5.5.2. Parenteral alternatives when artesunate is not available

Clinical Question/ PICO

Population: Adults with severe malaria (malaria-endemic countries)
Intervention: Intramuscular artemether
Comparator: Intravenous or intramuscular artesunate

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate	**Intervention** Artemether	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death	Relative risk 0.55 (CI 95% 0.34 — 0.92) Based on data from 494 participants in 2 studies. (Randomized controlled)	148 per 1000 Difference:	81 per 1000 **67 fewer per 1000** (CI 95% 98 fewer — 12 fewer)	Moderate Due to serious imprecision [1]	
Neurological sequelae at discharge	Relative risk		CI 95%		
Coma resolution time	Based on data from: 494 participants in 2 studies. (Randomized controlled)	Not pooled.		Moderate Due to serious imprecision [2]	
Parasite clearance time	Based on data from: 494 participants in 2 studies. (Randomized controlled)	Not pooled.		Moderate Due to serious imprecision [3]	
Fever clearance time	Based on data from: 494 participants in 2 studies. (Randomized controlled)	Not pooled.		Low Due to serious imprecision [4]	

1. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** There is no statistical heterogeneity. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These trials and the meta-analysis have inadequate power to detect a difference in mortality or to prove equivalence.
2. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** Both studies suggest an advantage with artesunate, although this was statistically significant only in the small trial. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These data could not be pooled.
3. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no**

serious. Neither study found a difference between treatments. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These data could not be pooled.
4. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** One trial found no statistically significant difference, and the other, small trial found a benefit with artesunate. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These data could not be pooled.

Clinical Question/ PICO

Population:	Children with severe malaria (malaria-endemic countries)
Intervention:	Intramuscular artemether
Comparator:	Intravenous or intramuscular quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death	Relative risk 0.96 (CI 95% 0.76 — 1.2) Based on data from 1,447 participants in 12 studies. (Randomized controlled)	170 per 1000 Difference:	163 per 1000 **7 fewer per 1000** (CI 95% 41 fewer — 34 more)	Moderate Due to serious imprecision [1]	
Neurological sequelae at discharge	Relative risk 0.84 (CI 95% 0.66 — 1.07) Based on data from 968 participants in 7 studies. (Randomized controlled)	220 per 1000 Difference:	185 per 1000 **35 fewer per 1000** (CI 95% 75 fewer — 15 more)	Low Due to very serious imprecision [2]	
Coma resolution time	Based on data from: 358 participants in 6 studies. (Randomized controlled)	Quinine: The mean time in control groups ranged from 17.4 to 42.4 h. Artemether: The mean time was 5.45 h shorter in the intervention groups (7.90 to 3.00 h shorter).		Low Due to very serious risk of bias [3]	
Parasite clearance time	Based on data from: 420 participants in 7 studies. (Randomized controlled)	Quinine: The mean time in control groups ranged from 22.4 to 61.3 h. Artemether: The mean time was 9.03 h shorter in the intervention groups (11.43 to 6.63 h shorter).		Moderate Due to serious inconsistency [4]	
Fever clearance time	Based on data from: 457 participants in 8 studies. (Randomized controlled)	Quinine: The mean time in control groups ranged from 18 to 61 h. Artemether: The mean time was 3.73 h shorter in the intervention groups (6.55 to 0.92 h shorter).		Low Due to serious risk of bias and serious inconsistency [5]	

