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Malaria: fluid therapy in severe disease

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ABSTRACT

INTRODUCTION: Severe malaria mainly affects children aged under 5 years, 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 may lead to neurological sequelae in survivors. Severe malarial anaemia may have a mortality rate of over 13%. The role of fluid resuscitation in severe malaria is complex and controversial. Volume expansion could help to improve impaired organ perfusion and correct metabolic acidosis. However, rapid volume expansion could aggravate intracranial hypertension associated with cerebral malaria, leading to an increased risk of cerebral herniation. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What is the optimal method of fluid resuscitation in patients with severe malaria? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 187 studies. After deduplication and removal of conference abstracts, 93 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 82 studies and the further review of 11 full publications. Of the 11 full articles evaluated, two systematic reviews and three RCTs were added at this update. We performed a GRADE evaluation for seven PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for three interventions based on information about the effectiveness and safety of human albumin, intravenous fluids, and whole blood or plasma.

QUESTIONS

INTERVENTIONS

Key points

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

  The manifestations of severe malaria depend on age. Severe anaemia and hypoglycaemia are more common in children. Acute pulmonary oedema, acute kidney injury, and jaundice are more common in adults, while acidosis and coma (cerebral malaria) occur in all age groups.

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

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

  The main aspect of malaria treatment is the use of appropriate antimalarial medications. However, for this update, we have decided to focus on fluid resuscitation in people with severe malaria, which is a complex and controversial issue.

  Volume expansion could help to improve impaired organ perfusion and correct metabolic acidosis. However, rapid volume expansion could aggravate intracranial hypertension associated with cerebral malaria, leading to an increased risk of cerebral herniation.

- For this overview, we evaluated evidence from RCTs and systematic reviews of RCTs on the following three intervention groups: intravenous fluids (such as normal saline, dextrose saline, dextrose, Hartmann's solution, Ringer's lactate, but not including human albumin or plasma substitutes such as gelatin); human albumin; and whole blood or plasma.

  We compared these interventions with usual standard treatment and with each other. We also included within-option comparisons (e.g., different volumes and regimen protocols).

- We don't know whether a routine blood transfusion is more effective than no blood transfusion with regards to mortality in children with severe anaemia and confirmed malaria parasitaemia, but who are otherwise not in distress or severely unwell.

- Much of the data for human albumin and intravenous fluid therapy come from a subgroup analysis of one large multicentre RCT, the FEAST trial.

  Overall, the FEAST trial found a significant increase in 48-hour mortality in children with severe febrile illness and impaired perfusion (including children with severe malaria) receiving fluid bolus (combined results for saline or albumin) compared with usual care (no fluid bolus, maintenance fluids only). It found that the excess mortality with fluid bolus compared with no fluid bolus also occurred in the subgroup of children with severe malaria.

  Data from a subgroup analysis of the FEAST trial (human albumin and intravenous saline considered as separate interventions) plus evidence from further RCTs found that a fluid bolus with human albumin may be associated with higher mortality than no bolus (maintenance intravenous fluids only) in children with severe malaria.

  We don't know whether a bolus of saline has a greater effect on mortality in children with severe malaria compared with maintenance fluids alone. There was a non-significant trend towards higher mortality with intravenous saline bolus compared with no bolus reported in the subgroup analysis of the FEAST trial.

- All the RCTs we found were in children, so may not be directly relevant to adult patients. While all these trials administered boluses of fluid determined by patient weight, the relative size of bolus varied between trials, meaning that 'bolus' is a heterogeneous intervention and care should be taken when interpreting collective findings. Quality of evidence may be reduced due to lack of blinding to the interventions administered in many of the RCTs, although blinding may be very difficult to achieve when comparing different fluid resuscitation regimens.

Clinical context

GENERAL BACKGROUND

Severe malaria mainly affects children aged under 5 years, 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 may lead to neurological sequelae in survivors. Severe malarial anaemia may have a mortality rate of over 13%.

FOCUS OF THE REVIEW

The main aspect of malaria treatment is the use of appropriate antimalarial medications. Please see previous versions of this overview. For this update, we have focused on fluid resuscitation in people with severe malaria.

COMMENTS ON EVIDENCE

All the RCTs we found were in children rather than adults, so may not be directly relevant to all patients. Some of the trials assessed 'bolus' administration of fluid. While all these trials administered boluses of fluid determined by patient weight, the relative size of bolus varied between trials, meaning that 'bolus' is a heterogeneous intervention and care should be taken when interpreting collective findings. Quality of evidence may be reduced due to lack of blinding to the interventions administered, although blinding may be very difficult to achieve when comparing different fluid resuscitation regimens. In some trials, the population included was broader than people with severe malaria and included people with severe febrile illness and impaired perfusion due to causes other than severe malaria.

