

The following sections, from 8.4 to 8.6 have been revised to reflect the change of treatment of severe falciparum malaria in children

8.4 Specific antimalarial treatment

It is essential that effective, parenteral (or rectal) antimalarial treatment in full doses is given promptly in severe malaria. Two classes of medicines are available for the parenteral treatment of severe malaria: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate, artemether and artemotil). Parenteral chloroquine is no longer recommended for the treatment of severe malaria, because of widespread resistance. Intramuscular sulfadoxine-pyrimethamine is also not recommended.

8.4.1 Artemisinin derivatives

Various artemisinin derivatives have been used in the treatment of severe malaria, including artemether, artemisinin, artemotil and artesunate. Randomized trials comparing artesunate and quinine from South-East Asia show clear evidence of benefit with artesunate. In a multi-centre trial, which enrolled 1461 patients (including 202 children < 15 years old), mortality was reduced by 34.7% in the artesunate group when compared to the quinine group. The results of this and smaller trials are consistent and suggest that artesunate is the treatment of choice for adults with severe malaria.

Until recently there was insufficient evidence to make a similar recommendation in children, from high transmission settings, so the guidelines for this important patient group did not recommend artesunate above treatment with either artemether or quinine. This has now changed with the publication of the AQUAMAT trial*, a multi-centre study conducted in African children hospitalized with severe malaria. This very large randomized controlled trial, which enrolled 5425 children < 15 years of age across Africa, showed a significant mortality reduction by 22.5% in the artesunate group when compared to the quinine group. The incidence of convulsions, coma, and hypoglycaemia developing after hospital was also significantly reduced. Importantly there was no significant difference in the incidence of severe neurological sequelae.

* Artesunate vs. quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label randomized trial. *Lancet* 2010; 376: 1647–57

BOX 8.1a

RECOMMENDATION: IV/IM artesunate treatment for severe *P. falciparum* malaria in adults

- ▶ **Intravenous artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults.** *Strong recommendation, high quality evidence*

GRADE evaluation (see Annex 8, Table A8.1.1)

Intravenous artesunate has been shown to significantly reduce the risk of death from severe malaria compared to intravenous quinine (6 trials, 1938 participants; RR 0.62, 95% CI 0.51–0.75; high quality evidence).

Intravenous artesunate was associated with a lower risk of hypoglycaemia (2 trials, 185 participants; RR 0.46, 95% CI 0.25–0.87; low quality evidence).

No difference has been shown in the risk of serious neurological sequelae (2 trials, 1253 participants, very low quality evidence).

Other consideration

- Artesunate offers a number of programmatic advantages over quinine in terms of not requiring rate-controlled infusion or cardiac monitoring.

BOX 8.1b

RECOMMENDATION: IV/IM artesunate treatment for severe *P. falciparum* malaria in children

- ▶ **Intravenous artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in children.** *Strong recommendation, high quality evidence*

Intravenous or intramuscular artesunate has been shown to reduce significantly the risk of death from severe malaria compared to intravenous quinine (4 trials, 5765 participants; RR 0.76, 95% CI 0.65–0.90; high quality evidence).

Intravenous artesunate was associated with a lower risk of hypoglycaemia (4 trials, 5765 participants; RR 0.62, 95% CI 0.45–0.87; high quality evidence).

No difference has been shown in the risk of serious neurological sequelae at day 28 (3 trials, 5163 participants, moderate quality evidence).

Other consideration

- Artesunate offers a number of programmatic advantages over quinine in terms of not requiring rate-controlled infusion or cardiac monitoring.

8.4.2 Quinine

Quinine treatment for severe malaria was established before modern clinical trial methods were developed. Several salts of quinine have been formulated for parenteral use, but the dihydrochloride is the most widely used. Peak concentrations following intramuscular quinine in severe malaria are similar to those following intravenous infusion. Pharmacokinetic modelling studies suggest that a loading dose of quinine (i.e. 20 mg salt/kg body weight – twice the maintenance dose) reduces the time needed to reach therapeutic plasma concentrations. The maintenance dose of quinine (10 mg salt/kg

body weight) is administered at 8-h intervals, starting 8 h after the first dose (*see* Annex 9, Section A9.3.2).

Rapid administration of quinine is unsafe. Each dose of parenteral quinine must be administered as a slow, rate-controlled infusion (usually diluted in 5% dextrose and infused over 4 h). The infusion rate should not exceed 5 mg salt/kg body weight per hour.

8.4.3 Quinidine

Quinidine commonly causes hypotension and concentration-dependent prolongation of ventricular repolarization (QT prolongation). Quinidine is thus considered more toxic than quinine and should only be used if no other effective parenteral drugs are available. Electrocardiographic monitoring and frequent assessment of vital signs are required if quinidine is used.

8.5 Follow-on treatment

Following initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial using a full course of an effective ACT (artesunate plus amodiaquine or artemether plus lumefantrine or dihydroartemisinin plus piperazine) or artesunate (plus clindamycin or doxycycline) or quinine (plus clindamycin or doxycycline). Doxycycline is preferred to other tetracyclines because it can be given once daily, and does not accumulate in renal failure. But as treatment with doxycycline only starts when the patient has recovered sufficiently, the 7-day doxycycline course finishes after the quinine, artemether or artesunate course. Where available, clindamycin may be substituted in children and pregnant women; doxycycline cannot be given to these groups. Regimens containing mefloquine should be avoided, if the patient presented initially with impaired consciousness. This is because of an increased incidence of neuropsychiatric complications associated with mefloquine following cerebral malaria.

