Acute anaemia after treatment of malaria with intravenous artesunate

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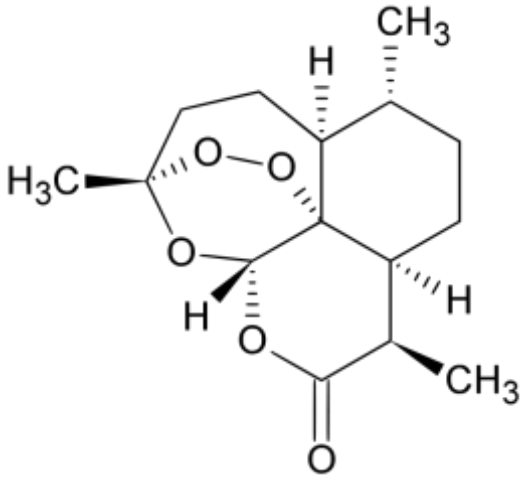
Antimalarial Drug Resistance and the Development of Artemisinin and Its Derivatives

- Drug resistance led to the need for new antimalarials
- Artemisinins were discovered and developed in Studies in China and Thailand between 1970-2000

- **Characteristics:**
  - Rapid activity
  - Good tolerability
  - High failure rate in monotherapy



Kano, S. (2010).J Infect Chemother.

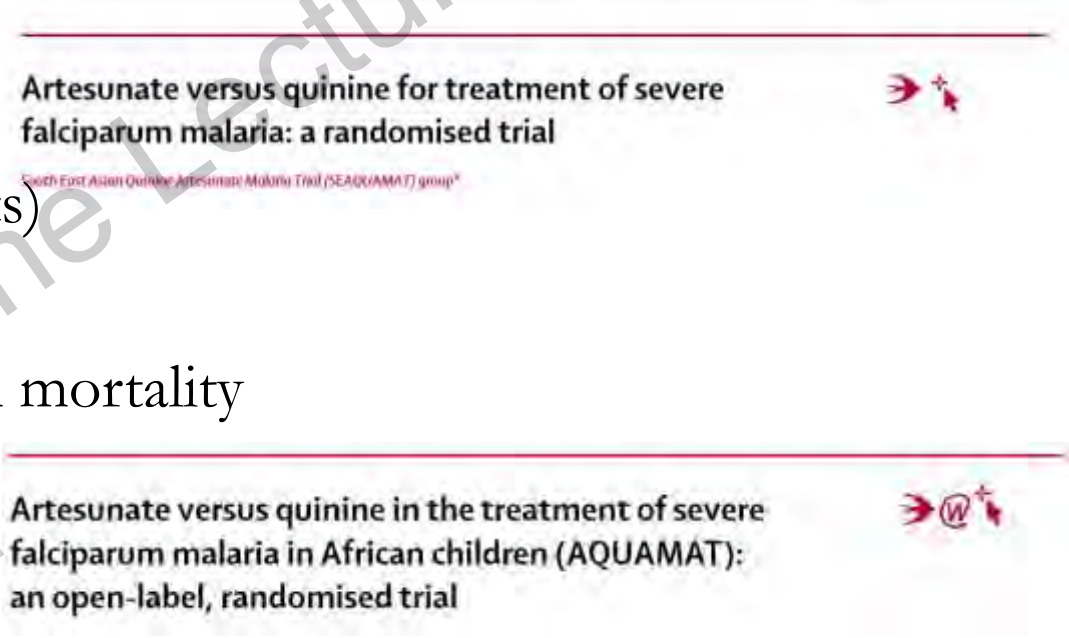
Artemisinin Combination Therapy: Oral treatment of uncomplicated malaria

- Development of artemisinin combination therapy
- Artesunate, artemether and dihydroartemisinin became most widely used antimalarials
- In 2011 a projected number of 287 million treatment courses with ACTs have been used

Intravenous Artesunate for Severe Malaria

- Comparison of iv artesunate versus i.v. quinine

- **SEAQUAMAT trial**
  - South East Asia (adults)
    - N=1461
    - ~35% reduction in mortality
- **AQUAMAT trial**
  - Africa (children)
    - N=5425
    - ~23% reduction in mortality


Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial

South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group*

Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial

Dondorp, A., *et al.* (2005).Lancet. Dondorp, A. M., *et al.* (2010).Lancet.

