia (8.9%), severe anaemia (3.3%), hyperparasitaemia (4.4%). The patients were treated either with quinine or with artemether. The two drugs were equally effective and no patient died.

The third study was carried out between November 1995 and November 1997 in the paediatric ward of the same hospital and 102 children were enrolled. All the patients had cerebral malaria with a Blantyre coma score of 2 or less. In addition to the above, the following signs of severe malaria were noted at presentation: repeated convulsion (94%), severe anaemia (36%), hypoglycaemia (18.6%). Patients were treated either with quinine or with arteether. There was an overall mortality rate of 21.6% with 15.7% in the arteether group versus 27.4% in the quinine group. Independent of the treatment received, the deep coma was the only adverse prognostic risk factor noted. (Moyou Somo et al 2001). Two patients in the arteether group and 1 in the quinine group survived with neurological sequelae. Arteether was shown to be at least as effective as quinine for the treatment of cerebral malaria in children in Yaounde.

### *2 - Management of severe malaria in Cameroon (recommendations of the National Malaria Control Programme).*

The recommended drug for the treatment of severe malaria in Cameroon is quinine or an artemisinin derivative in case of allergy to quinine.

#### a) – Treatment with quinine:

- Regimen 1: (with loading dose) This regimen entails a loading dose of quinine and is administered in two daily infusions:

Loading Dose: 16 mg/kg of quinine base (or 20mg/kg of quinine salt) in 5 % or 10% glucose with electrolytes (NaCl, KCl, Calcium gluconate), to be run in 4 hours.

Maintenance Dose: 12 hours after the onset of the loading dose, 8 mg/kg of quinine base or 10mg/kg of quinine salt in 5 % or 10% glucose to be run in 4 hours every 12 hours.

- Regimen 2 (without loading dose): This treatment is recommended in three infusions per day as follows: 8mg /kg/ of quinine base or 10 mg /kg of quinine salt in four-hour infusions, every 8 hours

**NB:** \* Whatever the chosen regimen, it is recommended to switch to oral treatment as soon as the patient is able to swallow.

\* If the patient is a pregnant woman, or if he/she had taken quinine within the previous 24 hours or Mefloquine within the 7 previous days, it is recommended to use regiment 2 (without loading dose)

b) Treatment with artemisinin derivatives:

In case of allergy to quinine, Artemether or arteether is recommended and should be given by intramuscular injection of 3.2 mg/kg on day 0, followed by 1.6 mg/kg on days 1 to 4.

c) – Complementary treatment:

Common complications of severe malaria (hyper-pyrexia, seizures, life threatening anaemia, coma), are managed according to guidelines published by WHO (2001)

**Conclusions**

The three studies conducted in Cameroon, showed that presenting signs and symptoms of severe malaria varied from one study to another, but were not different from the ones reported in the literature. In all the studies, quinine appeared to be very efficacious in the treatment of severe malaria in Cameroon. Artemether and arteether were as effective as quinine and are promising alternatives to quinine in case of allergy to the later. The recommendations of the National Malaria Control Programme are in accordance with the above findings.

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