SEARCH AND APPRAISAL SUMMARY

The literature search was carried out in December 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 187 studies. After deduplication and removal of conference abstracts, 93 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 82 studies and the further review of 11 full publications. Of the 11 full articles evaluated, two systematic reviews and three RCTs were included.

DEFINITION

Plasmodium falciparum malaria is caused by protozoan infection of red blood cells and comprises a variety of syndromes. This overview deals with 'severe' or clinically complicated malaria as defined by clinical or laboratory evidence of vital organ dysfunction. [1] This includes coma, severe anaemia, renal failure, respiratory distress syndrome, hypoglycaemia, shock, spontaneous haemorrhage, and convulsions. Cerebral malaria is defined as unrousable coma in the absence of any other cause of encephalopathy, and in the presence of *P falciparum* infection. [2] This overview does not currently cover the treatment of malaria in pregnancy. **Fluid resuscitation in severe malaria** The main aspect of malaria treatment is the use of appropriate antimalarial medications. [3] However, mortality remains high, even in the case of rapid administration of appropriate antimalarial chemotherapy. [4] There is, therefore, much interest in identifying supportive measures (such as fluid resuscitation) that could reduce malaria mortality. Metabolic acidosis is an important predictor of fatal outcome in severe malaria. [5] Hypoperfusion is thought to contribute to poor tissue perfusion and an increased rate of anaerobic glycolysis that results in metabolic acidosis. [6] [7] [5] It is postulated that treatment of hypovolaemia with intravenous fluid resuscitation could, therefore,

correct acidosis, and possibly improve outcomes. [5] However, in malaria, acidosis is likely to be multifactorial, and not simply explained by hypovolaemia. In addition, there are real risks that fluid resuscitation, in the context of severe malaria, could be associated with important deleterious effects. For example, rapid volume expansion could aggravate intracranial hypertension associated with cerebral malaria, leading to an increased risk of cerebral herniation. [8] In addition, in the context of acute respiratory distress syndrome rapid infusion of intravenous fluid can be lethal. [3] [9] The role of fluid resuscitation in severe malaria is, therefore, complex and controversial. This overview sets out to analyse the evidence base for the use of intravenous fluid resuscitation in the context of severe malaria.

INCIDENCE/ PREVALENCE

Malaria is a major health problem in the tropics, with an estimated 198 million clinical cases and 584,000 deaths worldwide in 2013. [10] More than 85% of malaria cases and 90% of malaria deaths occur in sub-Saharan Africa, mainly in young children (i.e., those aged younger than 5 years), [3] [11] mainly from cerebral malaria and anaemia. [3] Depending on the intensity of transmission, children in malaria-endemic regions become resistant to severe malaria by the age of 5 years; however, they remain susceptible to uncomplicated episodes of febrile infection until late childhood or early adolescence. [12] Non-immune travellers and individuals spending time away from malaria-endemic regions are also at risk of infection and severe malaria. [3] [13]

AETIOLOGY/ RISK FACTORS

Malaria is a protozoan parasite transmitted by the bite of infected female *Anopheles* mosquitoes. [3] There are five parasite strains responsible for malaria (*Plasmodium falciparum*, *P vivax*, *P ovale*, *P malariae*, and *P knowseli*); however, *P falciparum*, which causes 'severe' malaria, is the most important cause of mortality. Susceptibility to clinical disease is determined by the degree of prior exposure to *P falciparum*. [13] Genetic mutations that affect the ability of *P falciparum* to infect and/or replicate in RBCs, such as haemoglobin S (HbS) [14] and HbC, [15] ovalocytosis, [16] thalassaemias, [17] and glucose-6-phosphate dehydrogenase deficiency, [18] have also been shown to confer a survival advantage in the presence of malaria. For example, in the case of HbS, heterozygotes are protected against *P falciparum* (due to reduced cyto-adherence and parasite growth at low oxygen tensions). [3] (See also our *BMJ Clinical Evidence* overview on Sickle cell disease.)

PROGNOSIS

When treated promptly with effective antimalarial drugs, uncomplicated falciparum malaria has a mortality of roughly 0.1%. Mortality rises when the proportion of infected erythrocytes (parasitaemia) exceeds 2%, although the relationship between parasite density and prognosis in falciparum malaria is very variable. [3] The manifestations of severe malaria depend on age. Severe anaemia and hypoglycaemia are more common in children, and acute pulmonary oedema, acute kidney injury and jaundice more common in adults, while acidosis and coma (cerebral malaria) occur in all age groups. [3] In children aged under 5 years with cerebral malaria, the estimated case fatality of treated malaria is 19%, although reported hospital case fatality may be as high as 40%. [2] [19] 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%. [19] In adults, mortality of cerebral malaria is 20%; this rises to 50% in pregnancy. [20]

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

Mortality; **neurological sequelae at follow-up**; **hypotensive shock**; **coma recovery time**; **adverse effects** (pulmonary oedema, intracranial hypertension or severe allergic reaction in those receiving albumin).

