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Malaria Treatment Recommendations 2023

31. January 2023

1. Treatment of uncomplicated malaria

	1st-line treatment	Alternative treatment
P. falciparum	▪ **Artemether/lumefantrine (A/L)**🍂◊ (1 tabl. = 20 mg artemether/120 mg lumefantrine) 2 doses/day for 5 days🍂🍂: 0, 8, 24, 36, 48, 60, 72, 84, 96, 108 h 5◆–14 kg: 1 tabl./dose [total 10 tabl.] 15–24 kg: 2 tabl./dose [total 20 tabl.] 25–34 kg: 3 tabl./dose [total 30 tabl.] ≥35† kg: 4 tabl./dose [total 40 tabl.] OR ▪ **Dihydroartemisinin/piperaquine (DHA/PPQ)**🍂Ø (1 tabl. = 40 mg dihydroartemisinin/320 mg piperaquine) 1 dose/day for 3 days = at 0 h, 24 h, 48 h: 5◆–<7 kg: ¼ tabl./dose [total ¾ tabl.] 7–<13 kg: ½ tabl./dose [total 1½ tabl.] 13–<24 kg: 1 tabl./dose [total 3 tabl.] 24–<36 kg: 2 tabl./dose [total 6 tabl.] 36–<75 kg: 3 tabl./dose [total 9 tabl.] >75 kg: 4 tabl./dose [total 12 tabl.]	▪ **Atovaquone/proguanil (A/P)**◊ (1 tabl. = 250 mg atovaquone/100 mg proguanil) 1 dose/day for 3 days = at 0 h, 24 h, 48 h: 11–20 kg: 1 tabl./dose [total 3 tabl.] 21–30 kg: 2 tabl./dose [total 6 tabl.] 31–40 kg: 3 tabl./dose [total 9 tabl.] >40 kg: 4 tabl./dose [total 12 tabl.]† OR ▪ **[Mefloquine**❖ (1 tabl. = 250 mg mefloquine) 25 mg/kg given in 1–4 doses (if ≥2 doses# separate doses by 6–8 h and give the tablets of each dose over 30 min): 5–10 kg: ½–1 tabl. 10–20 kg: 1–2 tabl. 20–30 kg: 2–3 tabl. (#2 + 1 tabl.) 30–45 kg: 3–4 tabl. (#2 + 2 tabl.) 45–60 kg: 5 tabl. (#3 + 2 tabl.) >60 kg: 6 tabl. (#3 + 2 + 1 tabl.) >90 kg: 9 tabl. (#3 + 3 + 3 tabl.) >120 kg: 12 tabl. (#3 + 3 + 3 + 3 tabl.)**]**
P. vivax ***P. ovale*** ***P. cynomolgi***	▪ **Artemether/lumefantrine (A/L)**Δ Dosage analogue to *P.f.*, but 3 day regimen: 0, 8, 24, 36, 48, 60 h OR ▪ **Dihydroartemisinin/piperaquine (DHA/PPQ)** (see *P.f.*)ΔØ OR ▪ **Chloroquine**♂ Initially 10 mg base*/kg p.o. [adult: 600 mg] followed by 5 mg base*/kg p.o. [adult: 300 mg] after 12, 24, 36 h (alternatively: 6, 24, 48 h) ***followed by*** (after ruling out G6PD-deficiency) **Primaquine** 0.5 mg^ base§/kg/day [max. 30 mg] for 14 days **+ if initially treated with A/L: Chloroquine*** adults: 100–150mg/day for 14 days; children: *5–25 kg: 25mg/d, 25–35 kg: 50mg/d, 35–45 kg: 75mg/d* for 14 days OR [***Tafenoquine*** *300 mg single dose*]◈	▪ **Atovaquone/proguanil (A/P)**◊(see *P.f.*) OR ▪ **[Mefloquine**❖ (see *P.f.*)**]** ***followed by*** (after ruling out G6PD-deficiency) **Primaquine** 0.5 mg^ base§/kg/day [max. 30 mg] for 14 days **+ Chloroquine*** adults: 100–150mg/day for 14 days; children: *5–25 kg: 25mg/d, 25–35 kg: 50mg/d, 35–45 kg: 75mg/d* for 14 days
P. malariae	▪ **Dihydroartemisinin/piperaquine (DHA/PPQ)**Ø (see *P.f.*) OR ▪ **Chloroquine** Initially 10 mg base*/kg p.o. [adult: 600 mg] followed by 5 mg base*/kg p.o. [adult: 300 mg] after 12, 24, 36 h (alternatively: 6, 24, 48 h)	▪ **Mefloquine** (see *P.f.*)❖ OR ▪ **[Artemether/lumefantrine** (see *P.f.*)**]**♂♂ OR ▪ **[Atovaquone/proguanil (A/P)**(see *P.f.*)**]**♂♂
P. knowlesi	▪ **Artemether/lumefantrine** (see *P.f.*)‡ OR ▪ **Dihydroartemisinin/piperaquine** (see *P.f.*)‡Ø	▪ **Chloroquine** (see *P.v./o./c./m.*), if unavailable: ▪ **Atovaquone/proguanil or mefloquine** (see *P.f.*)

🍂 prefer A/P if *P.f.* infection was acquired in the Greater Mekong Subregion (Thailand, Laos, Cambodia, Myanmar, Vietnam): resistance related A/L treatment failure rates of ~20% are reported from the Thai-Cambodian border region and resistance related DHA/PPQ treatment failure rates of 44–87% are reported from Cambodia, Thailand, and Vietnam.

🍂🍂 high rates of late treatment failures have been observed in (non-immune) European travellers with uncomplicated *P.f.* malaria receiving the licensed standard 3-day A/L treatment regimen (see p. 3).

◆ Treat infants weighing <5 kg with the same mg/kg body weight target dose as children weighing ≥5 kg.

† Consider adjusting dose in patients >90 kg (see `treatment of uncomplicated malaria in overweight/obese patients´ below).

◊ DHA/PPQ & A/L provide more rapid symptomatic and parasitological recovery and a shorter hospitalisation compared to A/P[1].

Δ DHA/PPQ & A/L provide more rapid symptomatic and parasitological recovery compared to chloroquine[2].

Ø Risk of QTc prolongation. Avoid in patients at risk and with comedication known to prolong QTc. ECG before starting treatment and 4-6h after third dose.

