ClinicalEvidence

Malaria: severe, life-threatening

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ABSTRACT

INTRODUCTION: Severe malaria mainly affects children under 5 years old, non-immune travellers, migrants to malarial areas, and people living in areas with unstable or seasonal malaria. Cerebral malaria, causing encephalopathy and coma, is fatal in around 20% of children and adults, and neurological sequelae may occur in some survivors. Severe malarial anaemia may have a mortality rate of over 13%. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of antimalarial treatments; and adjunctive treatment for complicated falciparum malaria in non-pregnant people? We searched: Medline, Embase, The Cochrane Library and other important databases up to December 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 31 systematic reviews, RCTs, or observational studies that met our inclusion criteria. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: dexamethasone, exchange blood transfusion, initial blood transfusion, intramuscular artemether, intravenous artesunate,

QUESTIONS

INTERVENTIONS

Covered elsewhere in Clinical Evidence

Malaria: prevention in travellers

To be covered in future updates

Treatment in pregnancy

Footnote

*Based on consensus. RCTs would be considered unethical.

Key points

- Severe malaria mainly affects children under 5 years old, non-immune travellers, migrants to malarial areas, and people living in areas with unstable or seasonal malaria.

  Cerebral malaria, causing encephalopathy and coma, is fatal in around 20% of children and adults, and neurological sequelae may occur in some survivors.

  Severe malarial anaemia may have a mortality rate of over 13%.

- International consensus has historically regarded quinine as standard treatment for severe falciparum malaria. Controlled trials will generally compare new treatments against this standard.

  We found no clear evidence on the best quinine treatment regimen or route of administration to use, although high initial dose quinine clears parasites more rapidly compared with lower-dose quinine, but increases the risk of adverse effects.

  Intravenous artesunate is probably more effective than quinine in reducing mortality from severe malaria.

  Intramuscular artemether and rectal artemisinin, artemether, artesunate, and dihydroartemisinin may be as effective as quinine in reducing mortality from severe malaria.

  We don't know how intramuscular arteether compares with quinine.

Routine use of phenobarbitone in cerebral malaria may reduce convulsions compared with placebo, but can increase mortality.

Dexamethasone has not been shown to reduce mortality from severe malaria, and it increases the risk of gastrointestinal bleeding and seizures.

- We don't know whether initial blood transfusion or exchange blood transfusion reduce mortality from severe malaria as no adequate-quality studies have been found. Blood transfusion is associated with adverse effects, but is clinically essential in some circumstances.

DEFINITION

Falciparum malaria is caused by protozoan infection of red blood cells with *Plasmodium falciparum* and comprises a variety of syndromes. This review deals with clinically complicated malaria (i.e. malaria that presents with life-threatening conditions, including coma, severe anaemia, renal failure, respiratory distress syndrome, hypoglycaemia, shock, spontaneous haemorrhage, and convulsions). The diagnosis of cerebral malaria should be considered where there is encephalopathy in the presence of malaria parasites. A strict definition of cerebral malaria requires the presence of unrousable coma and no other cause of encephalopathy (e.g. hypoglycaemia, sedative drugs), in the presence of *P falciparum* infection. [1] This review does not currently cover the treatment of malaria in pregnancy.

INCIDENCE/ PREVALENCE

Malaria is a major health problem in the tropics, with 300–500 million clinical cases occurring annually and an estimated 1.1–2.7 million deaths each year as a result of severe malaria. [2] Over 90% of deaths occur in children under 5 years old, mainly from cerebral malaria and anaemia. [2] In areas where the rate of malaria transmission is stable (endemic), those most at risk of acquiring severe malaria are children under 5 years old, because adults and older children have partial immunity, which offers some protection. In areas where the rate of malaria transmission is unstable (non-endemic), severe malaria affects both adults and children. Non-immune travellers and migrants are also at risk of developing severe malaria.

AETIOLOGY/ RISK FACTORS

Malaria is transmitted by the bite of infected female anopheline mosquitoes. Certain haemoglobins such as haemoglobin S [3] and haemoglobin C [4] are protective against severe malaria (see aetiology in review on malaria: prevention in travellers). [5]

PROGNOSIS

In children under 5 years of age with cerebral malaria, the estimated case fatality of treated malaria is 19%, although reported hospital case fatality may be as high as 40%. [1] [6] Neurological sequelae persisting for more than 6 months may occur in some survivors, and include ataxia, hemiplegia, speech disorders, behavioural disorders, epilepsy, and blindness. Severe malarial anaemia may have a case fatality rate higher than 13%. [6] In adults, the mortality of cerebral malaria is 20%; this rises to 50% in pregnancy. [7]

AIMS OF INTERVENTION

To prevent death and cure the infection; to prevent long term disability; to minimise neurological sequelae resulting from cerebral malaria, with minimal adverse effects of treatment.

OUTCOMES

Death; parasite clearance; parasite clearance time; fever clearance time; time to walking and drinking; coma recovery time; neurological sequelae at follow up; adverse events.

METHODS

BMJ Clinical Evidence search and appraisal December 2006. We applied the World Health Organization criteria for severe malaria when deciding which RCTs to include. [1] International consensus has historically recommended quinine for the treatment of severe falciparum malaria. Placebo or no treatment controlled trials of antimalarial treatment in people with severe malaria would be considered unethical. The following databases were used to identify studies for this systematic review: Medline 1966 to December 2006, Embase 1980 to December 2006, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2006, Issue 4. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for evaluation in this review were: published systematic reviews and RCTs in any language, and containing more than 20 individuals of whom more than 80% were followed up. The minimum length of follow-up required to include studies was 28 days. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA), which are added to the reviews as required.