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date December 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to December 2014, Embase 1980 to December 2014, The Cochrane Database of Systematic Reviews 2014, issue 12 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, and containing 20 individuals or more, of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant

to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported questions from this overview: What are the effects of antimalarial treatments for complicated falciparum malaria in non-pregnant people? What are the effects of adjunctive treatment for complicated falciparum malaria in non-pregnant people? We have added the following question: What is the optimal method of fluid resuscitation in patients with severe malaria? **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What is the optimal method of fluid resuscitation in patients with severe malaria?

OPTION HUMAN ALBUMIN New

- For GRADE evaluation of interventions for Malaria: fluid therapy in severe disease, see table, p 15 .
- Fluid bolus with human albumin may be associated with higher mortality than no bolus (maintenance intravenous fluids only) in children with severe malaria. Much of the data for this comparison comes from a subgroup analysis in one large multicentre RCT, the FEAST trial.
- We don't know whether human albumin (bolus) has a greater effect on mortality in children with severe malaria than saline (bolus).
- The FEAST RCT compared fluid bolus (5% albumin or 0.9% saline) with no fluid bolus in children with severe febrile illness and impaired perfusion. It found a significant increase in mortality in children receiving any bolus treatment (5% albumin or 0.9% saline) compared with no bolus therapy.
- The excess mortality with fluid bolus compared with no fluid bolus also occurred in the subgroup of children with severe malaria.

Benefits and harms

Human albumin (bolus) versus usual care (no bolus):

We found one systematic review (search date 2012) that evaluated the effects of fluid bolus on mortality in children with shock due to sepsis or severe infection, including malaria. [21] Given that this review combined data on all types of fluid bolus in a meta-analysis of bolus versus no bolus, and our inclusion criteria required us to evaluate the evidence of individual fluid regimens with no combinations, we have reported directly from the relevant RCTs. [8] [22] [9] One large RCT, the FEAST trial, which was included in this systematic review, evaluated children with severe febrile illness with numerous different causes; only 57% of the children had malaria. [9] The analysis in the main publication of this study for children with severe malaria combined albumin and saline bolus groups, rather than reporting these interventions individually, therefore, not meeting the inclusion criteria for comparisons for this overview (see more details

on the main analysis of this RCT in the Comment section, p 4). However, we have included data from a subgroup analysis in this RCT of children with severe malaria, published in a supplementary appendix, as it reported on human albumin (bolus) and saline (bolus) as separate interventions compared with no bolus. [9]

Mortality

Human albumin (bolus) compared with usual care (no human albumin, maintenance fluid only) Human albumin (bolus) may be less effective than usual care (no human albumin, no bolus, maintenance intravenous fluids only) with regards to mortality in children with severe malaria (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[22] RCT **3-armed trial**	61 children aged >2 months with severe malarial anaemia and respiratory distress	**Mortality , timeframe not stated** 4/23 (17%) with human albumin (bolus over 1 hour) 3/18 (17%) with no human albumin (maintenance fluids only) The remaining arm evaluated 0.9% saline (bolus over 1 hour) All children subsequently received whole blood transfusion for the treatment of anaemia	Significance of difference between groups not assessed Difference across the three groups reported to be not significant (P = 0.97)		
[8] RCT **5-armed trial**	101 children presenting with severe malaria, positive test for *Plasmodium falciparum*, and moderate acidosis See Further information on studies	**Mortality , timeframe not stated** 0/33 (0%) with human albumin (bolus over 1 hour) 2/33 (6%) with no human albumin (maintenance fluids only)	Significance of difference between groups not assessed		
[9] RCT **3-armed trial**	1793 children with severe febrile illness and impaired perfusion, positive for malaria parasitaemia Subgroup analysis See Further information on studies	**Mortality , 48 hours** 57/590 (10%) with human albumin (bolus) 34/591 (6%) with no human albumin (no bolus, maintenance fluids only) The remaining arm evaluated saline (bolus)	RR 1.68 95% CI: 1.12 to 2.53	●○○	no human albumin (no bolus, maintenance fluids only)

Neurological sequelae at follow-up

Human albumin (bolus) compared with usual care (no human albumin, maintenance fluid only) We don't know whether human albumin (bolus) is more effective than usual care (no human albumin, maintenance intravenous fluids only) at reducing neurological sequelae (timeframe unclear) in children with severe malaria and moderate acidosis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neurological sequelae					
[8] RCT **5-armed trial**	101 children presenting with severe malaria, positive test for *Plasmodium falciparum*, and moderate acidosis See Further information on studies	**Neurological sequelae , timeframe not stated** 3/33 (9%) with human albumin (bolus over 1 hour) 0/30 (0%) with no human albumin (maintenance fluids only)	Significance of difference between groups not assessed		

No data from the following reference on this outcome. [21] [22] [9]