❖ Due to its unfavourable side-effect profile, mefloquine is nowadays only used if no alternative drug regimen is available.

♂ While *P. ovale* and *P. cynomolgi* are generally sensitive to chloroquine, chloroquine resistant *P. vivax* is wide spread (see p. 10). Consider chloroquine for *P. vivax* only if chloroquine resistance is unlikely.

* Oral chloroquine formulations: Plaquenil®: 1 tabl. = 200 mg hydroxychloroquinesulfate = 155 mg base (➔ 600 mg = 4 tabl.);
Hydroxychloroquine Zentiva®: 1 tabl. = 200 mg hydroxychloroquinesulfate = 155mg base (➔ 600 mg = 4 tabl.);
Nivaquine®: 1 tabl. = 136 mg chloroquinesulfate = 100 mg base (➔ 600 mg = 6 tabl.).

^ Note that for the eradication of *P. ovale* hypnozoites a lower primaquine dose of 0.25mg/kg/day is also considered sufficient.

§ Primaquine tablets are usually composed of 26.3 mg primaquine phosphate salt = 15 mg primaquine base. The recommended dose range of primaquine varies from 0.25 to 0.75 mg/kg/d; since lower doses are associated with treatment failure in *P. vivax* malaria, especially in Eastern Indonesia/Papua New Guinea, 0.5 mg/kg is the dose most widely recommended.

* Chloroquine and PPQ synergistically enhance the efficacy of primaquine. Thus, add chloroquine to primaquine if (1) neither chloroquine nor DHA/PPQ was used for treatment and if (2) primaquine treatment is delayed >3 weeks beyond chloroquine or DHA/PPQ treatment (see p. 3).

◈ Tafenoquine is licensed in the USA and Australia, but not (yet) in Europe (see p. 4).

♂♂ Considering the longer erythrocytic cycle of *P. malariae*, regimens/drugs with longer serum half-lives (DHA/PPQ, mefloquine) should be preferred over regimens/drugs with shorter serum half-lives (A/L, A/P).[3]

‡ The asexual cycle of *P. knowlesi* is the shortest of all human-pathogenic malaria species (24h) which potentially leads to high levels of parasitaemia ➔ the fast parasite clearance of artemisinin compounds makes them the favoured 1st line option.

2. Treatment of severe malaria

Criteria of `severe malaria´ – treat as severe malaria if ≥1 of the following complications is present:	
Prostration	Generalized weakness, unable to sit, stand or walk without assistance
Cerebral malaria	Impaired consciousness (GCS <11 in adults; BCS <3 in children), coma, seizures
Respiratory distress	Hypoxia, pulmonary oedema, acute respiratory distress syndrome (ARDS)
Acute renal failure	Urine output <0.4ml/kg/h or creatinine >265 µmol/l [>3.0 mg/dl] or urea >20 mmol/l
Acidosis	Arterial pH <7.3, plasma bicarbonate <15 mmol/l, lactate ≥5 mmol/l or BE <8mmol/l
Circulatory collapse	Shock (compensated [no hypotension but capillary refill time ≥3 sec or temperature gradient on leg (mid to proximal limb)]; decompensated shock [syst. RR <80mmHg in adults or <70 mmHg in children])
Jaundice	Bilirubin >50 µmol/l [>3 mg/dl] with a parasite count >100'000/µl (>2%) in *P. falciparum* or >20'000/µl (0.4%) in *P. knowlesi* malaria
Hypoglycemia	Blood glucose level <2.2mmol/l [<40 mg/dl]
Severe anaemia	Adults: Hb <7 g/dl or Hct <20%; children <12 years: Hb <5 g/dl or Hct <15% together with a parasite count >10'000/µl
Impaired coagulation	Spontaneous bleedings, disseminated intravascular coagulation (DIC)
Repeated vomiting	Inability to take oral medication
Hyperparasitaemia	≥2% (100'000/µl) in patients from malaria non-endemic regions [38] ≥4% in patients from and permanently living in a malaria holo-/hyperendemic region
≥3 days symptoms*	As indirect indicator of potentially high parasitaemia in the absence of laboratory values

Criteria adapted from [29]; * Swiss TPH in-house criterion.

	1st-line treatment	2nd-line treatment
P. falciparum **(*P. vivax*[Δ], *P. knowlesi*)**	**Artesunate i.v.** adults and children >20kg: 2.4 mg/kg; children <20kg: 3.0 mg/kg slow i.v. bolus injection over 5 minutes at 0h, 12 h and 24 h, then every 24 h[ψ] *switch to oral therapy as soon as the patient tolerates oral medication (but not before completing at least 24 h of i.v. treatment) and give a complete course (to be started 8–12 h after the last i.v. dose of artesunate) of:* ▪ **Artemether/lumefantrine**[◊] OR ▪ **Dihydroartemisinin/piperaquine**[◊] OR ▪ **Atovaquone/proguanil**[◊] (*regimens: see uncomplicated malaria*) *if the situation does not allow for switching to oral therapy, continue Artesunate for a total of 7 days and add* **Doxycycline i.v.:** adults: 100 mg BID; children (only if ≥8 years old): 2–4 mg/kg divided in 2 doses for a total of 7 days OR **Clindamycin i.v.:** adults: 10 mg/kg loading dose, followed by 5 mg/kg every 8 h for a total of 7 days; children: 15–20 mg/kg divided in 3 doses for a total of 7 days ☝ relevant key points of clinical management and adjunct treatment of severe malaria see 2.4. & 2.5	**Quinine dihydrochloride salt* i.v.** 1. loading dose[☝,†]: 20mg salt (=16.5 base)/kg over 4 h 2. continuation phase: 10 mg salt (=8.3 base)/kg over 4 h starting 8 h after initiation of treatment followed by 10 mg/kg over 4 h every 8h (=alternate 4 h drug administration and 4 h drug free interval), max. dosage 600 mg TID[‡§$] *switch to oral medication as soon as possible (but not before completing at least 24–48 h of i.v. treatment) and give a complete course (to be started 8–12 h after the last i.v. dose of quinine) of:* ▪ **Artemether/lumefantrine**[◊] OR ▪ **Atovaquone/proguanil**[◊] OR ▪ **Dihydroartemisinin/piperaquine**[◊] *(see regimens in table above)* OR ▪ **Quinine sulfate** 10 mg salt*(=8.3 mg base)/kg TID max. dosage: 600–650 mg TID for 7 days **+ Doxycycline p.o.:** adults: 100 mg BID; children (only if ≥8 years old): 2–4 mg/kg divided in 2 doses for a total of 7 days OR **+ Clindamycin p.o.:** adults and children: 5 mg/kg every 8 h for a total of 7 days

* Drug is labelled with the mass of drug expressed in salt rather than base (the active drug). Quinine dihydrochlorid is available as solution of various strengths in distilled water: 500 mg salt = 413 mg base in vials à 1ml; 600 mg salt = 496 mg base in vials à 2 ml; 1000 mg salt = 826 mg base in vials à 2 ml; 1200 mg salt = 1000 mg base in vials à 5 ml.