QUESTION **What are the effects of antimalarial treatments for complicated falciparum malaria in non-pregnant people?**

OPTION **INTRAMUSCULAR ARTEMETHER VERSUS QUININE**

Mortality
Compared with quinine Intramuscular artemether seems to be as effective as quinine at reducing mortality in people with severe malaria.

Fever clearance
Compared with quinine Intramuscular artemether seems to be as effective as quinine at eradicating fever in people with severe malaria.

Recovery from coma
Compared with quinine Intramuscular artemether seems to be as effective as quinine at reducing time spent in a coma in people with severe malaria.

Neurological sequelae
Compared with quinine Intramuscular artemether seems to be as effective as quinine at preventing neurological sequelae in people with severe malaria.

Benefits:

We found two systematic reviews [8] [9] and five subsequent RCTs. [10] [11] [12] [13] [14] The first review (search date not reported, 7 RCTs, 1919 adults and children) analysed individual participant data. [8] It found no significant difference in mortality between intramuscular artemether and either intravenous or intramuscular quinine (im quinine in 1 RCT only) in severe falciparum malaria (mortality: 136/961 [14%] with artemether *v* 164/958 [17%] with quinine; OR 0.80, 95% CI 0.62 to 1.02). Parasite clearance was faster with artemether than with quinine (HR 0.62, 95% CI 0.56 to 0.69). The review found no significant difference in the speed of coma recovery, fever clearance time, or neurological sequelae between artemether and quinine (coma recovery time with quinine: HR 1.09, 95% CI 0.97 to 1.22; fever clearance time with quinine: HR 1.01, 95% CI 0.90 to 1.15; neurological sequelae: 81/807 [10%] with artemether *v* 91/765 [12%] with quinine; OR 0.82, 95% CI 0.59 to 1.15). It found that rates for the combined outcome of death or neurological sequelae were significantly lower for artemether than for quinine (OR 0.77, 95% CI 0.62 to 0.96; P = 0.02). The second review (search date 1999, 11 RCTs, 2142 people) found a small significant reduction in mortality for intramuscular artemether compared with intravenous quinine (OR 0.72, 95% CI 0.57 to 0.91). [9] However, more rigorous analysis, excluding three poorer quality RCTs, found no significant difference in mortality (OR 0.79, 95% CI 0.59 to 1.05). The review found no significant difference in neurological sequelae at recovery between artemether and quinine (OR 0.8, 95% CI 0.52 to 1.25). The first subsequent RCT (105 people, aged 15–40 years, with cerebral malaria in Bangladesh) compared intramuscular artemether (160 mg initially, then 80 mg/kg once daily) versus intravenous quinine (loading dose 20 mg/kg, then 10 mg/kg 8-hourly). [10] It found no significant difference in death rates or neurological sequelae between artemether and quinine (death: 9/51 [18%] with artemether *v* 10/54 [19%] with quinine, OR 0.94, 95% CI 0.35 to 2.55; neurological sequelae: 3/51 [6%] with artemether *v* 1/54 [2%] with quinine, RR 3.18, 95% CI 0.34 to 29.56). Mean fever clearance time and coma recovery time were significantly longer for artemether than for quinine (fever clearance time: 58 hours with artemether *v* 47 hours with quinine, WMD 11.0 hours, 95% CI 1.6 hours to 20.4 hours; coma recovery time: 74 hours with artemether *v* 53 hours with quinine, WMD 20.8 hours, 95% CI 3.6 hours to 38.0 hours). There was no significant difference in mean parasite clearance time between artemether and quinine (52 hours with artemether *v* 61 hours with quinine; WMD –8.6 hours, 95% CI –22.5 hours to + 5.3 hours). The second subsequent RCT (41 children with severe malaria in Sudan, 40 analysed) compared intramuscular artemether (3.2 mg/kg loading dose, then 1.6 mg/kg daily) versus intravenous quinine (loading dose 20 mg/kg, then 10 mg/kg 8 hourly). [11] It found that artemether significantly increased fever clearance time but found no significant difference between artemether and quinine in time to parasite clearance (mean fever clearance time: 30.5 hours with artemether *v* 18 hours with quinine, P = 0.02; mean parasite clearance time: 16 hours with artemether *v* 22.4 hours with quinine, P > 0.05). It found that one child died with quinine compared with no deaths with artemether (0/20 [0%] with artemether *v* 1/21 [5%] with quinine; P value not reported). The third subsequent RCT (77 comatose children, aged 3 months to 15 years, with cerebral malaria) compared intramuscular artemether versus intravenous quinine. [12] It found no significant difference in death rates between artemether and quinine (3/38 [8%] with artemether *v* 2/39 [5%]; P value not reported). There was no significant difference in mean fever clearance time, coma recovery time, and parasite clearance time (fever clearance time: 31 hours with artemether *v* 36 hours with quinine; coma recovery time: 21 hours with artemether *v* 26 hours with quinine; parasite clearance time: 36 hours with artemether *v* 41 hours with quinine; P value not reported for any comparison). The fourth subsequent RCT (46 children, age up to 14 years, with severe malaria in India) compared intramuscular artemether versus intravenous quinine.