1. **Risk of Bias: no serious.** Various risks of bias, but exclusion of trials with high or unclear risk of selection bias did not change this result. **Inconsistency: no serious.** None of the individual trials found statistically significant effects, and there was no statistical heterogeneity between trials. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: serious.** These trials and the meta-analysis had inadequate power to detect a difference or to prove equivalence.
2. **Risk of Bias: no serious.** Various risks of bias, but exclusion of trials with high or unclear risk of selection bias did not change this result. **Inconsistency: no serious.** None of the individual trials found statistically significant effects, and there was no statistical heterogeneity between trials. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: very serious.** These trials and the meta-analysis have inadequate power to detect a difference or to prove equivalence. The 95% CI is very wide and includes clinically important differences and no effect.
3. **Risk of Bias: very serious.** Four of the six trials had unclear risk of selection bias. When these four trials are excluded, the result becomes nonsignificant. **Inconsistency: no serious.** Statistically significant differences were seen in only two of the six trials; however, statistical heterogeneity between trials was low, and the result of the meta-analysis is significant. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe

malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect.
4. **Risk of Bias: no serious.** Various risks of bias, but exclusion of trials with high or unclear risk of selection bias did not change this result. **Inconsistency: serious.** The mean difference in parasite clearance time ranged from a 2 h increase with artemether to a 15 h decrease. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect.
5. **Risk of Bias: serious.** Four of the seven trials had unclear risks of selection bias. When these four trials are excluded, the result becomes nonsignificant. **Inconsistency: serious.** The mean difference in fever clearance time ranged from a 25 h increase with artemether to an 18 h decrease. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: no serious.** The meta-analysis has adequate power to detect this effect. The result is statistically significant but may not be clinically important.

Clinical Question/ PICO

Population: Adults with severe malaria (malaria-endemic countries)
Intervention: Intramuscular artemether
Comparator: Intravenous or intramuscular quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death	Relative risk 0.59 (CI 95% 0.42 — 0.83) Based on data from 716 participants in 4 studies. (Randomized controlled)	208 per 1000 Difference:	123 per 1000 **85 fewer per 1000** (CI 95% 121 fewer — 35 fewer)	Moderate Due to serious imprecision [1]	
Neurological sequelae at discharge	Relative risk 2.92 (CI 95% 0.31 — 27.86) Based on data from 560 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	12 per 1000 **8 more per 1000** (CI 95% 3 fewer — 107 more)	Moderate Due to serious imprecision [2]	
Coma resolution time	Based on data from: 683 participants in 3 studies. (Randomized controlled)	Not pooled.		Low Due to serious inconsistency and serious imprecision [3]	
Parasite clearance time	Based on data from: 716 participants in 4 studies.	Not pooled.		Moderate Due to serious imprecision [4]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fever clearance time	Based on data from: 716 participants in 4 studies.	Not pooled.		Moderate Due to serious imprecision [5]	

1. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: no serious.** Statistically significant differences were seen in only one of the four studies; however, statistical heterogeneity among the trials was low, and the results of the meta-analysis are statistically significant. **Indirectness: no serious.** All four trials compared intramuscular artemether with intravenous quinine in adults: two studies in Thailand, one each in Papua New Guinea and Viet Nam. **Imprecision: serious.** These trials and the meta-analysis had inadequate power to detect a difference in mortality or to prove equivalence.
2. **Risk of Bias: no serious.** This single trial had a low risk of bias. **Imprecision: serious.** Neurological sequelae in adults were uncommon. This trial had inadequate power to detect or exclude clinically important differences.
3. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: serious.** One trial found a shorter median coma resolution time with quinine, and one trial found no difference; the third trial reported mean coma recovery time incompletely. **Imprecision: serious.** The data could not be pooled.
4. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: no serious.** The two largest studies both found shorter median clearance times with artemether. **Indirectness: no serious.** All four trials compared intramuscular artemether with intravenous quinine in adults: two studies in Thailand, one each in Papua New Guinea and Viet Nam. **Imprecision: serious.** The data could not be pooled.
5. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: no serious.** One trial found a shorter median fever clearance time with quinine, and two trials found a shorter time with artemether. **Indirectness: no serious.** All four trials compared intramuscular artemether with intravenous quinine in adults: two studies in Thailand, one each in Papua New Guinea and Viet Nam. **Imprecision: serious.** The data could not be pooled.