☝ Loading dose must not be used if patient received mefloquine within preceding 24 h.

† The rational to infuse each dose of quinine within 4 h is based on the instability of quinine solution when exposed to light.

‡ CAVE: monitor hypoglycaemia, hypotension, and cardiac arrhythmia! The quinine solution is diluted in isotonic fluid (e.g. 5% dextrose, normal saline) but preferably in 5% dextrose because of the quinine-induced insulin liberation leading to hypogycemia. Controlled infusion by infusion pump only!

§ *Quinine*: in the case of hepatic or renal impairment (GFR <10ml/min): no dose adjustment in the first 48 h of treatment; >48 h: reduce the dose by ⅓, to 10 mg salt/kg every 12 h. No dose adjustment in the case of haemodialysis or haemofiltration.

ψ *Artesunate*: no dose adjustment in the case of hepatic or renal impairment.

$ `Cinchonism´: comprising tinnitus, deafness, headache, nausea and visual disturbance, affects the majority of conscious patients with therapeutic levels and does not warrant dose reduction!

◊ If the infection has been acquired in Southeast Asia, where emerging artemisinin-resistant *P. falciparum* strains are of concern, atovaquone/proguanil might be the preferred sequential agent.

Δ In the case of *P. vivax* malaria: sequential treatment with primaquine or tafenoquine to eradicate hypnozoites; see p. 2.

Ad 1: Comments on the treatment of uncomplicated malaria

1.1. High rate of late treatment failures in (non-immune) travellers with uncomplicated *P. falciparum* malaria receiving the standard 3-day treatment regimen of artemether/lumefantrine (A/L):

Background:

Retrospective studies from Sweden[4] and the Czech Republic[5] showed that the standard 3-day A/L treatment regimen is associated with a high rate of late treatment failures in returning travellers (5.3[4] –13.9%[5]), whereas in the same studies no failures were observed with mefloquine or atovaquone/proguanil. A published British case series also highlighted identical treatment failures with A/L.[6] Of note, already in the only ever conducted prospective study of A/L in nonimmune patients, published in 2008[7], a failure rate of 5.3% (3/57) was observed in the unpublished subgroup analysis of nonimmune European travellers. Limited pharmacokinetic data from the Swedish study indicate that the observed treatment failures may be attributable to low lumefantrine plasma concentrations. It is known, that the area under the curve (AUC) of plasma lumefantrine concentration versus time, or its correlate, the plasma concentration on day 7, is the main determinant for eradication of residual parasites not eliminated by artemether and, thus the determinant of the combination's clinical efficacy.[8] Considering that (i) nonimmune patients, lacking acquired partial immunity, have a higher risk of treatment failure compared to patients from endemic regions, that (ii) the observed treatment failures with A/L are very likely attributable to low lumefantrine plasma levels, and that (iii) the failure rate in nonimmune European patients is considerable, the use of the 3-day A/L standard treatment regimen has to be seen critical.[9] The safety of an extended 5-day A/L treatment regimen has been demonstrated.[10]

Recommendation:

Concluding that the currently used standard 3-day treatment regimen of artemether/lumefantrine is apparently insufficient to clear *P. falciparum* malaria in >5% of nonimmune patients, we recommend to either:
(i) extend the standard 3-day treatment regimen by 4 additional doses (at 72, 84, 96, and 108 h) to 5 days or to
(ii) expand the standard 3-day regimen to 5 days by adapting the dosing intervals to 0, 8, 24, 48, 72, 96 h.[11-13]

1.2. Non-chloroquine treatment of *P. vivax* malaria:

Background:

(I) ACTs for non-falciparum malaria:

- *P. ovale, P. malariae, P. knowlesi* and *P. cynomolgi* are generally considered chloroquine sensitive, while chloroquine resistance in *P. vivax* (the most frequent among the non-*falciparum* malarias) has been reported from multiple countries (see p. 7). Especially in non-endemic countries it is difficult for physicans to assess the likelihood of chloroquine-resistant *P. vivax* infection in a patient.
- As in *P. falciparum* malaria, ACTs clear non-*falciparum* parasites more rapidly than chloroquine, clear fever more quickly than chloroquine, and are at least equivalently effective in treating non-*falciparum* blood-stage infections.[14,15] The best studied ACT in non-*falciparum* malaria is DHA/PPQ.[14,15]
- For uncomplicated non-*falciparum* malaria WHO now recommends to either treat with chloroquine (if chloroquine sensitivity is likely) or with an ACT.[16] The uniform application of an ACT for all uncomplicated malaria cases irrespective of species has the advantage of providing a pragmatic and easier to implement one-for-all solution in endemic countries and to ensure coverage of (overlooked and mostly chloroquine-resistant) *P. falciparum* mixed-infections.

