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Haemolysis associated with the treatment of malaria with artemisinin derivatives: a systematic review of current evidence

Khalid Rehman [a], Felix Lötsch [a,b], Peter G. Kremsner [b,c], Michael Ramharter [a,b,c,*]

[a] Department of Medicine I, Division of Infectious Diseases and Tropical Medicine, Medical University of Vienna, Vienna, Austria
[b] Centre de Recherches Médicales de Lambaréné, Hôpital Albert Schweitzer, Lambaréné, Gabon
[c] Institut für Tropenmedizin, Universität Tübingen, Wilhelm Straße 27, 72074 Tübingen, Germany

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SUMMARY

Background: Artemisinin derivatives are the mainstay of antimalarial treatment, both for uncomplicated malaria and for severe disease. Artemisinins are known for their rapid onset of action, good tolerability, and safety. However, besides the sporadic but worrying reports of delayed parasite clearance after treatment with artemisinins, there have been an increasing number of reports of acute haemolytic anaemia following their use and the safety of this class of antimalarials is being questioned.

Methods: In this systematic review, all reports of patients experiencing haemolysis following the use of artemisinins for the treatment of malaria were identified and collated into an electronic database. Summary statistics were calculated to characterize the epidemiology and clinical features of this safety concern related to artemisinin derivatives.

Results: A total of 37 patients were identified suffering from haemolysis following the treatment of severe malaria with artemisinin derivatives. Thirty-one cases had received intravenous artesunate, while the remaining cases were attributed to other parenteral or oral regimens of artemisinin derivatives. The majority of patients were returning travellers (n = 30), and six clinical cases had been reported in paediatric patients. The median onset of haemolysis was 15 (interquartile range (IQR) 13–15) days after the initiation of treatment for the 'delayed-onset' pattern and 17 (IQR 13–22) days for the 'persistent' haemolysis pattern. The median reduction in haemoglobin due to haemolysis was 6 g/dl (IQR 4–8 g/dl). The estimated proportion of patients suffering from severe malaria experiencing haemolysis after treatment with artemisinin derivatives was 13% (95% confidence interval 9–18%), and 73% of these (i.e., 9% of the total population) required blood transfusions. No fatal outcome has been reported in the literature to date.

Conclusions: Haemolysis is commonly associated with the class of artemisinin drugs when used for the treatment of severe malaria. Potential causes of this safety issue are discussed. Although no deaths attributed to haemolysis have been reported so far, this safety issue may lead to life-threatening anaemia and is particularly worrying for regions where safe blood products are not readily available.

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1. Introduction

Despite recent progress in rolling back malaria-related morbidity and mortality, the burden of disease remains unacceptably high with an estimated 207 million clinical cases of malaria each year and more than 600 000 malaria-related deaths.[1] Severe malaria therefore remains a serious clinical condition with considerable mortality, even in high-income regions.[2]

The artemisinin class of antimalarials following the spread of drug resistance in *Plasmodium falciparum* isolates to previously used first-line drugs.[3] Artemisinins were demonstrated to show unparalleled rapid parasite clearance, excellent tolerability, and were assumed to be exceptionally safe in the treatment of malaria.[4,5] Due to a high rate of recrudescence when used as monotherapy, the use of artemisinins has been recommended in combination with partner drugs for the treatment of uncomplicated malaria, in the form of artemisinin combination therapies (ACT).[6–8] Artesunate, artemether, and dihydroartemisinin became the most widely employed oral artemisinin derivatives used in ACT.

The intravenous administration of artesunate – a water soluble artemisinin derivative readily hydrolysed to the active metabolite dihydroartemisinin – was demonstrated to lead to improved survival rates compared to standard quinine therapy for severe

* Corresponding author. Tel.: +43 1 40400 44400; fax: +43 1 40400 44180.
E-mail address: michael.ramharter@medizin.uni-tuebingen.de (M. Ramharter).

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P. falciparum malaria. This was shown both for a predominantly adult Asian patient population, as well as for African children.[9,10] Parenteral artesunate became the treatment of choice for severe *P. falciparum* malaria based on these clinical trials.[11] Besides its efficacy, it was postulated that intravenous artesunate showed good tolerability and superior safety compared to the previous standard drug quinine.

Until recently, the rare occurrence of hypersensitivity reactions was considered the only clinically important safety issue associated with artemisinins. However, since then, the publication of an increasing number of cases and case series of patients experiencing late onset haemolysis following antimalarial treatment with artemisinin derivatives has raised important questions about the safety of this class of antimalarials.[12–19] To date, conclusive evidence about the frequency, clinical implications, pathophysiology, and importance of haemolysis associated with the use of artemisinin derivatives has been lacking. In this systematic review we collate all the available evidence to address these questions and to provide the basis for further discussions on the impact of this finding on our current management of patients with severe *P. falciparum* malaria.