The current recommendation from experts' opinion is to give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient is about to tolerate oral medication, before giving the oral follow-up treatment.

8.6 Pre-referral treatment options

The risk of death from severe malaria is greatest in the first 24 h, yet, in most malaria endemic countries, the transit time between referral and arrival at health facilities able to administer intravenous treatment is usually prolonged; this delays the commencement of appropriate antimalarial treatment. As during this time the patient may deteriorate or die,

it is recommended that patients be treated with the first dose of one of the recommended treatments before referral (unless the referral time is less than 6 h). Recommended pre-referral treatment options include intramuscular artesunate, artemether, or quinine, or rectal artesunate (*see* Annex 8, Section A8.5). Evidence from recent studies demonstrates that in situations where parenteral medication is not possible and intramuscular injection impractical, using a single dose of rectal artesunate as pre-referral treatment reduces the risk of death or permanent disability in young children.

BOX 8.2

RECOMMENDATION: *pre-referral treatment for severe P. falciparum malaria*

- **If complete treatment for severe malaria (as recommended in Section 8.4) is not possible, patients with severe malaria should be given pre-referral treatment and referred immediately to an appropriate facility for further treatment.**
 - The following are options for pre-referral treatment:
 - rectal artesunate
 - quinine IM
 - artesunate IM
 - artemether IM.
 - In young children of less than 5 years of age, the use of rectal artesunate (10 mg/kg) has been shown to reduce the risk of death and permanent disability.

8.6.1 Pre-referral and continued treatment with rectal artemisinins

The administration of an artemisinin derivative by the rectal route as pre-referral treatment is feasible and acceptable even at the community level.

There is insufficient evidence to show whether rectal artesunate is as good as intravenous or intramuscular options in the management of severe malaria. The recommendation, therefore, is to use artesunate or artemisinin suppositories only as pre-referral treatment and to refer the patient to a facility where complete parenteral treatment with artesunate, quinine or artemether can be instituted. If, however, referral is impossible, rectal treatment should be continued until the patient can tolerate oral medication; at this point, a full course of the recommended ACT for uncomplicated malaria in the locality can be administered.

8.6.2 Dosing for antimalarials given by rectal route

8.6.2.1 *Initial (pre-referral) treatment with rectal artesunate*

The 10 mg/kg body weight single dose of artesunate suppository should be administered rectally as soon as the presumptive diagnosis of severe malaria is made. In the event that an artesunate suppository is expelled from the rectum within 30 min of insertion, a second suppository should be inserted and, especially in young children, the buttocks should be held together for 10 min to ensure retention of the rectal dose of artesunate.

8.6.2.2 Artemether

Doses used have been variable and empiric: 10–40 mg/kg body weight (at 0, 4 or 12, 24, 48 and 72 h). Some studies have given a maintenance dose of one to two thirds of the initial dose.

8.6.2.3 Quinine

The intrarectal dose used in treatment trials in Africa was either 12 mg/kg BW quinine base (as Quinimax[®], a cinchona alkaloid combination containing 96.1% quinine, 2.5% quinidine, 0.68% cinchonine, and 0.67% cinchonidine as gluconate salts) every 12 h without a loading dose, or 8 mg/kg BW every 8 h without a loading dose. The retention and absorption of quinine is dependent on pH. Results with gluconate salts (pH 4.5) cannot be extrapolated to more acidic solutions (such as the dihydrochloride salt, pH 2).

BOX 8.3

Summary of recommendations on the TREATMENT OF SEVERE FALCIPARUM MALARIA

- ▶ **Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with any effective antimalarial first available.**
- ▶ **For adults, artesunate 2.4 mg/kg BW IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment. Artemether, or quinine, is an acceptable alternative if parenteral artesunate is not available: artemether 3.2 mg/kg BW IM given on admission then 1.6 mg/kg BW per day ; or quinine 20 mg salt/kg BW on admission (IV infusion or divided IM injection), then 10 mg/kg BW every 8 h; infusion rate should not exceed 5 mg salt/kg BW per hour.**
- ▶ **For children, artesunate 2.4 mg/kg BW IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment. Artemether, or quinine, is an acceptable alternative if parenteral artesunate is not available: artemether 3.2 mg/kg BW IM given on admission then 1.6 mg/kg BW per day ; or quinine 20 mg salt/kg BW on admission (IV infusion or divided IM injection), then 10 mg/kg BW every 8 h; infusion rate should not exceed 5 mg salt/kg BW per hour.**
- ▶ **Give parenteral antimalarials in the treatment of severe malaria for a minimum of 24 h, once started (irrespective of the patient's ability to tolerate oral medication earlier), and, thereafter, complete treatment by giving a complete course of:**
 - artemether plus lumefantrine,
 - artesunate plus amodiaquine,
 - dihydroartemisinin plus piperaquine,
 - artesunate plus sulfadoxine-pyrimethamine,
 - artesunate plus clindamycin or doxycycline,
 - quinine plus clindamycin or doxycycline.