(II) "Hypnozoitocidal co-drug synergy":

- coadministration of chloroquine and primaquine leads to significantly higher plasma levels of primaquine and its active metabolite carboxyprimaquine when compared to administration of primaquine alone.[17] This effect is explained by pharmacokinetic interactions between chloroquine and primaquine and is considered to be responsible for the observation that coadministration of the two drugs enhances the efficacy of primaquine against relapses (i.e. the eradication of hypnozoites).[18] Due to the extreme long plasma half-life of chloroquine (ranging from 70 to 300 hours and resulting in therapeutic blood drug levels for between 3 weeks to 3 months[17]), it can be assumed that primaquine administration may be delayed up to at least 3 weeks beyond chloroquine treatment without losing this synergistic effect.
- Artemisinins have apparently no effect on the metabolism of primaquine.[20]
- Analogous to chloroquine, coadministration of PPQ and primaquine leads to significantly higher plasma levels of primaquine and its active metabolite carboxyprimaquine when compared to administration of primaquine alone.[21] A clinical trial has confirmed the co-drug synergy of PPQ and primaquine against relapses.[22] Like chloroquine, the elimination half-life of PPQ is extremely long (~22 days) and it can be assumed that primaquine administration may be delayed up to at least 3 weeks beyond PPQ treatment without loosing this synergistic effect.
- To date, neither pharmacological nor clinical studies have assessed pharmacokinetic interactions or co-drug synergy of lumefantrine and primaquine or atovaquone/proguanil and primaquine.
- Coadministration of mefloquine and primaquine does not increase plasma levels of primaquine or carboxyprimaquine.[23]

Recommendation:

To assure "hypnozoitocidal co-drug synergy" chloroquine should be added to primaquine if (1) neither chloroquine nor DHA/PPQ has been used for initial treatment or if (2) primaquine treatment is delayed >3 weeks beyond chloroquine or DHA/PPQ treatment. [Note: in the case that mefloquine has been used for treatment, check QTc-time before administering primaquine together with chloroquine as all three drugs, and especially their combination, may lead to QTc-prolongation (see drug profiles)].

1.3. Treatment of uncomplicated malaria in overweight/obese patients >90 kg:

Recommendation:

Due to possibly skewed pharmacokinetics in obese patients either (1) prefer DHA/PPQ (the long half-life of PPQ should outweigh potential underdosing) or (2) consider extending treatment: e.g. A/L to 6 days and A/P to 4–5 days.

1.4. Treatment of uncomplicated malaria in pregnancy:

Background:

In the pre-artemisinin era, quinine and chloroquin were the recommended drugs in pregnancy. As evidence accumulated for the safety of ACTs, they replaced these drugs as first-line treatment in the 2nd and 3rd trimesters, while the combination of quinine and clindamycin (*P.f.* malaria) and chloroquin (non-*P.f.* malaria) remained the recommended first-line treatment in the 1st trimester.[24-27] In 2022, following a massive meta-analysis[28], the WHO finally endorsed the recommendation to not only use an ACT in the 2nd and 3rd trimester of pregnancy but to also use artemether-lumefantrine (A/L) in the 1st trimester.[29] Note that the recommendation is limited to A/L only, as there is (i) insufficient data for other ACTs (including DHA/PPQ) and

(ii) ACTs containing antifolates (e.g. sulfadoxine-pyrimethamine) are contraindicated during pregnancy. Data on A/P in pregnancy are still limited but its use may be considered if no other treatment option is available.

Recommendation:

P. falciparum malaria: 1st-line: Artemether/lumefantrine (for 5 days[30]); 2nd-line: either quinine + clindamycin or mefloquine. Due to the potential risk of recrudescence after completion of therapy, we recommend secondary prophylaxis with mefloquine [250 mg once weekly] until delivery[31]

non-_P.falciparum_ malaria: Artemether/lumefantrine or chloroquine (quinine may be used if there is concern about resistant *P. vivax* malaria). *P. vivax, P. ovale*: primaquine is contraindicated during pregnancy as the G6PD-status of the foetus is not determinable. Primaquine therapy to eradicate hypnozoites has to be delayed until after birth. To prevent relapses after completion of therapy, we recommend secondary prophylaxis with chloroquine [500mg once weekly] until delivery.[31]

1.5. Tafenoquine for radical cure of P. vivax

Background:

Tafenoquine has been approved by the US FDA in 2018 for the radical cure of *P. vivax*. The drug's long halflife promises to replace the 14-day primaquine regimen by a single dose regimen. However, the drug is not yet widely available, lacks EMA approval and several aspects deserve to be highlighted: in the USA, tafenoquine is approved for patients ≥16 years, in Australia for patients >2 years. Tafenoquine has been shown to be non-inferior to low dose primaquine regimens (0.25 mg/kg/day for 14 days) for radical cure of *P. vivax* in multicentre RCTs. However, these trials did (i) not account for reduced adherence and effectiveness of a prolonged primaquine regimen under programmatic conditions and did not compare tafenoquine with high dose primaquine regimens (0.5 mg/kg/day for 14 days), which are recommended in East Asia and Oceania and are also endorsed in this recommendation. The inital approval recommended tafenoquine in combination with any antimalarial appropriate for the treatment of *P. vivax* malaria. Following unpublished results from a RCT conducted in Indonesia, the FDA approval was changed in 2020 and now restricts tafenoquine to coadministration with chloroquine only. The trial also raised doubts about whether the currently approved single dose of 300 g is sufficiently high.[32]

Recommendation:

By the time tafenoquine will become more widely available, the question of the most effective dose will hopefully have been answered.

1.6. Primaquine / tafenoquine treatment of patients with Glucose-6-Phosphate-Dehydrogenase (G6PD)-deficiency:

Background:

- G6PD protects erythrocytes from oxidative stress. G6PD deficient individuals are prone to sustain haemolysis if they are exposed to oxidative stresses, e.g. certain drugs like primaquine. The severity of haemolysis depends upon the degree of enzyme deficiency (which is variant-dependent), the nature and total dose of the oxidative agent, the time course of exposure, the presence of additional oxidative stresses and pre-existing factors such as age, haemoglobin concentration and concurrent infection.
- The phenotypes of G6PD-deficiency are highly variable (reflecting ~300 genotypes). The African variant (A^-) mostly shows mild deficiency (>10% enzyme activity) and is relatively resistant to severe primaquine-induced haemolysis. Among Caucasians and Asians, however, the enzymatic activity in homozygotes is relatively low with a higher risk of severe primaquine-induced haemolysis. The Mediterranean variant (B^-) has especially minimal G6PD activity (often <1%) with a very high risk of sustaining severe haemolysis.
- The hypnozoitocidal efficacy of primaquine is determined by its cumulative total dose rather than by peak plasma levels. Extending the dosing regimen has shown to reduce toxicity in G6PD deficient individuals. In addition, extending the dosing schedule allows discontinuing treatment before the severity of haemolysis becomes critical. The most widely used regimen is a weekly single dose of 45 mg primaquine for 8 consecutive weeks.[33-35]
- In most cases with mild G6PD deficiency, haemolysis is self-limiting and ends a few days after stopping treatment. However, in patients with the Mediterranean variant (B^-), serious haemolysis may even be caused by extended dosing regimens of primaquine and, unlike with the A^- variant, haemolysis is not self-limiting. Therefore, primaquine administration to severely G6PD deficient patients remains controversial (e.g. WHO recommends against primaquine treatment). If treatment is considered, the dosage regimen should be modified to weekly doses of 30 mg primaquine for 15 weeks and patients should be closely monitored for haemolysis.[36]
- G6PD enzyme activity cut-off values for primaquine or tafenoquine treatment: *Men: >30%*: no risk; *<30%*: significant risk; Women: *>80%*: low risk; *30–80%*: potential risk; *<30%* significant risk. Levels >30% are generally considered to confer an acceptably risk when administering primaquine or tafenoquine in the normal therapeutic dose.[37]
- Tafenoquine shows similar risks to induce haemolysis in G6PD deficient individuals as primaquine. Since clinical experience is still limited, no recommendations can be given regarding its use in specific situations.