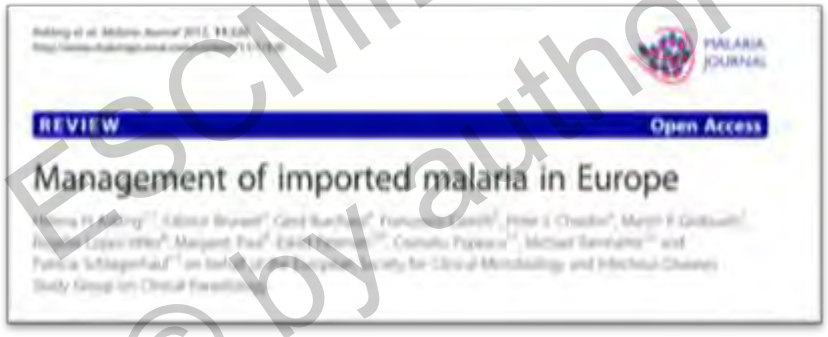
Advantages of iv Artesunate in Severe Malaria

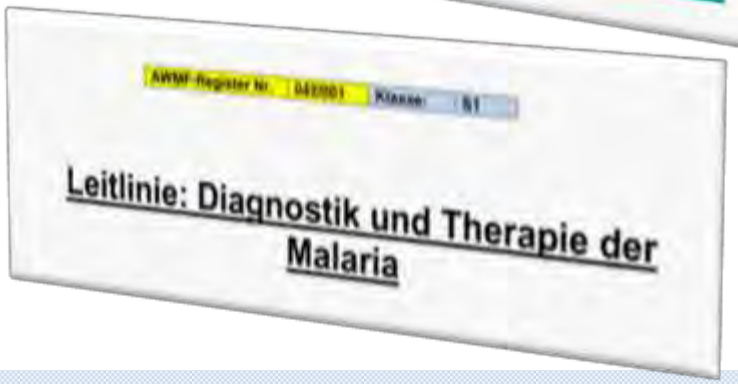
- Rapid activity
- Activity against broad range of developmental stages
- No resistance problem
- No treatment associated hypoglycaemia
- No treatment associated cardio-toxicity
- No need for monitoring of glucose, ECG
- No need for rate controlled parenteral administration
- Lower mortality

Intravenous Artesunate: First Line Treatment for Severe Malaria

- WHO Malaria treatment guidelines

- ESCMID position paper
- UK treatment guidelines
- German treatment guideleines
- Austria, …

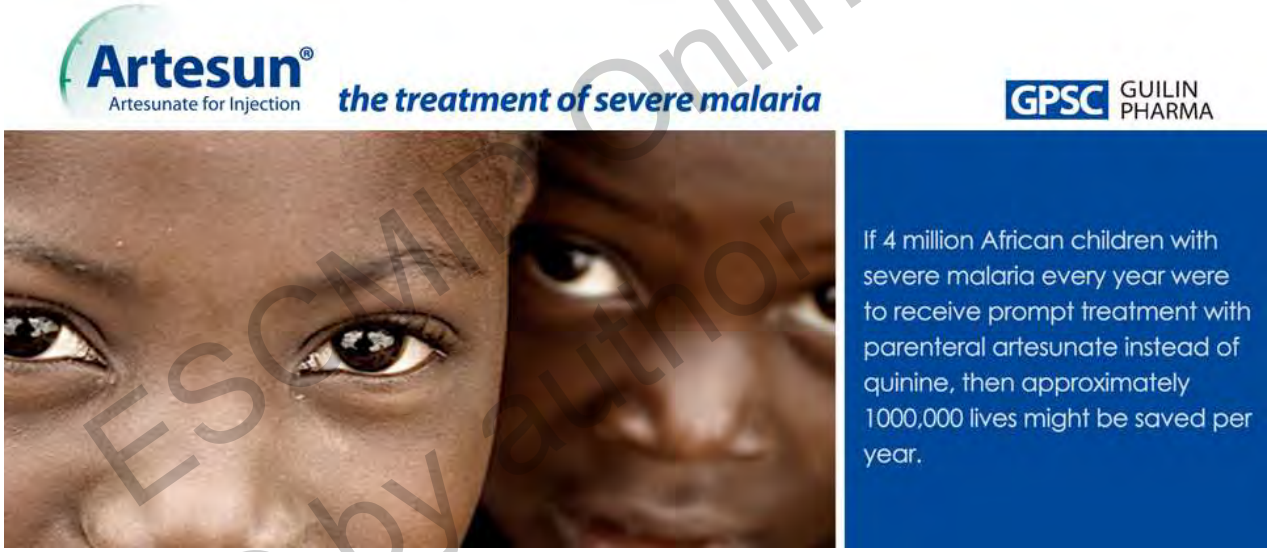




World Health Organization. (2010).Askling, H. H., *et al.* (2012).Malar J.