[13] It found no significant difference in mortality (5/23 with artemether *v* 6/23 with quinine; OR 0.79, 95% CI 0.2 to 3.06). It found that artemether significantly improved parasite clearance time and coma recovery time compared with quinine, but found no significant difference in fever clearance time (parasite clearance time: 40.9 hours with artemether *v* 51.9 hours with quinine, WMD –11.0 hours, 95% CI –14.47 hours to –7.53 hours; coma recovery time: 34.8 hours with artemether *v* 40.8 hours with quinine, WMD –6.0 hours, 95% CI –10.41 hours to –1.59 hours; fever clearance time: 44.5 hours with artemether *v* 45.9 hours with quinine, WMD –1.4 hours, 95% CI –5.71 hours to + 2.91 hours). The fifth subsequent RCT (37 children with cerebral malaria in Nigeria) compared intramuscular artemether (3.2 mg/kg stat, then 1.6 mg/kg every 12 hours for 3 days) versus intravenous quinine (10 mg/kg every 8 hours). [14] It found that artemether significantly reduced fever clearance time and coma recovery time compared with quinine, but found that quinine significantly increased parasite clearance on day 7 compared with artemether (fever clearance time: 34.7 hours with artemether *v* 53.2 hours with quinine, P < 0.01; coma recovery time: 12.5 hours with artemether *v* 17.4 hours with quinine, P < 0.05; parasite clearance on day 7: 15/18 [83.8%] with artemether *v* 19/19 [100%] with quinine, P < 0.05). There was no significant difference in mortality between treatment groups (AR 1/18 [5.5%] with artemether *v* 2/19 [10.5%] with quinine; P value not significant).

Harms: The second review stated that not all studies reported on harms. [9] Among those that did, the proportion affected was small and similar between groups. The harms reported included nausea, vomiting, diarrhoea, abdominal pain, pruritus, urticaria, rash and injection site pain, and abscess. The second subsequent RCT found that one child treated with quinine developed hypoglycaemia (0/20 [0%] with artemether *v* 1/21 [5%] with quinine; P value not reported). [11] It reported no neurological problems in either treatment group after 28 days of follow up. The third subsequent RCT found no significant difference in transient neurological sequelae between artemether and quinine (2/38 [5%] with artemether *v* 1/39 [3%] with quinine; P value not reported). [12] The fourth subsequent RCT reported no important adverse effects with either artemether or quinine, and provided no details. [13] The fifth subsequent RCT found no significant difference in neurological sequelae between treatment groups (AR 2/18 [11.1%] with artemether *v* 2/19 [10.5%]; P > 0.10). [14]

Comment: The third subsequent RCT did not use loading doses of either artemether or quinine at the beginning of treatment. [12] Treatment allocation in the fourth subsequent RCT was quasi-randomised by date of admission. [13] We found a sixth subsequent RCT (52 people). [15] However, it was not clear whether participants had severe malaria, and outcomes were poorly reported.

OPTION INTRAVENOUS ARTESUNATE VERSUS QUININE

Mortality

Intravenous artesunate compared with intravenous quinine Intravenous artesunate may reduce mortality compared with intravenous quinine.

Fever clearance time

Intravenous artesunate compared with intravenous quinine Intravenous artesunate may reduce the time to clearance of fever compared with intravenous quinine.

Coma recovery time

Intravenous artesunate compared with intravenous quinine Intravenous artesunate may be as effective as intravenous quinine at reducing the time taken to recover from coma.

Benefits: We found no systematic reviews. We found five RCTs. [16] [17] [18] [19] [20] The first RCT (113 adults with severe malaria in Thailand) compared intravenous artesunate (2.4 mg/kg initially, 1.2 mg/kg 12 hours later, then 1.2 mg/kg daily) versus intravenous quinine (20 mg/kg initially, then 10 mg/kg 8 hourly). [16] It found no significant difference between treatments in mortality after 300 hours (7/59 [12%] artesunate *v* 12/54 [22%] quinine; RR 0.53, 95% CI 0.23 to 1.26). It found that artesunate significantly improved parasite clearance time, but found no significant difference in fever clearance time or coma recovery time (parasite clearance time: 63 hours with artesunate *v* 76 hours with quinine, P = 0.019; fever clearance time: 41 hours with artesunate *v* 65 hours with quinine, P = 0.2; coma recovery time: 17 hours with artesunate *v* 18 hours with quinine, P = 0.6). The second RCT (80 children with complicated malaria in India) compared intravenous artesunate (2.4 mg/kg iv stat, followed by 1.2 mg/kg after 6 hours, then once daily for 5 days) versus intravenous quinine (20 mg/kg loading dose, followed by 10 mg/kg iv 8 hourly). [17] It found that artesunate significantly reduced parasite clearance time, fever clearance time, and coma recovery time compared with quinine, with no significant difference in mortality between treatment groups (parasite clearance time: 52.2 hours with quinine *v* 41.7 with artesunate, P < 0.05; fever clearance time: 62.2 hours with quinine *v* 43.6 hours with artesunate, P < 0.05; coma recovery time: 70.2 hours with quinine *v* 50.4 hours with artesunate, P < 0.05; mortality: 8/40 [20%] with quinine *v* 5/40 [12.5%] with artesunate, P > 0.05; see comment below). [17] The third small RCT (35 adults with severe

