

5.5.3. Pre-referral treatment options

Clinical Question/ PICO

Population: Children aged < 5 years with severe malaria (rural settings in Africa and Asia where parenteral treatment is not available)
Intervention: Rectal artesunate plus referral for definitive treatment
Comparator: Placebo plus referral for definitive treatment

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Rectal artesunate	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality (in Asia) 7-30 days	Relative risk 0.44 (CI 95% 0.23 – 0.82) Based on data from 2,010 patients in 1 studies. (Randomized controlled)	31 per 1000 Difference:	14 per 1000 17 fewer per 1000 (CI 95% 24 fewer – 6 fewer)	Low Due to serious inconsistency and serious imprecision ¹	
All-cause mortality (in Africa) 7-30 days	Relative risk 0.81 (CI 95% 0.63 – 1.04) Based on data from 6,040 patients in 1 studies. (Randomized controlled)	44 per 1000 Difference:	36 per 1000 8 fewer per 1000 (CI 95% 16 fewer – 2 more)	Low Due to serious inconsistency and serious imprecision ²	
All-cause mortality (overall) 7-30 days	Relative risk 0.74 (CI 95% 0.59 – 0.93) Based on data from 8,050 patients in 1 studies. (Randomized controlled)	41 per 1000 Difference:	30 per 1000 11 fewer per 1000 (CI 95% 17 fewer – 3 fewer)	Moderate Due to serious inconsistency ³	

- 1. Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** In Asia, older children and adults were also randomized to artesunate or placebo, and mortality was significantly higher in those given rectal artesunate; the cause is unclear. **Indirectness: no serious.** This trial was conducted in community settings in Bangladesh, Ghana and the United Republic of Tanzania. **Imprecision: serious.** The number of events was low.
- 2. Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** In Asia, older children and adults were also randomized to artesunate or placebo, and mortality was significantly higher in those given rectal artesunate; the cause is unclear. **Indirectness: no serious.** This trial was conducted in community settings in Bangladesh, Ghana and the United Republic of Tanzania. **Imprecision: serious.** The 95% confidence interval is wide and includes no difference.
- 3. Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** In Asia, older children and adults were also randomized to artesunate or placebo, and mortality was significantly higher in those given rectal artesunate; the cause is unclear. **Indirectness: no serious.** This trial was conducted in community settings in Bangladesh, Ghana and the United Republic of Tanzania. **Imprecision: no serious.** The result is statistically significant, and the study had adequate power to detect this effect.

Clinical Question/ PICO

Population: Children aged > 6 years and adults with severe malaria (rural settings where parenteral treatment is not available)
Intervention: Rectal artesunate plus referral for definitive treatment
Comparator: Placebo plus referral for definitive treatment

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Rectal artesunate	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality 7-30 days	Relative risk 2.21 (CI 95% 1.18 – 4.15) Based on data from 4,018 patients in 1 studies. (Randomized controlled)	7 per 1000 Difference:	15 per 1000 8 more per 1000 (CI 95% 1 more – 22 more)	Low Due to serious inconsistency and serious imprecision ¹	

1. **Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** Rectal artesunate appears beneficial in children < 5 years and harmful in older children and adults. This finding is difficult to explain. **Indirectness: no serious.** This trial was conducted in a single setting in Bangladesh. **Imprecision: serious.** There were few deaths in adults in this trial: 31/2009 in treated and 14/2009 in controls.