Potential Problems of iv Artesunate

- No studies in returning travellers
- Not licensed in Europe / USA /Japan
- Produced in PR China by Guilin Pharmaceuticals, Shanghai
- No GMP product available



Guilin Pharmaceuticals. Accessed. 04/2014.

Intravenous Artesunate for Severe Malaria in Travelers, Europe

Thomas Zoller, Thomas Junghanss, Annette Kapaun, Ida Gjørup, Joachim Richter, Mats Hugo-Persson, Kristine Mørch, Behruz Foroutan, Norbert Suttorp, Salih Yürek, and Holger Flick

Retrospective analysis of severe malaria cases

7 centres: 4 Germany, 1 Denmark, Norway, Sweden

25 patients with severe malaria (1 child, 24 adults)

18 travellers from Europe, 7 Visiting Friends and Relatives

Clinical presentation: 80% hyperparasitaemia, 32% cerebral malaria

All treated with iv artesunate (Guilin Pharma)

Zoller, T., *et al.* (2011).Emerg Infect Dis.

Haemolysis Associated with iv Artesunate

- 6 patients at 5 centres experienced haemolysis
  - After reduction/clearance of parasitaemia (PCT ~2-7 days)
  - Typical onset of haemolysis around day 14 (between days 14 and 31)

- 5 patients necessitated blood transfusion
  - Fall in haemoglobin: 2g/dl – 5.4g/dl

- Investigations
  - LDH: high; haptoglobin: low
  - Reticulocyte count: high
  - G6PD: normal
  - Coombs testing negative, no free or drug-dependent antibodies

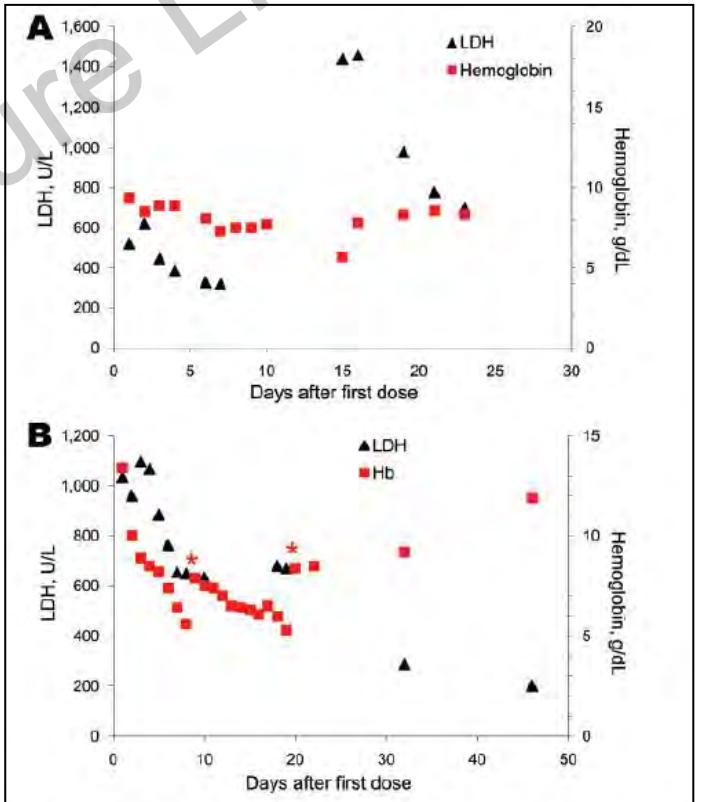


Figure. Typical patterns of hemolysis in 2 travelers with severe malaria treated with intravenous artesunate, Europe, January 2006–June 2010. A) Patient 6 with recurring hemolysis. B) Patient 9 with persisting hemolysis. LDH, lactate dehydrogenase. * indicates blood transfusion. Gaps between symbols indicate periods when samples were not obtained.