malaria in India) compared intravenous artesunate (2.4 mg/kg iv stat, followed by 1.2 mg/kg iv or 2 mg/kg orally for 6 days) versus intravenous quinine (20 mg/kg loading dose, then 10 mg/kg 8 hourly). [18] It found no significant difference between treatments in mortality (mortality: 1/17 [5.9%] with artesunate *v* 1/18 [5.6%] with quinine; P = 0.96). It found that artesunate significantly reduced the median fever clearance time compared with quinine (median fever clearance time: 32 hours with artesunate *v* 58 hours with quinine; P = 0.023). The intraquartile range for the time taken to clear 50% and 90% of the parasites suggested the fever clearance time with artesunate was shorter (for 50% clearance: quinine intraquartile range 14 to 24 hours, *v* artesunate intraquartile range 8 to 16 hours; P = 0.01). [18] The fourth large RCT (1259 adults and 202 children with severe malaria in Bangladesh, India, Indonesia, and Myanmar) compared intravenous artesunate (2.4 mg/kg iv stat, then at 12 hours and 24 hours, then daily) versus intravenous quinine (20 mg/kg loading dose, then 10 mg/kg three times daily). [19] It found that mortality was significantly lower with artesunate compared with quinine (mortality, intention to treat analysis: 107/730 [15%] with artesunate *v* 164/731 [22%] with quinine; P = 0.0002, RR 0.69, 95% CI 0.54 to 0.83). [19] The fifth RCT (61 adults with cerebral malaria in Vietnam) compared intravenous artesunate (60 mg at 0 hours and 4 hours, then 60 mg at 24 hours and 48 hours) versus intravenous quinine (500 mg 8 hourly). [20] It found no significant difference in mortality between the treatments (5/31 [16.5%] with artesunate *v* 8/30 [26.7%] with quinine; P value not stated).It reported that the parasite and fever clearance times were significantly faster with artesunate compared with quinine (parasite clearance time: 28.1 hours with artesunate *v* 51.2 hours with quinine, P value not stated; fever clearance time: 39 hours with artesunate *v* 78 hours with quinine, P value not stated). The mean coma recovery time was not significantly different between the groups (coma recovery time: 68.9 hours with artesunate *v* 58.1 hours with quinine; P value not stated).

Harms: The first RCT found that artesunate significantly reduced hypoglycaemia compared with quinine (6/59 [10%] with artesunate *v* 15/54 [28%] with quinine; RR 0.37, 95% CI 0.15 to 0.88). [16] It found that one person treated with artesunate developed an urticarial rash. The second RCT found no adverse events with artesunate, but found that people in the quinine group experienced nausea (20/40 [50%]), headache (16/40 [40%]), vomiting (12/40 [30%]), tinnitus (8/40 [20%]), vertigo (4/40 [10%]), circulatory failure (2/50 [4%]), and sudden blindness (1/40 [3%]) at 28 days. [17] The third RCT reported no significant adverse events. [18] The fourth RCT found the risk of hypoglycaemia was significantly higher with quinine compared with artesunate (19/731 [3%] with quinine *v* 6/730 [< 1%] with artesunate; P = 0.009, RR 3.2, 95% CI 1.3 to 7.8). There was no significant difference in the neurological sequelae between the two groups (7/730 [1%] with artesunate *v* 3/731[<1%] with quinine; P = 0.23). [19] The fifth RCT reported no significant adverse events in patients receiving artesunate. [20] It did not report on adverse effects with quinine.

Comment: Treatment allocation in the second RCT was quasi-randomised by odd and even numbers. [17] The first two RCTs and third and fifth RCTs may have been underpowered to detect a clinically important difference. [16] [17] [18] [20] . The fourth RCT was a large multicentre trial which showed a significant reduction in mortality with artesunate compared with quinine. [19] The intention to treat analysis included patients with unconfirmed malaria. In total, 79/1461 (5%) participants included had blood-smear negative malaria. [19] In the third RCT, all participants received at least 24 hours of intravenous therapy and completed a 7 day course of treatment. [18] Fixed doses of artesunate and quinine were used in the fifth RCT in contrast to the other RCTs which calculated doses based on bodyweight.

OPTION QUININE

Mortality

Compared with intramuscular artemether Intravenous or intramuscular quinine seems to be as effective as intramuscular artemether at reducing mortality in people with severe malaria.

Compared with intravenous artesunate Intravenous quinine may be less effective at reducing mortality compared with intravenous artesunate.

Compared with rectal artemisinin derivatives Quinine seems to be as effective as rectal artemether, artemisinin, artesunate, and dihydroartemisinin at reducing mortality in people with severe malaria.

Compared with intramuscular arteether Quinine seems to be as effective as intramuscular arteether at reducing mortality after 28 days in children with severe malaria.

Fever clearance

Compared with intramuscular artemether Intravenous or intramuscular quinine seems to be as effective as intramuscular artemether at eradicating fever in people with severe malaria.

Compared with intravenous artesunate Intravenous quinine may be less effective than intravenous artesunate at reducing the time to clearance of fever.

Compared with rectal artemisinin derivatives Quinine seems to be as effective as rectal artemether, artemisinin, artesunate, and dihydroartemisinin at reducing time to eradication of fever in people with severe malaria.

Compared with intramuscular arteether Quinine seems to be as effective as intramuscular arteether at reducing time to clearance of fever in children with severe malaria.

Recovery from coma
Compared with intramuscular artemether Intravenous or intramuscular quinine seems to be as effective as intramuscular artemether at reducing time spent in a coma in people with severe malaria.

Compared with intravenous artesunate Intravenous quinine may be as effective as intravenous artesunate at reducing the time taken to recover from coma.

Compared with rectal artemisinin derivatives Quinine seems to be as effective as rectal artemether and artemisinin at reducing time to recovery of coma in people with severe malaria.

Compared with intramuscular arteether Quinine seems to be as effective as intramuscular arteether at reducing time to recovery from coma in children with severe malaria.

Neurological sequelae
Compared with intramuscular artemether Intravenous or intramuscular quinine seems to be as effective as intramuscular artemether at preventing neurological sequelae in people with severe malaria.