2. Methods

In this systematic review, all reported cases of late onset haemolysis following treatment with artemisinin derivatives were identified. Published reports were sought using the following search terms: 'artemisinin', 'artesunate', and 'artemether' combined with one of the following keywords: 'haemolysis', 'delayed haemolysis', 'anaemia', and 'haemolytic anaemia'. Medline, Thomson Reuters Web of Science, Google Scholar, and conference abstracts were screened to identify further publications. The unpublished grey literature was searched using internet search engines, interviews of experts in the field, and references of published reports. There was no exclusion on the basis of time period or language of publication. All studies were assessed for risk of bias based on study design and the reporting of outcome variables. Data were entered into an electronic database for further analysis.

3. Definitions

'Returning traveller' was defined as anyone native to a non-malaria endemic region, visiting an endemic region and returning from there to his/her native non-endemic region. Consequently, a Nigerian man who was diagnosed and treated in Japan was not classified as a returning traveller as he was a native of an endemic region.[15] 'Haemolysis' is the destruction of red cells with subsequent release of haemoglobin. Published studies did not use uniform definitions for haemolysis. In this study, haemolysis associated with the use of artemisinin derivatives was therefore defined as the onset of haemolysis evidenced by a decrease in haemoglobin and an increase in lactate dehydrogenase (LDH) after the complete clearance of asexual parasitaemia from peripheral blood.

Two distinct patterns of haemolysis after the use of artemisinin therapy have been described and classified. These encompass a delayed onset and a persistent pattern of haemolysis (Figure 1).[14,16–19] 'Delayed haemolysis' was defined as the occurrence of a decrease in haemoglobin associated with low haptoglobin or increased LDH at >7 days following the initiation of artemisinin treatment.[19] 'Persistent haemolysis' was defined as continuing haemolysis starting from or around day 7 of artemisinin treatment and persisting beyond day 14. 'Severe malaria' was defined by the authors of the published reports in accordance with the World Health Organization (WHO) recommendations,[20] a modification of this as summarized in the German national guidelines,[13] or based on a definition used by the 'Severe Malaria in African Children Network' (SMAC).[19] Data were extracted by the investigators from the original reports and were entered into a purpose built database. The statistical analysis encompassed descriptive statistics (JMP 10.0; SAS Institute, NC, USA). Median and interquartile ranges were used to describe distributions.

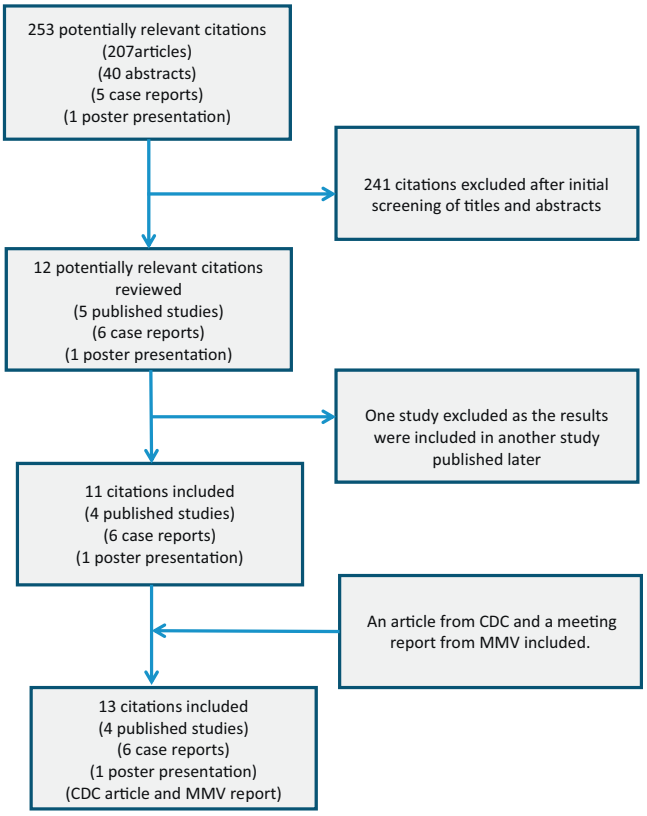

Figure 1. Identification of clinical reports of haemolysis associated with the use of artemisinins.