Recommendation:

- *Mild to moderate G6PD deficiency / non-Mediterannean G6PD variants:* give primaquine in a weekly single dose of 45 mg (below 60 kg of body weight give 0.75 mg/kg) for 8 consecutive weeks and closely monitor haemolysis parameters. In affected patients, the haemoglobin level starts falling 1–2 days after starting treatment, reaches a nadir after 5–6 days and then starts rising again despite continued treatment (by then old RBCs with low G6PD concentrations have been depleted and young RBCs with highter G6PD concentrations enter the circulation).
- *Severe G6PD deficiency / Mediterranean G6PD variant:* there are two options:
  - (1) If the patient does not want to risk haemolysis, abstain from primaquine treatment and inform the patient about the possibility of future relapse(s). If there is a risk that the patient may sustain a relapse without timely access to appropriate health care, the patient should receive malaria emergency stand-by self medication.
  - (2) If primaquine treatment is agreed upon, give primaquine in a weekly single dose of 30 mg (below 60 kg of body weight give 0.5 mg/kg) for 15 consecutive weeks and closely monitor haemolysis parameters.
- Case reports of severe haemolysis in only mildly G6PD deficient individuals highlight that even extended dosing regimens cannot eliminate the risk: closely monitor haemolysis parameters!

1.7. Suggested treatment monitoring of uncomplicated malaria:

- Treatment efficacy is primarily assessed by clinical improvement, normalisation of platelet (PLT) count, and clearance of asexual parasite forms from the blood. Note that the parasite count may temporarily increase in the first 24–36h of treatment (fluctuation of parasitemia depending on the timing of the erythrocytic cycle and blood sampling) without demanding action.

- Full blood count every 24 h. Microscopy with assessment of parasitaemia every 24 h until negative. Note that the parasite clearance assessment refers to the trophozoite/ring stages; gametocytes may persist and can be detected in the blood for prolonged periods even in cured patients.
- If treating with DHA/PPQ: ECG (QTc assessment) before starting treatment and 4–6h after third dose.
- Consider monitoring for delayed haemolysis in patients treated with ACT who are at risk for anaemia; see comment on *Post-Artesunate Delayed Haemolysis (PADH)* on p. 7.

Ad 2: Comments on the treatment of severe malaria

2.1. Summary of the advantages and disadvantages of artesuante and quinine treatment:

i.v. Artesunate	i.v. Quinine
Pro ▪ Compared to quinine significant survival benefit if parasitaemia >10% [39-41] ▪ Fast parasite clearance time: ~20 h ▪ Kills circulating early ring-stages before they mature and cause RBC sequestration in capillaries ▪ No cardiac drug toxicity & safe in black-water fever	***Pro*** ▪ Probably same survival rate as with artesunate in patients with parasitaemia <10%
Contra ▪ Delayed haemolysis (day 7–28) in patients with high parasitaemia due to simultaneous removal of once-infected erythrocytes [42,43] ▪ Resistance reported, but currently only from Southeast Asia	***Contra*** ▪ Inferior to artesunate if parasitaemia >10% [39-41] ▪ Slow parasite clearance time: ~49 h ▪ Kills later trophozoites, thus its effect on preventing RBC sequestration is inferior to artesunate ▪ QT-prolongation, proarrhythmic (Torsade de pointes) ▪ Hypotension if infused rapidly ▪ Hypoglycemia due to insulin liberation ▪ Resistance rare, but possible

2.2. Treatment of severe malaria in pregnancy:

Background:

In the pre-artemisinin era, i.v. quinine (+ clindamycin) used to be the standard treatment for severe malaria in pregnancy. However, artesunate gradually replaced quinine for this indication and today most guidelines recommend i.v. artesunate as first-line treatment for severe malaria in pregnancy (now also regardless of trimester).[24-26,29] Note however that, although artesunate is clearly recommended for the treatment of severe malaria in pregnancy, the drug is not approved for this indication, neither by the EMA in Europe nor by the FDA in the USA.

***Recommendation*:**

All species: 1st-line treatment: artesunate, followed by artemether/lumefantrine for 5 days[30]
2nd-line treatment: quinine + clindamycin

Note: *P. falciparum*: due to the potential risk of recrudescence after completion of therapy, we recommend secondary prophylaxis with mefloquine [250 mg once weekly] until delivery.[31]

P. vivax/ovale: ◆ Primaquine is contraindicated during pregnancy as the G6PD-status of the foetus is not determinable. Primaquine therapy to eradicate hypnozoites has to be delayed until after birth. To prevent relapses after completion of therapy, we recommend secondary prophylaxis with chloroquine [500mg once weekly] until delivery.[31]

2.3. Post-Artesunate Delayed Haemolysis (PADH):[42,43]

Background:

Malaria parasites killed by artesunate are removed from erythrocytes by the spleen and the `cleaned´ erythrocytes are released back into circulation. These morphologically altered (`pitted´) erythrocytes (or `once-infected erythrocytes´, `o-iE´) remain in circulation but with a considerably decreased life span of 7 to 21 days. Artemisinins are more likely than quinine to result in the creation of significant numbers of o-iEs. Patients with higher initial parasitaemia have higher numbers of o-iEs after treatment with artemisinin drugs. When these erythrocytes with decreased lifespan are simultaneously cleared en masse, it results in a brief haemolytic episode that does not recur. PADH has been observed in ~27% of European travellers receiving i.v. artesunate and some required blood transfusion. Therefore, standard monitoring of haemolysis parameters following i.v. artesunate treatment of severe malaria is recommended on days 7, 14, 21 and 28 (see below) or until laboratory parameters clearly indicate that the haemolytic episode has ended [in rare cases prolonged haemolysis has been described for >4 weeks]. PADH has also been observed after oral artemisinin treatment of uncomplicated malaria.[44]