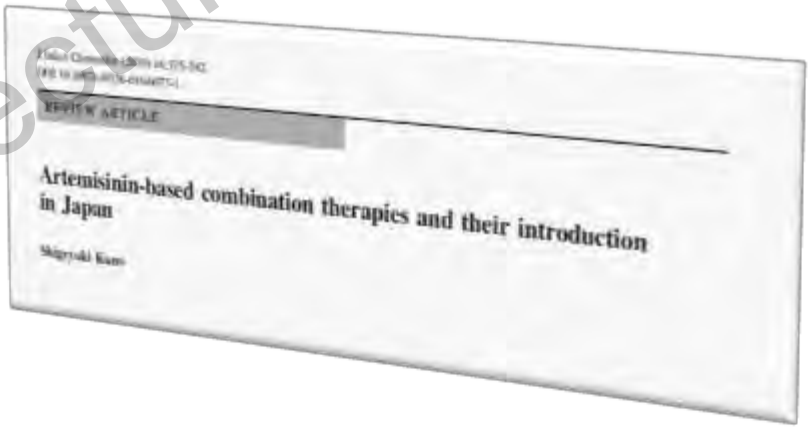
Zoller, T., *et al.* (2011).Emerg Infect Dis.

A Previous Report from Japan

First use of iv artesunate in 2000

Adult patient

Experience delayed haemolysis


REVIEW ARTICLE

Artemisinin-based combination therapies and their introduction in Japan

2001-2010

3 Japanese adults with hyperparasitaemia

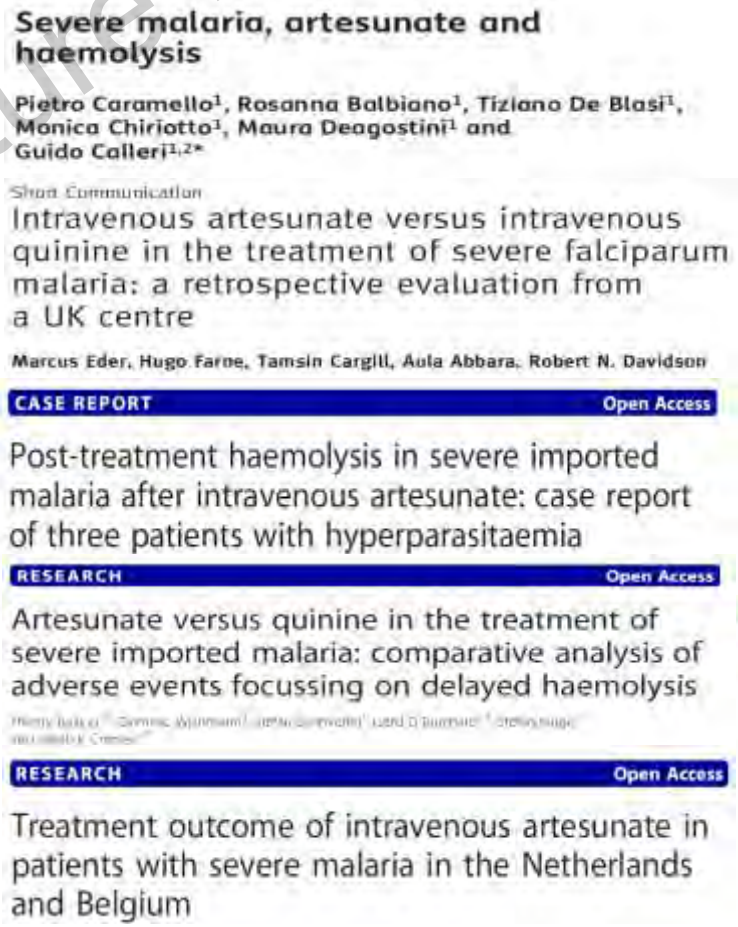
All experienced delayed haemolysis necessitating blood transfusions

All iv artesunate preparations from Guilin Pharmaceuticals

Kano, S. (2010).J Infect Chemother.