Note
We found no direct information about whether quinine is better than no active treatment in people with severe malaria.

Benefits:

Quinine versus placebo:
We found no systematic reviews or RCTs comparing quinine with placebo in people with severe, life-threatening malaria. Placebo or no treatment controlled trials of antimalarial treatment in people with severe malaria would be considered unethical.

Quinine versus intramuscular artemether:
See benefits of intramuscular artemether, p 3 .

Quinine versus intravenous artesunate:
See benefits of intravenous artesunate, p 4 .

Quinine versus intramuscular arteether:
See benefits of intramuscular arteether, p 9 .

Quinine versus rectal artemisinin derivatives:
See benefits of rectal artemisinin derivatives, p 8 .

Harms:

We found no systematic reviews or RCTs comparing quinine with placebo in people with severe, life-threatening malaria.
Quinine versus intramuscular artemether:
See harms of intramuscular artemether, p 3 .

Quinine versus intravenous artesunate:
See harms of intravenous artesunate, p 4 .

Quinine versus intramuscular arteether:
See harms of intramuscular arteether, p 9 .

Quinine versus rectal artemisinin derivatives:
See harms of artemisinin derivatives, p 8 .

Comment:

Clinical guide:
International consensus has historically recommended quinine for the treatment of severe falciparum malaria. Controlled trials will generally compare new treatments against this standard.

OPTION HIGH INITIAL DOSE QUININE COMPARED WITH STANDARD REGIMES

Mortality

High initial dose compared with standard regimens Giving a high initial dose of quinine does not seem to reduce mortality compared with standard regimens.

Fever clearance time

High initial dose compared with standard regimens Giving a high initial dose of quinine reduces the time to clearance of fever compared with standard regimens.

Coma recovery time

High initial dose compared with standard regimens Giving a high initial dose of quinine does not seem to reduce the time to recovery from coma compared with standard regimens.

Adverse effects

High initial dose compared with standard regimens Initial high-dose quinine regimens do not seem to increase the risk of neurological sequelae compared with standard regimens. High-initial-dose quinine may increase transient partial hearing loss compared with no loading dose.

Benefits: We found one systematic review (search date 2004, 4 RCTs, 144 people). [21] The systematic review found no significant difference in mortality between high initial dose of quinine (20 mg salt/kg or 16 mg base/kg given im or iv) and no loading dose, followed in both groups by standard dose quinine (3 RCTs; 4/70 [5.7%] died with high initial dose *v* 7/74 [9.5%] with no loading dose; RR 0.62, 95% CI 0.19 to 2.04). Two RCTs (99 children) found no significant difference between high initial dose and no loading dose in mean time to recover consciousness (WMD + 5.17 hours, 95% CI –1.14 hours to + 11.47 hours). Parasite clearance time and fever clearance time were shorter for the high initial dose quinine group than for the group with no loading dose (parasite clearance time: 2 RCTs, 67 people, WMD –7.4 hours, 95% CI –13.2 hours to –1.6 hours; fever clearance time: 2 RCTs, 68 people, WMD –11.1 hours, 95% CI –20.0 hours to –2.2 hours).

Harms: The systematic review found no significant difference between high initial dose of quinine and no loading dose in the rate of hypoglycaemia (2 RCTs; 4/35 [11%] had hypoglycaemia with high initial dose *v* 3/37 [8%] with no loading dose; RR 1.39, 95% CI 0.32 to 6.00). [21] One RCT (33 people) included in the review found that high initial dose quinine significantly increased transient partial hearing loss compared with no loading dose (10/17 [59%] with high initial dose *v* 3/16 [19%] with no loading dose; RR 3.14, 95% CI 1.05 to 9.38). [22] Another RCT (three arm RCT; 59 children) included in the review found no significant difference between high initial dose of quinine and no loading dose in neurological sequelae (1/18 [6%] with high initial dose *v* 2/21 [10%] with no loading dose; RR 0.58, 95% CI 0.06 to 5.91). [23]

Comment: The RCTs may have been too small to detect a clinically important difference. [23] [22] [24] [25]

Clinical guide:
International consensus has historically recommended quinine for the treatment of severe falciparum malaria. Controlled trials will generally compare new treatments against this standard.

OPTION INTRAMUSCULAR VERSUS INTRAVENOUS QUININE

Mortality

Intramuscular quinine compared with intravenous quinine Mortality rates are similar with high-dose intramuscular quinine compared with high-dose intravenous quinine.

Benefits: We found no systematic review but found one RCT. [23] The RCT (59 Kenyan children < 12 years old in 1989–1990) compared high loading dose intramuscular quinine (20 mg salt/kg initially followed by 10 mg salt/kg 12 hourly) versus high loading dose intravenous quinine (20 mg salt/kg initially followed by 10 mg salt/kg 12 hourly) versus standard dose intravenous quinine (10 mg salt/kg 12 hourly) in severe falciparum malaria. [23] It found no significant difference in mortality, mean parasite clearance time, or recovery time to drinking or walking between high dose intramuscular and high dose intravenous quinine, but lacked power to detect a clinically important difference (mortality: 3/20 [15%] deaths with im quinine *v* 1/18 [5.6%] with iv quinine, RR 2.7, 95% CI 0.3 to 23.7; mean parasite clearance time: 57 hours with im quinine *v* 58 hours with iv quinine, WMD –1.0 hours, 95% CI –12.2 hours to + 10.2 hours; mean recovery times to drinking: 47 hours with im quinine *v* 32 hours with iv quinine, WMD + 15 hours, 95% CI –5.6 hours to + 35.6 hours; mean recovery times to walking: 98 hours with im quinine *v* 96 hours with iv quinine, WMD + 2.0 hours, 95% CI –24.5 hours to + 28.5 hours).