***Recommendation*:**

- Monitor for delayed haemolysis in patients treated with i.v. artesunate (especially important if initial parasitemia was high!) at day 7, 14, 21 and 28 (see `Suggested treatment monitoring of severe malaria´ below)
- Although the lower initial parasitaemia in uncomplicated malaria leads to lower numbers of o-IE after treatment and PADH is apparently less pronounced and clinically irrelevant in almost all cases, analogous monitoring of haemolysis parameters may be considered in patients with predisposing factors for anaemia.[44]

2.4. Adjunct treatment of severe malaria:

- In contrast to children, the prevalence of concomitant bacteraemia in adults with severe malaria is low. Thus, the administration of empirical antibiotics, in addition to artesunate, is not generally indicated in adults with severe malaria but warranted in the few patients with very high parasitaemia.[45] If the patient is in shock, consider blood culture and empirical coverage for possible gram-negative sepsis.
- Acetaminophen/paracetamol: adjunct acetaminophen (1 g 6-hourly for 72 h) shows a kidney-protective effect in patients with severe malaria.[46,47]
- Avoid NSARDs because of the associated renal toxicity and risk of renal failure.
- If patient is unconscious: consider cranial CT and lumbar puncture to rule out concomitant bacterial meningitis.
- The use of prophylactic anticonvulsants is contraindicated as their use is associated with increased mortality.
- Corticosteroids and mannitol are contraindicated in adult patients with cerebral malaria and cranial hypertension. Both drugs prolong coma and worsen prognosis.

- Limit fluid replacement to diuresis and compensation for perspiration/fever. Malaria patients are prone to fluid overload and pulmonary oedema (pathophysiological correlate: endothelial damage). In low resource settings, bedside sonography of the vena cava is a simple tool to evaluate the patient's volume status and guide volume therapy. In high resource settings a central venous catheter (monitoring of CVP) or a PiCCO catheter (monitoring of extravascular lung water, lung oedema) may be used.
- Consider physical measures to control hyperpyrexia.
- Exchange transfusion and quinine-artesunate combination therapy: see `special considerations´ below.
- Switching from parenteral to oral therapy is mostly possible after stabilization of the patient (able to swallow, no vomiting) and once the parasitaemia has fallen below 1%.

***Recommendation*:**

Patients with severe malaria treated with i.v. artesunate should receive adjunct acetaminophen/paracetamol (1g 6-hourly for 72 h) for kidney protection.

2.5. Suggested treatment monitoring of severe malaria:

- Treatment efficacy is assessed by clinical improvement, normalisation of platelet (PLT) count and LDH level, and decreasing number of asexual parasite forms in the blood (after 48 h at the latest) [Note: gametocytes may persist and can be detected in the blood for prolonged periods even in cured patients].
- RCTs and PCR are <u>not</u> suitable for monitoring parasite clearance (see 3. below)
- Check parasitaemia every 12 h until sustained decline (i.e. <1%), then every 24 h until negative (Note: parasite count may temporarily increase in the first 24–36h of treatment).
- Full blood count (incl. differential blood count) every 12 h.
- Perform blood gas analysis (BGA) latest every 6 h (+ in the case of quinine therapy additionally at 3 h after starting therapy) until patient's conditions are stabilised.
- Check blood glucose level ever 4 h, 2-hourly during quinine infusion [quinine-induced hyperinsulinemia!], and at any time that reduced consciousness occurs.
- Additonal laboratory/diagnostics: blood cultures, ECG (esp. under i.v. quinine [QTc?]).
- Monitor for delayed haemolysis in patients treated with i.v. artesunate at days 7, 14, 21 and 28.

2.6. Exchange transfusion/erythrocytapheresis for severe malaria

Background:

Exchange transfusion (ET) has been used as an adjunct treatment of severe malaria presenting with hyperparasitaemia and organ failure since its first reported use in 1974. The rationale of ET is based on its biological plausibility, the fast removal of infected red blood cells (RBCs) and toxic byproducts. The accelerated parasite clearance time (PCT) is supposed to prevent further sequestration of infected RBCs, thus preventing further microvascular blockage and organ failure. The used techniques included `traditional´/manual ET and, more recently, erythrocytapheresis (`automated RBC ET´). While traditional ET is a time-consuming and complex process involving intermittent or continuous venesection and transfusion, with inherent risks of haemodynamic compromise, erythrocytapheresis allows for the rapid removal of altered RBCs and replacement with normal cells (usually in <2 h) by maintining haemodynamic stability and retaining platelets and plasma components such as clotting factors. In the absence of scientific evidence, ET has been recommended, based on pathophysiological plausibility, by many expert societies in the past.[48] Up to 2012, 37 clinical case reports on the use of automated RBC exchange as an adjunctive treatment option for severe malaria have been published in the form of case series and case reports. All but one report included patients with hyperparasitaemia (>10%) and critical organ dysfunction. RBC exchange was most often considered in cases with extremely high parasite counts (median 30%) and the presence of neurological symptoms suggestive of cerebral malaria.[48] Whether ET contributes to survival has been an on-going debate for decades. Randomized controlled trials have not been possible for returning travellers with malaria in the past and are unlikely to be conducted in the future. Furthermore, the introduction of i.v. artesunate with its rapid clearance of parasites from the blood (PCT: i.v. quinine/quinidine: 49 h; i.v. artesunate: 20 h) has questioned the benefit of adjunct ET in severe malaria. In summary, only limited evidence from case reports and case series is available to support ET as adjunctive treatment.