Hypotensive shock

No data from the following reference on this outcome. [8] [21] [22] [9]

Coma recovery time

No data from the following reference on this outcome. [8] [21] [22] [9]

Adverse effects

No data from the following reference on this outcome. [8] [21] [22] [9]

Human albumin (bolus) versus intravenous saline (bolus):

We found one systematic review (search date 2012) that evaluated the effects of fluid bolus on mortality in children with shock due to sepsis or severe infection. [21] The review synthesised data for the comparison of human albumin with intravenous saline (2 RCTs; 170 children). We have included additional reporting from one of the RCTs [8] on the subgroups of children with moderate metabolic acidosis (see Further information on studies) and data from a subgroup analysis in another RCT, included in the systematic review, [21] published in a supplementary appendix to the main trial report. [9]

Mortality

Human albumin (bolus) compared with intravenous saline (bolus) We don't know how human albumin (bolus) and intravenous saline (bolus) compare with regard to mortality in children with severe malaria (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[21] Systematic review	Children with severe malaria 2 RCTs in this analysis	**Mortality , timeframe not stated** 6/79 (8%) with human albumin (bolus over 1 hour) 14/91 (15%) with 0.9% saline (bolus over 1 hour)	RR 0.46 95% CI 0.18 to 1.19 See Further information on studies	⟷	Not significant
[8] RCT **5-armed trial**	101 children presenting with severe malaria, positive test for *Plasmodium falciparum* and moderate acidosis In review [21] See Further information on studies	**Mortality, moderate acidosis subgroup (20 mL/kg bolus) , timeframe not stated** 0/33 (0%) with human albumin (bolus over 1 hour) 3/35 (9%) with saline (bolus over 1 hour) The remaining arms evaluated human albumin (bolus over 1 hour) and saline (bolus over 1 hour) for severe acidosis (40 mL/kg bolus), and placebo; see Further information on studies	Significance not assessed See Further information on studies		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[9] RCT **3-armed trial**	1793 children with severe febrile illness and impaired perfusion, positive for malaria parasitaemia Subgroup analysis See Further information on studies	**Mortality , 48 hours** 57/590 (10%) with human albumin (bolus) 53/612 (9%) with saline (bolus) The remaining arm evaluated no bolus	RR 1.11 95% CI: 0.78 to 1.59	⟷	Not significant

Neurological sequelae at follow-up

Human albumin (bolus) compared with intravenous saline (bolus) We don't know how human albumin (bolus) and intravenous saline (bolus) compare at reducing neurological sequelae in children with severe malaria and moderate acidosis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neurological sequelae					
[8] RCT **5-armed trial**	101 children presenting with severe malaria, positive test for *Plasmodium falciparum* and moderate acidosis See Further information on studies	**Neurological sequelae, moderate acidosis subgroup (20 mL/kg bolus) , timeframe not stated** 3/33 (9%) with human albumin (bolus over 1 hour) 1/32 (3%) with saline (bolus over 1 hour) The remaining arms evaluated human albumin (bolus over 1 hour) and saline (bolus over 1 hour) for severe acidosis (40 mL/kg bolus), and placebo; see Further information on studies	Significance of difference between groups not assessed		

No data from the following reference on this outcome. [21] [22] [9]

Hypotensive shock

No data from the following reference on this outcome. [8] [21] [22] [9]

Coma recovery time

No data from the following reference on this outcome. [8] [21] [22] [9]

Adverse effects

No data from the following reference on this outcome. [8] [21] [22] [9]

Human albumin versus whole blood or plasma:

We found no systematic review or RCTs.

Further information on studies

[22] Children randomised to intravenous volume resuscitation (with either human albumin [4.5%] or saline [0.9%]) received 20 mL/kg over the first hour, while awaiting whole blood transfusion (packed red cells were not available at the institution in which the study was conducted). Study children were otherwise managed according to a standard treatment protocol including intravenous quinine, maintenance fluid (4% dextrose/0.18% saline at a rate of 4 mL/kg/hour), face mask oxygen (if oxygen saturation was <95%), and potassium supplements (if the plasma potassium level was <3.5 mmol/L).

[22] *Neurological sequelae and adverse effects* The RCT reported that no study participants developed clinical features suggestive of raised intracranial pressure or had evidence of neurological sequelae at discharge. No study participants developed pulmonary oedema, cardiorespiratory deterioration, worsening acidosis, or worsening anaemia. The difference in adverse effects across the three groups was reported as not significant (P = 0.97).