Harms: In the RCT, neurological sequelae were reported in two children in the intramuscular group, and one child in the intravenous group had transient neurological sequelae that were not specified (2/20 [10%] with im quinine *v* 1/18 [5.6%] with iv quinine; RR 1.8, 95% CI 0.2 to 18.2). [23]

Comment: Quinine concentration profiles were similar with both routes of administration, and peak concentrations were achieved soon after intramuscular injection. The sample size might have been insufficient to rule out clinically important differences. [23]

Clinical guide:
International consensus has historically recommended quinine for the treatment of severe falciparum malaria. Controlled trials will generally compare new treatments against this standard.

OPTION RECTAL ARTEMISININ DERIVATIVES (ARTEMETHER, ARTEMISININ, ARTESUNATE, OR DIHYDROARTEMISININ) VERSUS QUININE

Mortality
Compared with quinine Rectal artemether, artemisinin, artesunate, and dihydroartemisinin seem to be as effective as quinine at reducing mortality in people with severe malaria.

Fever clearance time
Compared with quinine Rectal artemether, artemisinin, artesunate, and dihydroartemisinin seem to be as effective as quinine at reducing time to eradication of fever in people with severe malaria.

Coma recovery time
Compared with quinine Rectal artemether and artemisinin seem to be as effective as quinine at reducing time to recovery of coma in people with severe malaria.

Benefits:

Rectal artemether versus quinine:
We found one RCT conducted in Uganda comparing rectal artemether (children weighing up to 8.9 kg given 40 mg daily; children 9–18.9 kg given 80 mg dose immediately, then 40 mg daily; children 19–27.9 kg given 120 mg dose immediately, then 80 mg daily) versus intravenous quinine (20 mg/kg dose immediately, then 10 mg/kg 8 hourly) over 7 days. [26] The RCT found no significant difference in mortality between rectal artemether and intravenous quinine treatment (103 children with cerebral malaria, aged 6 months to 5 years; mortality: 6/51 [12%] with artemether *v* 10/52 [19%] with quinine; RR 0.78, 95% CI 0.50 to 1.19). It found no significant difference in the parasite and fever clearance times (mean parasite clearance time: 54.2 hours with artemether *v* 55.0 hours with quinine, P = 0.48; mean fever clearance time: 33.2 hours with artemether *v* 24.1 hours with quinine, P = 0.08). There was no significant difference in the time taken to regain consciousness (mean time: 30.1 hours with artemether *v* 22.7 hours with quinine; P = 0.1).

Rectal artemisinin versus quinine:
We found one systematic review (search date 1999, 3 RCTs) comparing rectal artemisinin versus quinine in severe malaria. [9] Two RCTs were conducted in Vietnam and one in Ethiopia (1996–1997). Meta-analysis found lower mortality with artemisinin and quicker coma recovery time, but the differences were not significant (mortality: 3 RCTs, 9/87 [10%] with artemisinin *v* 16/98 [16%] with quinine, RR 0.73, 95% CI 0.35 to 1.50; coma recovery time: 2 RCTs, 59 people, WMD –9.0 hours, 95% CI –19.7 hours to + 1.7 hours). Fever clearance time was not significantly different (no figures provided).

Rectal artesunate versus quinine:
We found one RCT (144 people with moderately severe malaria: 109 children in Malawi and 35 adults in South Africa) comparing rectal artesunate (single dose 10 mg/kg) and intravenous quinine (10 mg/kg at 0, 4, and 10 hours, then every 12 hours until oral treatment was tolerated). [27] It found no deaths in either treatment group. In children, artesunate significantly reduced fever clearance time and parasite clearance time compared with quinine (median fever clearance time: 20 hours with artesunate *v* 44 hours with quinine, P < 0.0001; mean parasite clearance time: 36 hours with artesunate *v* 45 hours with quinine, P = 0.0003). It found no significant difference in the proportion of children able to drink at 24 hours (AR 77/87 [89%] with artesunate *v* 21/22 [95%] with quinine; P = 0.3). In adults, there was no significant difference in fever clearance time and parasite clearance time (mean parasite clearance time: 49 hours with artesunate *v* 63 hours with quinine, P = 0.10; median fever clearance time: 36 hours with artesunate *v* 23 hours with quinine, P = 0.116).

Rectal dihydroartemisin versus quinine:
We found one RCT (67 people aged 2–60 years with severe malaria in Kenya in 1998), which compared rectal dihydroartemisin (160 mg initially, then 80 mg for 2 days for people > 16 years; variable dosage depending on age in people < 16 years) versus intravenous quinine (20 mg/kg initially, then 10 mg/kg 8 hourly). [28] It found no deaths with either treatment. It found that dihy-

droartemisinin significantly improved parasite clearance time compared with quinine, but found no significant difference in fever clearance time (mean parasite clearance time: 38 hours with dihydroartemisinin *v* 49 hours with quinine, P = 0.04; mean fever clearance time: 27.9 hours with dihydroartemisinin *v* 22.0 hours with quinine, P = 0.25).

Harms:

Rectal artemether versus quinine:
The RCT found no significant difference in the number of children vomiting (2/51 with artemether *v* 5/52 with quinine; P = 0.235). [26]

Rectal artemisinin versus quinine:
One RCT found that artemisinin significantly reduced the risk of hypoglycaemia compared with quinine (3/30 [10%] with artemisinin *v* 19/30 [63%] with quinine; RR 0.16, 95% CI 0.05 to 0.48). [29]

Rectal artesunate versus quinine:
The RCT found no significant difference in adverse events between treatment groups (data not reported) at 28 days, but found local reactions at quinine injection sites in three adults. [27] No adverse neurological events were reported with artesunate, and 1/8 (12.5%) adults treated with quinine developed transient dysdiadochokinesis.