Recent data and recommendations:

- *Holland:* In 2013, Kreeftmeijer-Vegter et al. published a retrospective cohort study on ET adjunct to i.v. quinine and i.v. artesunate therapy. They found, that ET does not significantly contribute to parasite clearance in artesunate-treated individuals (there may be a small effect of ET on parasite clearance under quinine treatment), and conclude that ET cannot be recommended in patients treated with i.v. artesunate.[49]
- *USA:* In 2013, the US CDC malaria branch published an analysis and review of ET and came to the conclusion that `despite rapid parasite clearance times resulting from ET, there is no evidence for efficacy of ET as adjunctive therapy in severe malaria. Adjunct ET cannot be recommended. When rapidly acting antimalarials, specifically artemisinins, become more widely available, the biologic plausibility argument for ET will become less relevant´.[50] Thus, ET is no longer recommend by the US CDC.[51]
- The current British and German malaria treatment guidelines do no longer recommend ET.[25,26]

Recommendation:

Severe malaria cases presenting with hyperparasitaemia >10% and organ complications

- treated with i.v. quinine: if available, change to i.v. artesunate; if i.v. artesunate is unavailable but erythrocytapheresis is available, discuss the option of exchange transfusion with a malaria specialist.
- treated with i.v. artesunate: no evidence that ET is beneficial. [Note: provided erythrocytapheresis is available, some specialists still opt for ET in the case of extreme hyperparasitaemia ≥30%].

2.7. Artesunate-quinine combination treatment of severe malaria

Background:

A study in Thailand evaluated the efficacy of i.v. artesunate alone versus i.v. artesunate + i.v. quinine in uncomplicated and severe malaria.[52] No survival benefit was observed with the combination treatment. More adverse events (not severe and completely reversible after therapy) were observed in the group receiving combinaion therapy, but parasite clearance time did not differ between the two treatment groups.

***Recommendation*:**

Artesunate-quinine combination therapy is not recommended.

► **Recommended review on the clinical management of malaria:**
Plewes K et al. Malaria: what's new in the management of malaria? Infect dis Clin N Am 2019;33:39-60.

3. Diagnostics

3.1. Microscopy:

Thick and thin (EDTA) blood films/smears remain the gold standard in malaria diagnostic. A single negative blood smear does not rule out malaria. Because non-immune individuals may be symptomatic at very low parasite densities, which initially may be undetectable by microscopy, blood smears (± a rapid diagnostic test) should be repeated every 12–24 h for a total of at least 3 sets. If these 3 investigtations are negative, malaria is, with a probability bordering on certainty, ruled out. However, if the clinical suspicion remains high and no alternative diagnosis can be established, more than 3 sets can be indicated.

3.2. Rapid diagnostic tests (RDT):

RDTs are based on the detection of circulating parasite antigene(s). Depending on the test, different antigens are targeted alone or in combination: (I) Histidin-rich-protein-2/HRP2 (*P. falciparum*-specific); (II) Parasite lactate dehydrogenase / pLDH (either *P. falciparum-, P. vivax-*, or pan-[all species] specific); (III) Aldolase (pan-specific). *Pitfalls:*

- False-negative results may occur in cases of very low or very high parasitaemia. HRP2-only RDTs are especially problematic in the case of very high parasitaemia as they show a `prozone effect´ (which is not observed with pLDH- or aldolase-based tests).[53] Thus, HRP2-mono RDTs should not be used!
- False-negative HRP2-based test results are increasing worldwide and are linked to an antigenic variant form of HRP2 selected for by the use of HRP2-based RDTs.[54] Overview: http://apps.who.int/malaria/maps/threats/.
- False-positive RSR results may occur in patients with high concentrations of rheumatoid factor.
- *P. ovale*, *P. malariae* and *P. knowlesi* are not specifically targeted by the currently available RDTs and therefore RDTs are not suitable for diagnosing/excluding these infections (e.g. in *P. knowlesi* malaria pan-pLDH- and aldolase-based tests may be positive, *P. falciparum*-specific pLDH-based tests may be positive, and HRP2-based tests will be negative[55,56]).
- HRP2-based tests may be false-positive in the case of acute schistosomiasis due to *S. mekongi*.[57]
- HRP2- and pan-pLDH-based test may be false positive in the case of African trypanosomiasis.[58]
- HRP2 is cleared very slowly from the blood, therefore, HRP2-based tests may remain positive >1 month after successful treatment, particularly if initial parasitaemia was high. In addition, HRP2, pLDH and aldolase are also produced by gametocytes and, depending on the drug regimen used, gametocytes may circulate after successful treatment for days to weeks. Therefore, these tests are not useful to monitor immediate treatment success!

3.3. PCR:

Excellent tool for species determination in unclear cases and for screening of low-parasitaemic samples for potential mixed-infections. PCR is the method of choice to diagnose zoonotic malaria infections and to rule out mixed infections in some cases difficult to judge by microscopy. Like RDTs, PCR remains positive for a while following treatment. Therefore, PCR is not useful to monitor immediate treatment success!

4. Epidemiology of drug resistance

P. falciparum

- *Chloroquine: P. falciparum* remains sensitive to chloroquine only in Central America and Hispaniola (Dominican Republic and Haiti).[59] Nevertheless, genetic chloroquine resistance markers are reported from the region.[59]
- *Mefloquine:* mefloquine resistance is a concern in the Greater Mekong subregion, in particular in Thailand and in Cambodia. A case report on failure of mefloquine therapy due to drug resistance in a traveller returning from Benin has been published.[60]
- *Atovaquone/proguanil:* molecular analysis of recrudescent isolates showed that atovaquone resistance is associated with a single mutation in the parasite's cytochrome *b* gene.[61] Mutations in this gene have been reported in Burkina Faso, Cameroon, the Comoros, Ivory Coast, French Guiana, Guinea, India, Kenya, Mali, Mozambique, Nigeria, Senegal, Sierra Leone and Uganda.[62]
- *ACTs:* artemisinin-based combination therapies (ACTs) remain highly efficacious in most parts of the world, with the exception of the Greater Mekong Subregion (Laos, Thailand, Vietnam, Cambodia), where emerging artemisisin partial resistance (defined as a increased parasite-clearance half-life of more than 5 hours linked to specific K13 mutations) challenges the efficacy of various ACTs, including artemether/lumefantrine and dihydroartemisinin/piperaquine (the latter is especially problematic due to the high co-prevalence of piperaquine resistance.[59] K13 mutations of concern have also been reported from Rwanda and Guyana, although no evidence for clinical failures is reported from these countries.[59]

P. vivax

Reported resistance of *P. vivax* is limited to chloroquine, sulfadoxine/pyrimethamine and (low dose) primaquine. Chloroquine reatment failure has been observed in Afghanistan, Bolivia, Brazil, Cambodia, China, Colombia, Democratic People's Republic of Korea, Ethiopia, French Guiana, Guyana, India, Indonesia, Madagascar, Malaysia, Myanmar, Nepal, Pakistan, Papua New Guinea, Peru, Republic of Korea, Solomon Islands, Sri Lanka, Thailand, Timor-Leste, Turkey, Vanuatu and Viet Nam.[59]

