Clinical review

Extracts from "Clinical Evidence Concise"

Severe life threatening malaria in endemic areas

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Definition Severe malaria is caused by the protozoan infection of red blood cells with *Plasmodium falciparum* and comprises a variety of syndromes requiring hospitalisation. Clinically complicated malaria presents with life threatening conditions, which include 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 is unrousable coma and no other cause of encephalopathy (for example, hypoglycaemia, sedative drugs) in the presence of *P falciparum* infection. This review does not include the treatment of malaria in pregnancy.

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

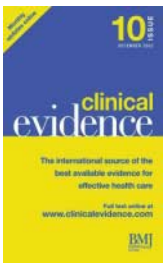
Likely to be beneficial

Artemether
Two systematic reviews and one subsequent randomised controlled trial (RCT) found no significant difference between artemether versus quinine for preventing death in people with severe malaria.

High first dose quinine
One systematic review and one additional RCT found no significant difference in mortality between quinine regimens with high initial quinine dose versus no loading dose. The systematic review found that high first dose of quinine reduced parasite clearance time and duration of fever compared with no loading dose.

Quinine
We found no RCTs comparing quinine versus placebo or no treatment, but there is consensus that treatment is likely to be beneficial.

Rectal artemisinin
One systematic review found no significant difference in mortality with rectal artemisinin versus quinine.



Clinical Evidence (www.clinicalevidence.com) is a compendium of the best available evidence on common and important clinical questions

Unknown effectiveness

Chloroquine versus quinine
Two RCTs in children found no significant difference in mortality with chloroquine versus quinine. However, these RCTs were conducted in the Gambia between 1988 and 1994, when chloroquine resistance was uncommon.

Desferrioxamine mesylate
One systematic review found weak evidence that desferrioxamine mesylate versus placebo reduced the risk of persistent seizures in children with cerebral malaria.

Exchange blood transfusion
One systematic review has found no suitable RCTs.

Initial blood transfusion
One systematic review found no significant difference in deaths in clinically stable children who received an initial blood transfusion for malarial anaemia; it found more adverse events.

Intramuscular versus intravenous quinine
One RCT in children found no significant difference with intramuscular versus intravenous quinine in recovery times or deaths in Kenya in 1990.

Sulfadoxine-pyrimethamine versus quinine
One RCT found that sulfadoxine-pyrimethamine versus quinine cleared parasites faster in children with complicated non-cerebral malaria in 1992-4 in the Gambia, but it found no significant difference in mortality.

Likely to be ineffective or harmful

Dexamethasone
One systematic review found no significant difference in mortality with dexamethasone versus placebo, but gastrointestinal bleeding and seizures were more common with dexamethasone.

In the next update of *Clinical Evidence* (issue 11), the options on chloroquine and sulfadoxine-pyrimethamine will be removed at the authors' request on the grounds of clinical relevance (see commentary).

The full content of Clinical Evidence (and Clinical Evidence Concise) is available online (www.clinicalevidence.com); topics are updated every eight months.

Commentary: Treating severe and complicated malaria

Umberto D'Alessandro

Clinical attacks are usually uncomplicated and can be managed with an effective oral drug. Most occur in sub-Saharan Africa. Of the 200 million episodes of clinical malaria that occur each year among African children, 4-6 million are severe and life threatening, and most of the 1 million deaths from malaria worldwide are in Africa.[1] Although some risk factors for severe malaria have been identified—for example, human leucocyte antigens (HLA Bw 53 is associated with protection from severe malaria), it is still unclear why only some children develop severe disease.

The clinical manifestations of severe malaria are complex and may vary between age groups and according to the intensity of transmission that determines the speed at which partial immunity is acquired. Case management is also complex and is not limited to giving efficacious antimalarial drugs—it includes proper management of complications such as hypoglycaemia and metabolic acidosis.

Quinine remains the most widely used antimalarial drug in the treatment of severe malaria,[1] but decreased sensitivity has been detected in areas of South East Asia.[2] Nowadays, drug resistance is probably the major problem for malaria control countries where malaria is endemic. This extract from *Clinical Evidence* defined chloroquine and sulfadoxine-pyrimethamine as drugs of "unknown effectiveness"; in the light of the widespread resistance to chloroquine and the emerging resistance to sulfadoxine-pyrimethamine, these two drugs should not be considered in severe cases.

Slow, constant intravenous infusion is the preferred route for giving quinine.[3] This is not always possible and quinine can also be given by deep intramuscular injection into the anterior thigh. Intragluteal injection should be avoided because of the risk of sciatic nerve damage, and the absorption is slow and uncertain.[4] A few studies have shown good efficacy and tolerability for rectal administration, without the problems of the intramuscular route or the complexity of intravenous administration.[4]

In children able to attend a health facility that is well staffed and with adequate supplies, most deaths occur within 24 hours after admission,[5] underscoring the importance of early treatment for preventing deaths.[6] It is therefore important to improve access to appropriate care. One way of tackling this problem is to simplify the treatment by using rectal quinine or rectal artemisinin or artesunate, which could be given promptly even at basic health facilities. A trial on prompt administration of rectal artesunate is ongoing and should provide some data on its usefulness in early treatment.

Artemether is rightly classified among the interventions likely to be beneficial and has a marginal advantage over quinine. It is easier to use (intramuscularly) and is less likely to cause hypoglycaemia, but the cost of injections for treating an adult is about three times that of quinine.[2] In settings with poor resources, cost has to be taken into account when drug policies are formulated. Nevertheless, the drug accounts for only a fraction of the total cost of managing cases of severe malaria. A careful evaluation is needed.

Another message comes from the small sample size of most of the reviewed studies, which underlines the difficulties of carrying out research on treatment of severe malaria.

Competing interests: None declared.

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One hundred years ago

Hypnotism in Abyssinia

M. Ilg, described as a confidential adviser of His Majesty Menelek, Emperor of Abyssinia, appears to have confided to a French interviewer some curious facts as to the uses to which hypnotism is put in Abyssinia. From time to time a number of children under the age of 12 are selected for the position of *labascha* or detector of crime. They are believed to have the power, when hypnotized, of revealing to the proper authorities the identity of any criminal who may be "wanted" for a given offence. For instance, not long ago there was a case of arson at Adis-Ababa. A *labascha* was taken to the scene of the crime and there thrown into hypnotic sleep. The child forthwith set off in the direction of Harrar. He ran without stopping for sixteen hours on end, and his pace was so severe that the professional runners told off to accompany him gave up one after the other. When he got near Harrar, the boy suddenly took a path which led into a field where he laid hold of a labourer who was quietly at work there.

Thereupon the man confessed his guilt. Again, a robbery with murder was committed in the neighbourhood of Adis-Ababa. A *labascha* was procured, and after being hypnotized proceeded to visit a number of churches and private houses, and at last lay down at the door of an empty hut. The owner on his return was arrested. He at first denied all knowledge of the crime and was subjected to a searching interrogatory. His movements were traced, and it was found that they corresponded exactly to the course taken by the *labascha* in finding the hut. The criminal, tortured by remorse, had thrown himself down at the door just as the *labascha* had done. There must be a considerable number of criminals at large in this country. On the venerable principle *Anceps renedium melites quam nullum* we venture to commend the Abyssinian method to the attention of Scotland Yard.

(*BMJ* 1904;i:96)