

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	Relative risk 0.44 (CI 95% 0.23 – 0.82)	31 per 1000	14 per 1000	Low Due to serious	

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Rectal artesunate	Certainty of the Evidence (Quality of evidence)	Plain language summary
Asia) 7-30 days	Based on data from 2,010 participants in 1 studies. (Randomized controlled)	Difference:	17 fewer per 1000 (CI 95% 24 fewer – 6 fewer)	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 participants 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 participants 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	

- 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.
- 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.
- 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 participants 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.