P. ovale, P. malariae, P. knowlesi

P. ovale, P. malariae and *P. knowlesi* are generally considered sensitive to chloroquine.[59] Only one study from Sumatra, Indonesia suggests local resistance of *P. malariae* to chloroquine.[63]

▶ **Up-to-date information on antimalarial drug resistance:** www.wwarn.org/explorer/app

5. Zoonotic malaria

P. knowlesi

P. knowlesi is a primate malaria parasite endemic in some parts of Southeast Asia (Map: see p. 182). *P. knowlesi* is morphologically (microscopically) difficult to differentiate from *P. falciparum* and *P. malariae*.[69] Cases of *P. knowlesi* infections in travellers have repeatedly been reported.[70]

P. simium

P. simium is a primate malaria parasite endemic in some parts of Brasil. *P. simium* is morphologically (microscopically) not differentiable from *P. vivax*.[71] In 2015-2016, 49 human *P. simium* infections were reported in the Atlantic forest region of Rio de Janeiro State (a region where *P. vivax* is not endemic).[72] (Map: see p. 182)

P. brasilianum

P. brasilianum, causing quartan malaria in Uakari monkeys, was discovered in 1908. Recently it has been shown that *P. brasilianum* is not only microscopically but also genetically identical to *P. malariae*.[73]

P. cynomolgi

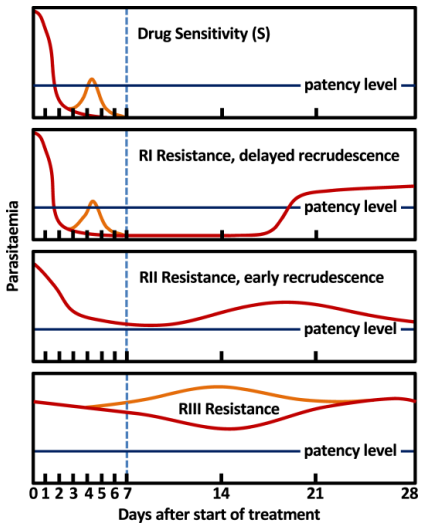
After a single case reported in 2014, a cluster of 5 patients infected with the primate malaria parasite *P. cynomolgi* has been reported from the Kapit region in the centre of Borneo in 2018.[74] *P. cynomolgi* is microscopically indistinguishable from *P. vivax* and even some widely used PCR methods show cross-reactivity with *P. vivax*.[75]

▶ **Recommended review on zoonotic malaria:** Ramasamy R. Zoonotic malaria. Front Public Health 2014;2:123.

6. Treatment failure: recrudescence / resistance / relapse

Definition of "treatment failure"*:*
Failure to clear malarial parasitaemia and/or resolve clinical symptoms despite administration of an antimalarial.

Treatment failure	Causes	Comments
`Recrudescence´	▪ Incorrect dosing ▪ Treatment adherence (compliance) ▪ Poor drug quality ▪ Drug interactions ▪ Unusual drug metabolisation ▪ Compromised intestinal drug absorption ▪ *R1 drug resistance**	• *Definition of `recrudescence´: the situation in which parasitaemia falls below detectable levels and then later increases to a patent parasitaemia.* • Most recrudescence episodes occur more than 2 weeks (mostly between 2–6 weeks) after treatment, but up to 10 weeks following mefloquine treatment. • The risk of recrudescence even after treatment with modern artemisinin-based combination therapy (ACT) should not be underestimated. • *Without sophisticated laboratory work-up R1 drug resistance cannot be differentiated from other causes of recrudescence.
`Drug Resistance´	▪ Drug resistance	*Definition of `drug resistance´: the ability of a parasite strain to survive and/or multiply despite the proper administration and absorption of an antimalarial drug in the dose normally recommended.*



Drug sensitivity: The asexual parasite count reduces to <25% of the pre-treatment level within 48 hours after starting the treatment, the asexual parasitaemia is completely cleared within 7 days, no subsequent recrudescence.

R1 Resistance: The asexual parasitaemia reduces to <25% of pre-treatment level within 48 hours after starting the treatment, asexual parasitaemia is completely cleared within 7 days but reappears between 2–4 weeks.

R2 Resistance: Marked reduction in asexual parasitaemia (decrease >25% but <75% of pre-treatment level) within 48 hours but no complete clearance of parasitaemia within 7 days.

R3 Resistance: Minimal reduction in asexual parasitaemia (decrease <25%) or an increase in parasitaemia after 48 hours.

patency level = microscopical detection level of parasites in the blood
(graphic adapted from WHO)

`Relapse´	Activation of hypnozoites in *P. vivax* / *P. ovale* malaria	• Relapse episodes may occur weeks, months or even years after primary infection. • The proportion of cases relapsing and the interval between relapses vary between parasite strains (tropical *P. vivax* strains: 3–6 weeks, [or 6–8 weeks after treatment with slowly eliminated drugs, which suppress the first relapse]; subtropical *P. vivax* strains and strains from temperate regions: often >8 months–5 years). • Efficacy of primaquine and tafenoquine, both `pro-drugs´, may largely depend on the individual hepatic (cytochrome P-450-2D6 dependent) metabolisation to the active drug (see drug profiles).[64-66] However, recent data suggest that CYP2D6 reduced metabolism is apparently less problematic for tafenoquine than for primaquine.[67]

Treatment of recrudescence and relapse episodes

- `Recrudescence´ and `relapse´ episodes can generally be retreated with the first-line regimen. However, in the case of recrudescence following the standard 3-day regimen of artemether/lumefantrine, consider to extend the retreatment course to 5–6 days (see 'Comments on the treatment of uncomplicated malaria' above).
- Recrudescence following artemether/lumefantrine in patients with *P. falciparum* malaria acquired in South East Asia may best be treated with atovaquone/proguanil because of emerging artemisinin-resistance in this region.
- The reuse of mefloquine within 28 days of first-line treatment is associated with an increased risk of neuropsychiatric sequelae and is therefore, not recommended.
- In the case of relapse following adequate primaquine therapy, consider increasing the primaquine dose up to 60mg/day.[68]

▶ All patients treated for malaria must be informed about the risk of recurrence/relapse!

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