Rectal dihydroartemisin versus quinine:
The RCT found that dihydroartemisin significantly reduced tinnitus compared with quinine (1/30 [3%] with dihydroartemisinin *v* 10/37 [27%] with quinine; OR 0.09, 95% CI 0.01 to 0.78). [28]

Comment:

Rectal artesunate versus quinine:
In the RCT, the sample size of the adult group may have been too small to detect a clinically important difference. [27]

Clinical guide:
A single dose of rectal artesunate does not cure malaria and must be followed by a full course of known effective treatment.

OPTION INTRAMUSCULAR ARTEETHER VERSUS QUININE

Mortality
Compared with quinine Intramuscular arteether seems to be as effective as quinine at reducing mortality after 28 days in children with severe malaria.

Fever clearance time
Compared with quinine Intramuscular arteether seems to be as effective as quinine at reducing time to clearance of fever in children with severe malaria.

Coma recovery time
Compared with quinine Intramuscular arteether seems to be as effective as quinine at reducing time to recovery from coma in children with severe malaria.

Benefits:

We found one systematic review (search date 2004, 2 RCTs, 194 children) comparing arteether versus quinine in children with cerebral malaria. [30] It found no significant difference in mortality, time to regain consciousness, parasite clearance time , fever clearance time, and parasite clearance on days 7 and 28 between treatment groups (mortality: 2 RCTs, 194 people, AR 18/99 [18%] with arteether *v* 23/95 [24%] with quinine, RR 0.75, 95% CI 0.43 to 1.30; time to regain consciousness: 2 RCTs, 153 people, 81 hours with arteether *v* 72 hours with quinine, WMD + 6.69 hours, 95% CI –3.19 hours to + 16.57 hours; parasite clearance time: 2 RCTs, 153 people, 81 hours with arteether *v* 71 hours with quinine, WMD + 1.32 hours, 95% CI –6.48 hours to + 9.11 hours; fever clearance time: 2 RCTs, 146 people, 75 hours with arteether *v* 71 hours with quinine, WMD + 5.10 hours, 95% CI –5.76 hours to + 15.95 hours; presence of parasites at day 7: 2 RCTs, 151 people, AR 5/79 [6%] with arteether *v* 8/72 [11%] with quinine, RR 0.57, 95% CI 0.19 to 1.67; presence of parasites at day 28: 1 RCT, 78 people, AR 11/41 [27%] with arteether *v* 13/37 [35%] with quinine, RR 0.76, 95% CI 0.39 to 1.49).

Harms:

One RCT identified by the review found no significant difference in adverse events or residual neurological complications between treatment groups at 28 days (adverse events: 36/48 [75%] with arteether *v* 34/44 [77%] with quinine, RR 0.97, 95% CI 0.77 to 1.22; residual neurological complications: 5/34 [14.7%] with arteether *v* 3/24 [12.5%] with quinine, RR 1.18, 95% CI 0.31 to 4.46). [31]

Comment:

The RCTs included in the review were small and the review reported that it lacked power to detect clinically important differences. [30]

QUESTION **What are the effects of adjunctive treatment for complicated falciparum malaria in non-pregnant people?**

OPTION EXCHANGE BLOOD TRANSFUSION

Mortality

Compared with no exchange blood transfusion Exchange blood transfusion may not reduce mortality rates compared with no exchange transfusion in people with severe malaria taking antimalarial drugs.

Benefits: We found one systematic review (search date 2001). [32] It found no suitable RCTs in people with malaria. We found no additional RCTs that met our inclusion criteria (see comment below).

Harms: We found no RCTs.

Comment: We found one systematic review of case control studies [32] and one small RCT. [33] The review (search date 2001, 8 studies, 279 people) found no significant difference in mortality between exchange transfusion plus antimalarial drugs and antimalarial drugs only (8 studies; OR for death 1.2, 95% CI 0.7 to 2.1). [32] Admission criteria for exchange transfusion varied in the included studies, but generally, parasitaemia was greater than 10%, and most people had failed to improve after 24 hours of antimalarial treatment. The methods and volumes used for exchange transfusion also varied. Those who received exchange blood transfusions had higher mean levels of parasitaemia before treatment began (26% with exchange transfusion *v* 11% with no exchange transfusion; $P < 0.05$) and fulfilled more World Health Organization criteria for the diagnosis of severe malaria (mean 3.6 with exchange transfusion *v* 2.8 with no exchange transfusion; $P = 0.03$). The RCT compared exchange transfusion plus antimalarial drugs versus antimalarial drugs alone, but it included only eight people. [33]

OPTION INITIAL BLOOD TRANSFUSION FOR TREATING MALARIAL ANAEMIA

Mortality

Compared with no transfusion Initial blood transfusion may not reduce mortality in clinically stable children with severe malaria compared with conservative treatment or iron supplements.

Adverse effects

Adverse effects may be more common overall with initial blood transfusion, although the risk of severe adverse effects may not be increased.