Further Reports of Haemolysis following iv Artesunate from European Centres

- Germany:
  - 3 further cases
- UK
  - 1 case
- Italy
  - 1 case
- Netherlands and Belgium
  - 7 cases



Severe malaria, artesunate and haemolysis

Pietro Caramello[1], Rosanna Balbiano[1], Tiziano De Blasi[1], Monica Chiriotto[1], Maura Deagostini[1] and Guido Calleri[1,2*]

Short Communication

Intravenous artesunate versus intravenous quinine in the treatment of severe falciparum malaria: a retrospective evaluation from a UK centre

Marcus Eder, Hugo Farne, Tamsin Cargill, Aula Abbara, Robert N. Davidson

CASE REPORT Open Access

Post-treatment haemolysis in severe imported malaria after intravenous artesunate: case report of three patients with hyperparasitaemia

RESEARCH Open Access

Artesunate versus quinine in the treatment of severe imported malaria: comparative analysis of adverse events focussing on delayed haemolysis

RESEARCH Open Access

Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium

Caramello, P., *et al.* (2012).J Antimicrob Chemother. Eder, M., *et al.* (2012).Pathog Glob Health. Kreeftmeijer-Vegter, A. R., *et al.* (2012).Malar J. Rolling, T., *et al.* (2012).Malar J. Rolling, T., *et al.* (2013).Malar J.

CDC investigation

- Review of patients in the US
- Artesunate is produced by US Army Medical Materiel Development Activity compliant with GMP standards
- No reports from US about haemolysis after use of iv artesunate 39 treatment courses with iv artesunate in US

CDC (2012).

Potential Causes for Haemolysis

Reasons

1. *Direct suppressive effect of artesunate on bone marrow?*
2. *Auto-immune haemolysis ?*
3. **Host factors in returning travellers?**
4. **Production problem in Chinese** factory?
   - Non GMP process
   - Toxic substances?
5. **Due to malaria?**
6. Any other underlying cause???

Pro and Con

1. *Reticulocytes increased*
2. *Autoantibody mediated hemolysis detected only in minority of cases*
3. African children?
4. Other derivatives? US-artesunate?

5. Why reports for artesunate but not for quinine?

Hypothesis: Host factors in returning travellers: African Children and Haemolysis

Prospective clinical trial in African children in Gabon and Ghana

iv or im artesunate

Age: 0.5-10 years

Severe malaria

Strict definition for delayed haemolysis

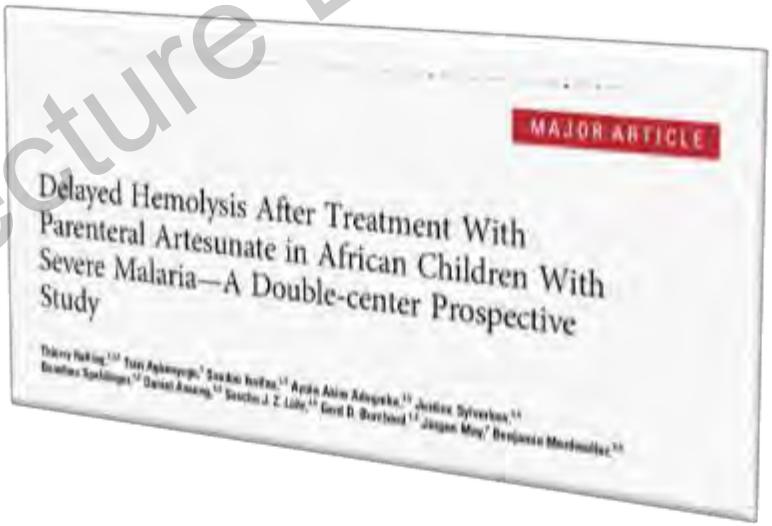
- Day 14
- Low haptoglobin, decrease in Hb between days 7 and 14, increase in LDH (>350U/l)

n=102

Parasitaemia: 125,769/µl

Analysable population: n=72

5 patients with haemolysis (7%)


MAJOR ARTICLE

Delayed Hemolysis After Treatment With Parenteral Artesunate in African Children With Severe Malaria—A Double-center Prospective Study

No parasitaemia at haemolysis

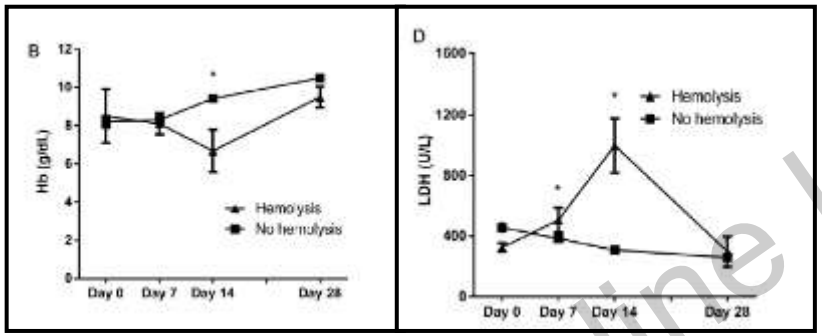
One patient with Hb 2.8g/dl

All recovered completely

Rolling, T., *et al.* (2014).J Infect Dis.