4. Results

A total of 11 published studies and one poster presentation reporting artemisinin-associated haemolysis were identified and included in this review.[12–19,21–24] One study was excluded from further analysis,[12] since the reported patients were part of a second publication, which was used for the purpose of this systematic review.[13] In addition to the above-mentioned scientific papers, reports by the Centers for Disease Control and Prevention (CDC, Atlanta, USA)[25] and by the Medicines for Malaria Venture (Geneva, Switzerland) were identified and included in this analysis[26] (Figure 1). All published cases were reported from non-malaria endemic regions except for one paper investigating paediatric patients in Africa.[19] Details of patient characteristics, the treatment given, and laboratory findings are summarized in the **Supplementary Material** (Supplementary File 1).

4.1. Description of study characteristics

A total of 37 cases of haemolysis associated with the use of artemisinin derivatives in the treatment of malaria have been reported so far.[12–19,21,23,24,26] Thirty-three cases have been published in research papers and four cases are referred to in a meeting report (one from China, one from the USA, and two from Canada).[26] In addition, surveillance data from France were discussed in that report but have not yet been published and were therefore not available for the purpose of this review. The reports are mainly retrospective studies ($n = 5$) and case reports

($n = 5$), as well as two prospectively designed studies. The most important prospective study was conducted in Africa and investigated 72 Gabonese and Ghanaian children for the potential occurrence of artemisinin-associated haemolysis.[19]

4.2. Description of the patient population

Fifteen patients were female and 16 were male; information on gender was not available for six patients. The median age of patients was 45 years ($n = 33$; interquartile range (IQR) 25–54 years); the youngest was a 6-month-old child and the oldest was a 78-year-old returning traveller. No information on age was available for four cases. The majority of reported cases ($n = 31$) were returning travellers, including 30 adults and one child (median age 49, IQR 32–54, range 5–78 years). Among these, 24 attended health care institutions in Europe, three in Japan, two in Canada, and one in China.

To date, six paediatric cases of artemisinin-associated haemolysis have been published.[18,19] Five were Africans treated at local health care centres in Gabon and Ghana,[19] and one child received treatment in Europe.[18] All children were treated with intravenous artesunate and received artemether–lumefantrine as follow-on treatment. The median age of paediatric patients was 24 months (IQR 10–60 months, range 6–60 months).

4.3. Description of treatment modality and artemisinin derivatives

Clinical reports encompassed the use of several different artemisinin derivatives and modes of administration. The majority of patients experiencing haemolysis after the administration of artemisinin therapy were treated with intravenous artesunate. Out of a total of 37 cases, 31 developed haemolysis following treatment with intravenous artesunate (Table 1). Two returning travellers – one reported from China and one from the UK – experienced haemolysis after the administration of intramuscular artemether.[21,26] Intra-rectal administration of artesunate was similarly associated with haemolysis in two case reports, and both patients were also treated with quinine–clindamycin.[13] Finally, two adult patients experiencing late onset haemolysis following the use of oral ACTs were reported from Italy.[23,24] One of these patients was HIV-positive and was treated with intravenous quinine before receiving artemether–lumefantrine as follow-on treatment.[24]

4.4. Description of pharmaceutical products

The majority of clinical cases of haemolysis following the use of artemisinin derivatives involved intravenous artesunate. Interestingly, the pharmaceutical product in use for all except three cases was manufactured by the Chinese company Guilin Pharma, which is the main global supplier of intravenous artesunate preparations. A CDC evaluation reported no case of haemolysis after the use of intravenous artesunate preparations produced under strict good manufacturing practice (GMP) conditions by the US Army Medical Material Development Activity in 2013, including a study in 197 African children with severe malaria treated with GMP-compliant intravenous artesunate.[25,27] However, Bryan et al. subsequently identified one case of artemisinin-associated haemolysis in the USA and two cases in Canada, both following the use of the GMP-compliant drug formulation.[26] Both cases of haemolysis associated with the use of oral artemether–lumefantrine involved a GMP-compliant product from Novartis.[23,24] Intra-rectal artesunate preparations were produced by Mepha, Switzerland,[13] and no further information was available for the intramuscular artemether drugs.[21,26]

Table 1
Region and study type categorization of cases

Region	Retrospective		Prospective	
	Adults	Children	Adults	Children
Europe	15 (IV)[a] 2 (oral)[b] 2 (IR)[c] 1 (IM)[d]	1 (IV)	3 (IV)	0
Africa	0	0	0	5 (IV)
Asia (Japan)	4 (IV)	0	0	0
USA and Canada	3 (IV)	0	0	0
China	1 (IM)	0	0	0
Total	28	1	3	5

IV, intravenous; IM, intramuscular.
[a] IV: intravenous artesunate.
[b] Oral: oral artemether–lumefantrine.
[c] IR: intra-rectal artesunate.
[d] IM: intramuscular artemether.