[8] *Randomisation* Baseline level of acidosis influenced randomisation as the study committee and external reviewers deemed that it would be inappropriate to withhold resuscitation fluids from children with severe acidosis. Eligible children with moderate acidosis at baseline (base deficit 8–15 mmol/L) were randomly assigned to groups receiving a bolus of 20 mL/kg of either 4.5% human albumin solution or 0.9% saline, or to the control group (maintenance only). Eligible children with severe acidosis at presentation (base deficit >15 mmol/L) were randomised to receive a bolus of 40 mL/kg of either 4.5% albumin or 0.9% saline. The intervention groups received a single bolus infused over the first hour. Additional boluses were prescribed for children who fulfilled the criteria for rescue therapy. All participants also received the standard treatment protocol: intravenous quinine, maintenance fluid (4% dextrose/0.18% saline at a rate of 4 mL/kg/hour), face mask oxygen (if oxygen saturation decreased to <95%), rectal paracetamol to control fever, and potassium supplements (if the plasma potassium level was <3.5 mmol/L).

[8] *Analysis* For the purposes of comparison of human albumin and saline, the authors of the study combined results for children with moderate and severe acidosis. Here, we have limited the reporting of results versus usual care (no human albumin, maintenance fluid only) to those from children with moderate acidosis, because the design of the RCT meant that no children with severe metabolic acidosis were randomised to receive usual care (no human albumin, maintenance fluid only).

[8] *Mortality* The RCT is underpowered to detect a difference between treatments for the outcome of mortality. After adjustment for baseline factors (hypotension, presence of coma, hypoglycaemia, and seizures), the OR for mortality for saline (bolus) compared with human albumin (bolus) was reported to be 8.3 (95% CI 1.3 to 51.6, P = 0.007).

[8] *Adverse effects* The frequency of pulmonary oedema reported to be secondary to intravenous fluid resuscitation was 0.9% (1/115) of the children randomised to receive saline. No children in the other two groups developed pulmonary oedema. Of the eight children who developed elevated intracranial pressure, seven had been randomised to receive saline, and one to receive albumin. All of these eight children died within 48 hours of being admitted to hospital.

[21] *Human albumin versus intravenous saline* For the meta-analysis, the authors of the review combined results for children with moderate and severe acidosis from one RCT. [8]

[9] The data we have reported from this RCT is a subgroup analysis of children with severe malaria. It has been published in a supplementary appendix of the main report and includes data on human albumin (bolus) and saline (bolus) as separate interventions compared with each other and no bolus. Please see the Comment section for more detail on this RCT.

Comment:

Bolus versus no bolus therapy

One multi-centre RCT (Uganda, Kenya, Tanzania) [9] assessed mortality in children with severe febrile illness and impaired perfusion following fluid bolus compared with no fluid bolus. A total of 3141 children were randomly allocated to 5% albumin bolus, 0.9% saline bolus, or no bolus at admission. All children also received maintenance fluid as recommended by national guidelines. Only 57% of the population were children with malaria. Although the RCT did perform a subgroup analysis included in the main publication of the population with malaria, the analysis combined saline and human albumin in the bolus group and compared this with no fluid bolus. Mortality at

48 hours for the entire population was as follows: 10.6% with albumin bolus; 10.5% with saline bolus; 7.3% with no bolus. The increase in mortality was significant for any bolus versus no bolus (RR 1.45; 95% CI 1.13 to 1.86; P = 0.003) at 48 hours, and also at 4 weeks (any bolus *v* no bolus; P = 0.004). The authors reported that excess mortality associated with fluid bolus versus no fluid bolus was found across all of the subgroup analyses performed, including for the subgroup of children with malaria. This landmark study suggests that fluid bolus of either albumin or saline is associated with increased mortality in children with severe malaria.

OPTION INTRAVENOUS FLUIDS New

- For GRADE evaluation of interventions for Malaria: fluid therapy in severe disease, see table, p 15 .
- For this option, we evaluated evidence on intravenous fluids (such as normal saline, dextrose saline, dextrose, Hartmann's solution, Ringer's lactate, but not including human albumin in this intervention group). We did not include plasma substitutes such as gelatin.
- Based on the data from RCTs meeting the inclusion criteria for the comparisons and population in this overview, we don't know whether intravenous saline (bolus) has a greater effect on mortality compared with maintenance fluids only or human albumin (bolus) in children with severe malaria.
- The FEAST trial compared fluid bolus (5% albumin or 0.9% saline) with no fluid bolus in children with severe febrile illness and impaired perfusion. It found a significant increase in mortality in children receiving any bolus treatment (5% albumin or 0.9% saline) compared with no bolus therapy.
- The FEAST trial found that the excess mortality with fluid bolus compared with no fluid bolus also occurred in the subgroup of children with severe malaria.