African Children and Haemolysis

With vs Without Haemolysis



Haemolysis

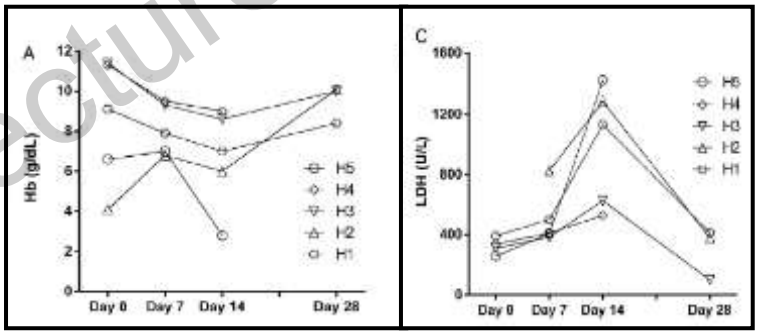


Table 2. Baseline Characteristics of Patients With Signs of Hemolysis Compared to Patients Without Hemolysis on Day 14

	No Hemolysis on Day 14	Hemolysis on Day 14	*P* Value
N	67	5	
Age in months, median (IQR)	43 (24–78)	24 (9–43)	**.046**
Female gender, n (%)	21 (31)	2 (40)	.652
GMPD, /μL	92 642 (66 456–129 159)	306 968 (199 825–471 512)	**.028**
Hb, g/dL	8.2 (7.6–8.7)	8.5 (4.6–12.4)	.703
WBC, $\times 10^3$/μL	9.8 (8.9–10.7)	13.3 (6.4–20.3)	.110
Glucose, mmol/L	4.8 (4.2–5.3)	4.8 (1.0–8.4)	.936
Creatinine, μmol/L	40.8 (24.6–57.0)	27.8 (6.6–49.0)	.463
Total bilirubin, mg/dL	1.4 (1.1–1.8)	0.9 (0.3–1.5)	.618
Transfusion during acute malaria	18 (27)	2 (40)	.616

Rolling, T., *et al.* (2014).J Infect Dis.

Hypothesis: Production Problem in Chinese Factory

Oral Artemether-Lumefantrine and US iv Artesunate

Oral Artemether-Lumefantrine	North America: iv Artesunate
Italy 2012-2013	
HIV positive returning traveller 6% P. falciparum parasitaemia Quinine+doxycyclin Oral AL treatment after 12 hours Day 10: severe haemolytic anaemia 6x RBC transfusions	Retrospective review of 186 patients in US and 101 patients in Canada 1 case in US 2 cases in Canada
Adult returning traveller 6% parasitaemia Reported intolerance of quinine Oral AL treatment Day 9: 4x RBC transfusions due to severe haemolytic anaemia	All cases had high parasitaemia All treated with GMP compliant artesunate preparation

Corpolongo, A., *et al.* (2012).Malar J.
De Nardo, P., *et al.* (2013).Infection.

Artesunate, Pitting, and RSA in Severe Malaria

In Vivo Removal of Malaria Parasites From Red Blood Cells Without Their Destruction in Acute Falciparum Malaria

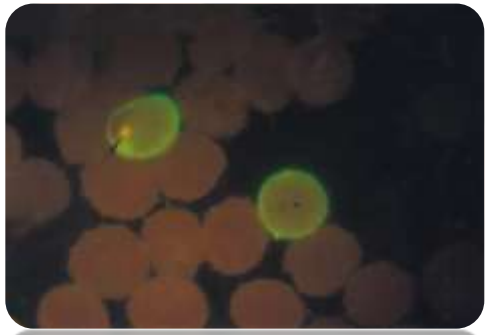
By Brian J. Angus, Kesinee Chotivanich, Rachanee Udomsangpetch, and Nicholas J. White

Significant increase in RSA-positive RBC after artesunate treatment within first hours

No RSA-RBC in in vitro cultured and treated P falciparum

Parasites are pitted out of RBC (by spleen?)

No significant increase after quinine treatment



Natural destruction/haemolysis of pitted RBC 14 days after initiation of treatment with artesunate?