4.5. Description of timing, pattern, and impact of haemolysis associated with artemisinin use

The onset and duration of haemolysis after the administration of artemisinin derivatives was categorized into the two main patterns of 'delayed' and 'persistent' haemolysis, with some cases not falling into either of these categories and termed 'complex pattern' (Figure 2 and Table 2).

Among all published patient reports, information for further classification was available for 26 cases ($n = 23$ for intravenous artesunate, $n = 1$ for intramuscular artemether, $n = 2$ for oral

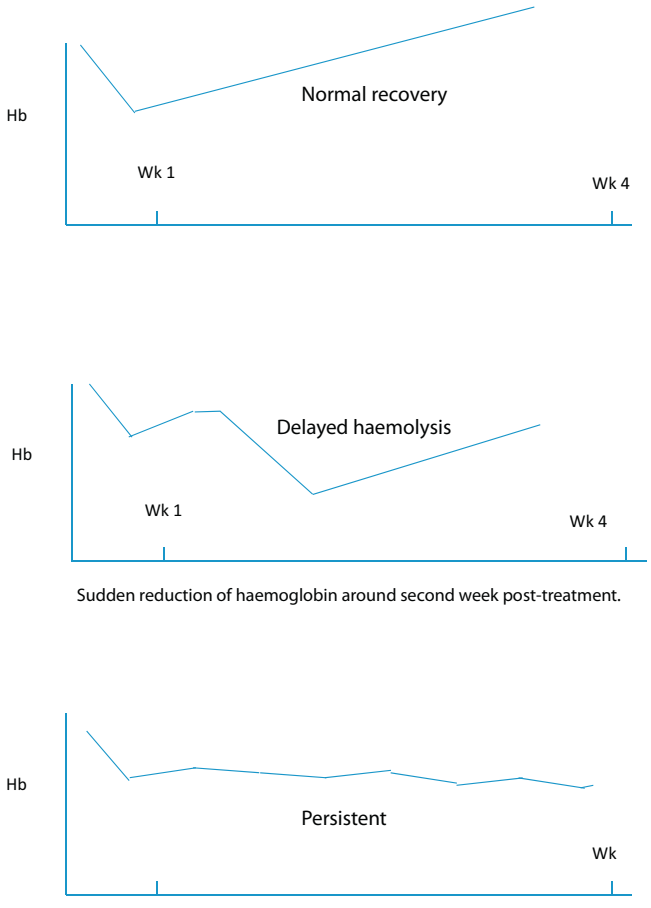

Figure 2. Patterns of haemolysis associated with the use of artemisinin drugs.

Table 2
Pattern of haemolysis with respective artemisinin derivatives and routes of administration

Pattern of haemolysis	IV artesunate	IR artesunate	IM artemether	Oral artemether–lumefantrine
Delayed	15	0	1	1
Persistent	8	0	0	1
Limited or no information available[a]	8	2	1	0
Total	31	2	2	2

IV, intravenous; IR, intra-rectal; IM, intramuscular.
[a] The information was not sufficient to classify it as a recurrent or persistent haemolysis pattern or even as a complex pattern.

artemether–lumefantrine). Fifteen patients in the intravenous artesunate group displayed a delayed pattern of haemolysis,[13,14,17–19] and eight showed persistent haemolysis[16] (Table 2). The patient treated with intramuscular artemether was classified as experiencing delayed haemolysis.

Among the two patients with oral artemether–lumefantrine use, one patient showed signs of delayed haemolysis and the other persistent haemolysis.[23,24]

The lowest haemoglobin levels in the delayed haemolysis group occurred at a median 15 days post-treatment initiation (n = 14; IQR 13–15, range 8–30 days). Four cases had the lowest haemoglobin before 2 weeks (days 8, 9, 10, and 11).[15,18,22,23,26] Another case had two nadirs (oral artemether–lumefantrine), on days 8 and 22, respectively.[23] Patients in the persistent haemolysis group showed varying reductions in haemoglobin with a nadir at a median day 17 (n = 6; IQR 13–22, range 13–32 days). The median reduction in haemoglobin concentration compared to baseline was 6 g/dl (n = 19; IQR 3.6–8.1, range 1.5–9.8 g/dl). Other reported markers of haemolysis included haptoglobin and LDH.

4.6. Estimates of frequency of haemolysis and severe haemolysis after the therapeutic use of artemisinins

The majority of published reports are case reports and case series and, as a result of this study design, no conclusion about the potential frequency of haemolysis could be drawn from these reports. Therefore only a subset of studies including retrospective cohort studies (n = 4)[13,14,17,18] and prospective studies (n = 1)[19] were used to estimate the frequency of haemolysis following treatment with artemisinin antimalarials.