Benefits and harms

Intravenous fluids (bolus) versus usual care (no bolus, maintenance fluids only):

We found one systematic review (search date 2012) that evaluated the effects of fluid bolus on mortality in children with shock due to sepsis or severe infection. [21] The review combined data on all forms of fluid bolus in a meta-analysis of bolus versus no bolus. Our inclusion criteria required us to evaluate the evidence of individual fluid regimens with no combinations; therefore, we have reported directly from the relevant RCTs. [8] [22] [9] One large RCT, the FEAST trial, which was included in the systematic review, evaluated children with severe febrile illness with numerous different causes; only 57% of the children had malaria. [9] The analysis in the main publication of this study of children with severe malaria combined albumin and saline bolus groups, rather than reporting these interventions individually, therefore, not meeting the inclusion criteria for comparisons for this overview (see more details on the main analysis of this RCT in the Comment section, p 9). However, we have included data from a subgroup analysis in this RCT of children with severe malaria, published in a supplementary appendix, as it reported on human albumin (bolus) and saline (bolus) as separate interventions compared with no bolus. [9]

Mortality

Intravenous saline (bolus) compared with usual care (no bolus, maintenance fluids only) We don't know whether intravenous saline (bolus) is more effective than usual care (no bolus, maintenance fluids only) with regards to mortality in children with severe malaria. One large RCT found an increase in mortality at 48 hours with intravenous saline (bolus), however the results did not reach statistical significance. (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[22] RCT **3-armed trial**	61 children aged >2 months with severe malarial anaemia and respiratory distress	**Mortality , timeframe not stated** 3/20 (15%) with 0.9% saline (bolus over 1 hour) 3/18 (17%) with usual care (no bolus, maintenance fluids only) The remaining arm evaluated human albumin (bolus over 1 hour) All children subsequently received blood transfusion for the treatment of anaemia	Significance of difference between groups not assessed Difference across the three groups reported to be not significant (P = 0.97)		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[8] RCT **5-armed trial**	101 children presenting with severe malaria, positive test for *Plasmodium falciparum*, and moderate acidosis See Further information on studies	**Mortality , timeframe not stated** 3/35 (9%) with 0.9% saline (bolus over 1 hour) 2/33 (6%) with usual care (no bolus, maintenance fluids only)	Significance of difference between groups not assessed		
[9] RCT **3-armed trial**	1793 children with severe febrile illness and impaired perfusion, positive for malaria parasitaemia Subgroup analysis See Further information on studies	**Mortality , 48 hours** 53/612 (9%) with saline (bolus) 34/591 (6%) with usual care (no bolus, maintenance fluids only) The remaining arm evaluated human albumin (bolus)	RR 1.51 95% CI: 0.99 to 2.28; the result was of borderline significance	⟷	Not significant

Neurological sequelae at follow-up

Intravenous saline (bolus) compared with usual care (no bolus, maintenance fluids only) We don't know whether intravenous saline (bolus) is more effective than usual care (no bolus, maintenance fluids only) at reducing neurological sequelae (timeframe unclear) in children with severe malaria and moderate acidosis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Neurological sequelae					
[8] RCT **5-armed trial**	101 children presenting with severe malaria, positive test for *Plasmodium falciparum*, and moderate acidosis See Further information on studies	**Neurological sequelae , timeframe not stated** 1/35 (3%) with saline bolus (bolus over 1 hour) 0/33 (0%) with usual care (no bolus, maintenance fluids only)	Significance of difference between groups not assessed		

No data from the following reference on this outcome. [21] [22] [9]

Hypotensive shock

No data from the following reference on this outcome. [8] [21] [22] [9]

Coma recovery time

No data from the following reference on this outcome. [8] [21] [22] [9]

Adverse effects

No data from the following reference on this outcome. [8] [21] [22] [9]

Intravenous fluid versus human albumin:

See option on Human albumin, p 4 .

Intravenous fluid versus whole blood or plasma:

We found no systematic review or RCTs.

Further information on studies

[22] Children randomised to intravenous volume resuscitation (with either human albumin [4.5%] or saline [0.9%]) received 20 mL/kg over the first hour while awaiting whole blood transfusion (packed red cells were not available at the institution in which the study was conducted). Study children were otherwise managed according to a standard treatment protocol, including intravenous quinine, maintenance fluid (4% dextrose/0.18% saline at a rate of 4 mL/kg/hour), face mask oxygen (if oxygen saturation was <95%), and potassium supplements (if the plasma potassium level was <3.5 mmol/L).

[22] *Neurological sequelae and adverse effects* The RCT reported that no study participants developed clinical features suggestive of raised intracranial pressure or had evidence of neurological sequelae at discharge. No study participants developed pulmonary oedema, cardiorespiratory deterioration, worsening acidosis, or worsening anaemia. The difference in adverse effects across the three groups was reported as not significant (P = 0.97).