Angus, B. J., *et al.* (1997).Blood.
Chotivanich, K., *et al.* (2000).J Infect Dis.

Why was it not detected earlier?

- SEAQUAMAT
  - N=730: estimated 80 patients with haemolysis?
  - Geometric mean parasitaemia: 39,850/µl (95% CI: 33,300-47,700)
  - Follow-up period: until hospital discharge
- AQUAMAT
  - N=2712: estimated 298 patients with haemolysis?
  - Geometric mean parasitaemia: 47,922/µl
  - Follow-up period: routinely until discharge of hospital
- Oral ACTs
  - Projected ~300 million treatment courses per year
  - Not used for hyperparasitaemic patients

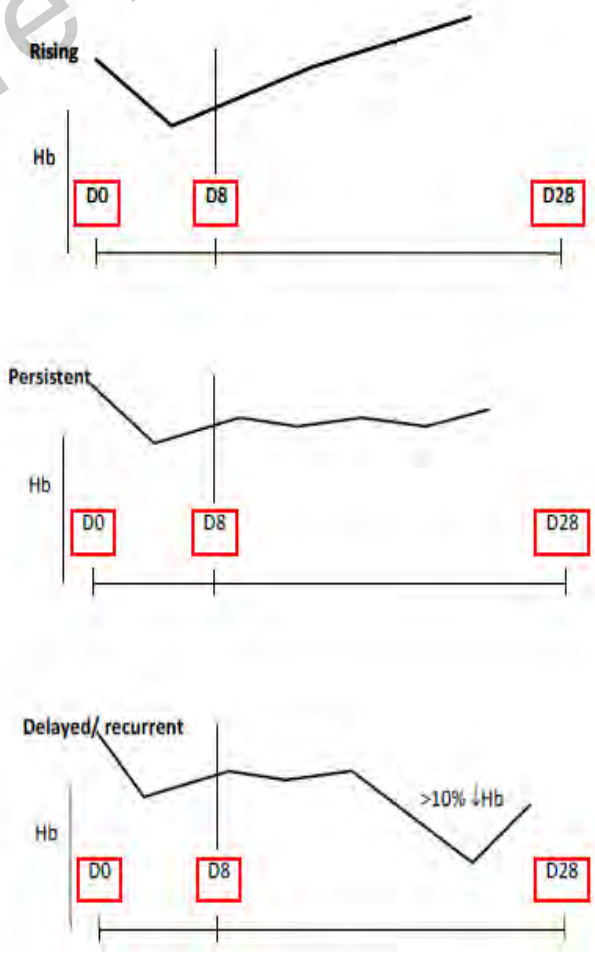
Dondorp, A., *et al.* (2005).Lancet. Dondorp, A. M., *et al.* (2010).Lancet.

Summary of What We Know: I

Route of administration

Pattern	iv AS	ir AS	im AM	AL
Delayed	15	0	1	1
Persistent	8	0	0	1
no info	8	2	1	0
Total	31	2	2	2

Total N° of reported cases: 37



Medicines for Malaria Venture. (2013).

Summary of What We Know: II
Description of haemolysis

Day of lowest Hb in delayed haemolysis group

15 (IQR: 13-15)

Day of lowest Hb in persistent haemolysis group

17 (IQR: 13-22)

Median reduction in Hb compared to baseline

6g/dl (IQR: 3.6-8.1, range 1.5-9.8g/dl)

Summary of What We Know: III
Estimation of Frequency of Haemolysis

Analysis based on retrospective cohort studies (n=4) and prospective study (n=1)

Total number of patients: 192

Total number of haemolysis cases: 24 (**13%**; 95% CI: 9-18%)

Information about RBC transfusion (n=15)

Transfusion necessary: 11 (**73%**; 95% CI: 48-89%)

Estimated 9% of treated patients required RBC transfusions

Implications for Clinical Practice

1. **Be aware of potential of post-treatment haemolysis!!!**

2. Assure **follow up for 4-6 weeks post treatment**
   - in returning travellers
   - **in African children**!!!

3. **iv Artesunate remains treatment of choice for severe malaria**

4. Consider more prudent use of artesunate in moderately severe malaria ?

5. Further research is needed to fully understand pathophysiology of haemolysis associated with the use of artemisinin derivatives

Acknowledgments

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Prof DDr Wolfgang Graninger