Benefits: We found one systematic review (search date 2005, 2 RCTs, 230 children with malarial anaemia; packed cell volume range 12–17%). [34] The first RCT (116 children) compared initial blood transfusion versus conservative treatment in children from Tanzania, and the second RCT (114 children) compared blood transfusion versus iron supplements in children from the Gambia. Both trials excluded children who were clinically unstable with respiratory distress or signs of cardiac failure. Meta-analysis found fewer deaths in the transfused children, but the difference was not significant (1/118 [1%] with transfusion *v* 3/112 [3%] with control; RR 0.41, 95% CI 0.06 to 2.70). We found no RCTs examining the effects of transfusion in adults with malaria.

Harms: Coma and convulsions occurred significantly more often after transfusion (8/118 [6.8%] with transfusion *v* 0/112 [0%] without transfusion; RR 8.6, 95% CI 1.1 to 66.4). [34] Seven of the eight adverse events occurred in one RCT. Meta-analysis combining deaths and severe adverse events found no significant difference between people who received transfusions and people who did not (8/118 [7%] with transfusion *v* 3/112 [3%] without transfusion; RR 2.5, 95% CI 0.7 to 9.3). Transmission of hepatitis B or HIV was not reported.

Comment: Studies were small and loss to follow up was greater than 10%, both of which are potential sources of bias. [34] In the first RCT, one child in the transfusion group and one child in the conservative treatment group required an additional transfusion after clinical assessment. In the second RCT, 10 children allocated to receive iron supplements later required transfusion when packed cell volume fell below 12% or they showed signs of respiratory distress.

Clinical guide:

Transfusion may be clinically essential in some circumstances.

OPTION ANTICONVULSANTS (PHENOBARBITONE)

Mortality

Compared with no anticonvulsants Phenobarbitone, especially at higher doses, may increase mortality compared with no anticonvulsants in people with cerebral malaria.

Convulsions
Compared with no anticonvulsants Phenobarbitone reduces the risk of convulsions in people with cerebral malaria over 4 weeks.

Benefits: We found one systematic review comparing anticonvulsants versus control (placebo or no anticonvulsants) for treating cerebral malaria. [35] It examined the routine use of anticonvulsants for treating people with cerebral malaria. The review identified three RCTs, all of which assessed phenobarbitone. The review found that phenobarbitone significantly reduced convulsions within 4 weeks of attending hospital compared with control (search date 2004, 3 RCTs, 573 participants; convulsions: 24/296 [8%] with phenobarbitone *v* 78/277 [28%] with control; RR 0.27, 95% CI 0.14 to 0.52). Overall, the review found no significant difference in mortality between phenobarbitone and control (AR of death: 67/296 [23%] with phenobarbitone *v* 52/277 [19%] with control; RR 1.30, 95% CI 0.58 to 2.88). However, meta-analysis of only the two trials with adequate allocation concealment found a significant increase in mortality with phenobarbitone (2 RCTs, 388 participants; AR of death: 38/194 [20%] with phenobarbitone *v* 19/194 [10%] with control; RR 1.98, 95% CI 1.19 to 3.28).

Harms: The review found limited evidence that phenobarbitone can increase mortality (see benefits section above).

Comment: The RCTs included in the review used different doses of phenobarbitone (3.5 mg/kg, 10 mg/kg, and 20 mg/kg). [35] The highest dose of phenobarbitone (20 mg/kg) significantly increased mortality compared with placebo (AR: 30/170 [18%] with phenobarbitone *v* 14/170 [8%] with placebo; RR 2.14, 95% CI 1.18 to 3.90).

OPTION DEXAMETHASONE

Mortality
Compared with placebo Dexamethasone does not reduce mortality compared with placebo.

Coma recovery time
Compared with placebo The effects of dexamethasone on time to recover from coma are unclear compared with placebo.

Adverse effects
Dexamethasone has been associated with increased risks of gastrointestinal bleeding and seizures.

Benefits: **Dexamethasone versus placebo:**
We found one systematic review (search date 2004, 2 RCTs, 143 people with severe/cerebral malaria treated with quinine), which compared dexamethasone versus placebo over 48 hours. [36] One RCT was conducted in Indonesia and the other in Thailand. The review found no significant difference in mortality (14/71 [20%] with dexamethasone *v* 16/72 [23%] with placebo; RR 0.89, 95% CI 0.48 to 1.68). One RCT found a longer mean time between start of treatment and coma recovery with dexamethasone (76 hours with dexamethasone *v* 57 hours with placebo; $P < 0.02$), [37] but the other RCT found no significant difference (83.4 hours with dexamethasone *v* 80.0 hours with placebo; WMD + 3.4 hours, 95% CI –31.3 hours to + 38.1 hours). [38]

Harms: The review found that dexamethasone significantly increased gastrointestinal bleeding and seizures compared with placebo (gastrointestinal bleeding: 7/71 [10%] with dexamethasone *v* 0/72 [0%] with placebo, RR 8.17, 95% CI 1.05 to 63.6; seizures: 11/71 [15.5%] with dexamethasone *v* 3/72 [4%] with placebo, RR 3.32, 95% CI 1.05 to 10.47). [36]

Comment: No effect of steroids on mortality was shown, but the trials were small. The effect of steroids on disability was not reported.

GLOSSARY

Coma recovery time The time between commencing treatment and regaining consciousness.
Fever clearance time The time between commencing treatment and the temperature returning to normal.
Parasite clearance time (PCT) The time between commencing treatment and the first negative blood test. PCT 50 is the time taken for parasites to be reduced to 50% of the first test value, and PCT 90 is the time taken for parasites to be reduced to 10% of the first test value.

SUBSTANTIVE CHANGES

Intravenous artesunate versus quinine Three RCTs added. [18] [19] [20] benefits and harms data enhanced; re-categorised from Unknown effectiveness to Likely to be beneficial.

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