[8] *Randomisation* Baseline level of acidosis influenced randomisation as the study committee and external reviewers deemed that it would be inappropriate to withhold resuscitation fluids from children with severe acidosis. Eligible patients with moderate acidosis at baseline (base deficit 8–15 mmol/L) were randomly assigned to groups receiving a bolus of 20 mL/kg of either 4.5% human albumin solution or 0.9% saline, or to the control group (maintenance only). Eligible children with severe acidosis at presentation (base deficit >15 mmol/L) were randomised to receive a bolus of 40 mL/kg of either 4.5% albumin or 0.9% saline. The intervention groups received a single bolus infused over the first hour. Additional boluses were prescribed for children who fulfilled the criteria for rescue therapy. All participants also received the standard treatment protocol: intravenous quinine, maintenance fluid (4% dextrose/0.18% saline at a rate of 4 mL/kg/hour), face mask oxygen (if oxygen saturation decreased to <95%), rectal paracetamol to control fever, and potassium supplements (if the plasma potassium level was <3.5 mmol/L).

[8] *Analysis* For the purposes of comparison of human albumin and saline, the authors of the study combined results for children with moderate and severe acidosis. Here, we have limited the reporting of results versus usual care (no human albumin, maintenance fluid only) to those from children with moderate acidosis because the design of the RCT meant that no children with severe metabolic acidosis were randomised to receive usual care (no human albumin, maintenance fluid only).

[8] *Mortality* The RCT is underpowered to detect a difference between treatments for the outcome of mortality. After adjustment for baseline factors (hypotension, presence of coma, hypoglycaemia, and seizures), the OR for mortality for saline (bolus) compared with human albumin (bolus) was reported to be 8.3 (95% CI 1.3 to 51.6, P = 0.007).

[8] *Adverse effects* The frequency of pulmonary oedema reported to be secondary to intravenous fluid resuscitation was 0.9% (1/115) of the children randomised to receive saline. No children in the other two groups developed pulmonary oedema. Of the eight children who developed elevated intracranial pressure, seven had been randomised to receive saline, and one to receive albumin. All of these eight children died within 48 hours of being admitted to hospital.

[9] The data we have reported from this RCT is a subgroup analysis of children with severe malaria. It has been published in a supplementary appendix of the main report and includes data on human albumin (bolus) and saline (bolus) as separate interventions compared with each other and no bolus. Please see the Comment section for more detail on this RCT.

Comment: **Bolus versus no bolus therapy**

See the Comment in the option on Human albumin, p 4 for further information on this RCT comparing bolus with no bolus therapy. [9]

OPTION WHOLE BLOOD OR PLASMA New

- For GRADE evaluation of interventions for Malaria: fluid therapy in severe disease, see table, p 15 .
- We don't know whether routine blood transfusion is more effective than no blood transfusion with regards to mortality in children with severe anaemia and confirmed malaria parasitaemia, but who are otherwise not in distress or severely unwell.

Benefits and harms

Blood transfusion versus usual care (no blood transfusion):

We found one systematic review (search date 2010, 2 RCTs, 230 children) evaluating the effectiveness of routine blood transfusion in patients with malaria and severe anaemia, but otherwise not in distress or severely unwell (see Further information on studies). [23] The systematic review did not identify any RCTs in adults. We found one additional RCT that compared two different volumes of blood transfusion in children with acute severe anaemia. [24] This RCT did not meet our inclusion criteria. See Comment, p 12 for further details.

Mortality

Blood transfusion compared with usual care (no blood transfusion) We don't know whether a blood transfusion is more effective than no blood transfusion with regards to mortality in children with severe anaemia and confirmed malaria parasitaemia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[23] Systematic review	Children with severe anaemia and confirmed malaria parasitaemia 2 RCTs in this analysis	**Mortality , timeframe not stated** 1/118 (<1%) with blood transfusion 3/112 (3%) with no blood transfusion	RR 0.41 95% CI 0.06 to 2.70 P = 0.35	⟷	Not significant

Neurological sequelae at follow-up

No data from the following reference on this outcome. [23]

Hypotensive shock

No data from the following reference on this outcome. [23]

Coma recovery time

No data from the following reference on this outcome. [23]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] Systematic review	Children with severe anaemia and confirmed malaria parasitaemia 2 RCTs in this analysis	**Severe adverse effects** 8/118 (7%) with blood transfusion 0/112 (0%) with no blood transfusion Severe adverse effects included convulsions (4 children), coma (3 children) and chills and fever (1 child) Neither trial had long enough follow-up to assess risk of HIV or hepatitis B transmission	RR 8.60 95% CI 1.11 to 66.42	●●●	no blood transfusion

Whole blood or plasma versus human albumin:

We found no systematic review or RCTs.

Whole blood or plasma versus intravenous fluids:

We found no systematic review or RCTs.

Further information on studies

[23] *Methods* Both RCTs were open-label in design, including children only. The authors of the review commented that, due to the nature of the interventions (blood transfusion versus no blood transfusion), blinding would have been difficult. Both RCTs had a high loss to follow-up (13.8% and 22.8% by eighth weeks). Severe anaemia was defined as a haematocrit <20%.

[23] *Exclusion* Both RCTs excluded children with "very severe" anaemia (based on haematocrit), haemorrhage, or features of congestive cardiac failure. Children with sickle cell anaemia were excluded from one RCT, and this was unclear in the other trial.

[23] *Interventions* Both trials used whole blood for transfusion, but different volumes were transfused (15 mL/kg in one study and 20 mL/kg in the other). Non-transfused participants received oral iron supplements in one study but not in the other.

[23] *Malaria treatment* In one RCT all patients received treatment for malaria with chloroquine and mebendazole followed by chloroquine prophylaxis. The other RCT used an initial combination of chloroquine and sulfadoxinepyrimethamine, with chemoprophylaxis in randomly selected subgroups only.

Comment: We found one multi-centre open-label RCT (2 centres in Uganda) that compared two different volumes of blood transfusion in 160 children (aged between 60 days–12 years) admitted to hospital with severe anaemia; 59% of these children had malaria. [24] There was no subgroup analysis of the children with malaria, so we have reported the results in the Comment section rather than the main Benefits and Harms section of this option. Children were randomly assigned to receive initial transfusion with either a bolus of 20 mL/kg whole blood (or 10 mL/kg packed red cells) or 30 mL/kg whole blood (or 15 mL/kg packed red cells). An initial volume of 30 mL/kg is higher than the usual standard care as recommended by WHO guidelines. Further transfusion was allowed after 8 hours following reassessment for children who had a haemoglobin less than 4 g/dL or a haemoglobin of 4–6 g/dL plus signs of increased severity (such as respiratory distress or impaired consciousness). It found that significantly more children receiving the higher volume of blood transfusion had corrected their severe anaemia by 24 hours compared to those receiving the standard volume transfusion (70 children [90%] in the 30 mL/kg group compared with 61 children [74%] in the 20 mL/kg

group; RR 1.54, 95%CI 1.09 to 2.18, P = 0.01). There was no significant difference in serious adverse events, deaths before 48 hours, deaths before 28 days post-admission, and severe anaemia or mortality at 28 days. [24]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Human albumin New option. One systematic review [21] and three RCTs [8] [9] [22] added. Categorised as 'unlikely to be beneficial'.

Intravenous fluids New option. One systematic review [21] and three RCTs [8] [9] [22] added. Categorised as 'unlikely to be beneficial'.

Whole blood or plasma New option. One systematic review added. [23] Categorised as 'unknown effectiveness'.

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GRADE **Evaluation of interventions for Malaria: fluid therapy in severe disease.**

Important outcomes	Coma recovery time, Hypotensive shock, Mortality, Neurological sequelae at follow-up								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What is the optimal method of fluid resuscitation in patients with severe malaria?									
3 (1288) [8] [22] [9]	Mortality	Human albumin (bolus) versus usual care (no bolus)	4	–1	0	–1	0	Low	Quality point deducted for methodological flaws (open-label nature of studies and subgroup analysis in largest RCT); directness point deducted for uncertainty about generalisability of population (evidence in children only)
1 (63) [8]	Neurological sequelae at follow-up	Human albumin (bolus) versus usual care (no bolus)	4	–3	0	–2	0	Very low	Quality points deducted for sparse data, methodological flaws (open-label nature of study), and incomplete reporting of results (lack of statistical assessment); directness points deducted for uncertainty about generalisability of population (includes moderate acidosis only) and evidence in children only
3 (1372) [21] [9]	Mortality	Human albumin (bolus) versus intravenous saline (bolus)	4	–1	0	–1	0	Low	Quality point deducted for methodological flaws (open-label nature of studies and subgroup analysis in largest RCT); directness point deducted for uncertainty about generalisability of population evidence (in children only)
1 (63) [8]	Neurological sequelae at follow-up	Human albumin (bolus) versus intravenous saline (bolus)	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, methodological flaws (open-label nature of study), and incomplete reporting of results (lack of statistical assessment); directness point deducted for uncertainty about generalisability of population evidence (in children only)
3 (1309) [8] [22] [9]	Mortality	Intravenous fluids (bolus) versus usual care (no bolus, maintenance fluids only)	4	–1	0	–1	0	Low	Quality points deducted for methodological flaws (open-label nature of studies and subgroup analysis in largest RCT); directness point deducted for uncertainty about generalisability of population (evidence in children only)
1 (68) [8]	Neurological sequelae at follow-up	Intravenous fluids (bolus) versus usual care (no bolus, maintenance fluids only)	4	–3	0	–2	0	Very low	Quality points deducted for sparse data, methodological flaws (open-label nature of study), and incomplete reporting of results (lack of statistical assessment); directness points deducted for uncertainty about generalisability of population (includes moderate acidosis only) and evidence in children only
2 (230) [23]	Mortality	Blood transfusion versus usual care (no blood transfusion)	4	–2	0	–1	0	Very low	Quality points deducted for methodological flaws (open-label nature of studies) and for uncertainty about result due to low event rate; directness point deducted for uncertainty about generalisability of population (evidence in children only)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.