Signs of haemolysis associated with artemisinin treatment were evident in 24 of a total of 192 treated patients (13%; 95% confidence interval (CI) 9–18%). These patients were African children (n = 5) and returning travellers (n = 19). Importantly, 11 patients among 15 with information about the use of blood products experienced haemolysis severe enough to necessitate the use of blood transfusions (73%; 95% CI 48–89%). Consequently, 9% (95% CI 6–14%) of the total patient population suffering from severe malaria and treated with artemisinin derivatives required blood transfusions late haemolysis.

4.7. Description of the total dose of artemisinins in clinical cases of haemolysis

The total dose of artemisinin derivatives administered in the reported cases was reviewed for potential association with this safety concern. For intravenous artesunate, the median dose administered to patients (n = 23) was 9.6 mg/kg bodyweight (IQR 7.5–12, range 7.5–19.2 mg/kg). Details of intravenous artesunate received by these patients are summarized in Table 3. Intra-rectal artemether was administered at a total dose of 200 mg per dose, administered five times. Finally, oral artemether–lumefantrine was administered at 20/120 mg of artemether–lumefantrine twice daily for 3 days. Total doses of artemisinin treatment are depicted in Table 3 and may add up to 20 mg/kg when considering follow-on therapy.

Table 3
Intravenous artesunate dosage received by patients

Intravenous artesunate: cumulative dosage (mg/kg)	Number of cases
7.5	7
8	1
9	2
9.6	2
12	10
19.2	1
Unkown	8
Total	31

Several patients reported in this context had received oral ACTs or other antimalarials following parenteral treatment with artemisinins. Out of 31 cases who received intravenous artesunate as antimalarial therapy, 12 received follow-on treatment with artemether–lumefantrine, atovaquone–proguanil (n = 6), or mefloquine (n = 1). Six cases did not receive any further antimalarials and for eight cases no information was available.

4.8. Analysis of potential co-variables associated with the risk of late onset haemolysis following treatment with artemisinin derivatives

Age and parasitaemia were both associated with the risk of the occurrence of late onset haemolysis in the prospective clinical study in African children.[19] Geometric mean parasitaemia was 92 642 (66 456–129 159)/μl blood in those without haemolysis and 306 968 (199 825–471 512)/μl blood in those with evidence of haemolysis. To further investigate the association of parasitaemia with the occurrence of haemolysis, median parasitaemia was calculated for all reported cases in the published literature. This analysis showed a median parasitaemia of 13% (IQR 7–29%) in all patients experiencing haemolysis following the treatment of severe malaria with artemisinin derivatives.

5. Discussion

Following initial case reports of returning travellers experiencing artemisinin-associated haemolysis, reports from several independent groups in different endemic and non-endemic countries have substantiated the description of this phenomenon.[12–19,21,24] Current estimates stemming from cohort studies indicate that haemolysis may occur in an estimated 13% of all patients treated with artemisinin derivatives for severe *P. falciparum* malaria.[13,14,17,18]

Importantly, haemolysis occurred in all patient populations including adult and paediatric patients, returning travellers and individuals residing in malaria endemic regions, and patients of both sexes.[13,15–19,21–24,26,28] The observation of a predominantly adult patient population in returning travellers may be due to better follow-up in this patient population rather than to differences in the risk for this safety concern.

The absolute reduction in haemoglobin due to late onset haemolysis is of great clinical importance. A median reduction of 6 g/dl is an important medical event and may indeed become life-threatening in the absence of readily available blood transfusions. Importantly, the onset of haemolysis in the second to third week post-treatment initiation makes it most likely to occur – in the case of an uneventful recovery – when patients have already been discharged from hospital. Active screening for this complication

therefore appears essential, and a better identification of patients most at risk of haemolysis would constitute major progress in the future management of severe malaria.

Interestingly, late onset haemolysis following treatment with artemisinins does not present with a uniform pattern or timing. Whereas the majority of patients in this review experienced delayed onset of haemolysis after initial cessation of malaria-associated haemolysis,[13,14,17–19] a sub-set of patients clearly showed prolonged and continuous haemolysis.[16–19] It is currently unclear whether these two clinical presentations represent distinct pathophysiological conditions or whether they constitute extremes of a spectrum of clinical presentations. The retrospective nature of the majority of publications and a lack of standardization of the definition of late onset haemolysis employed in the respective case reports and case series, further add to the complexity of this assessment and are limitations of our analysis. The adoption of a strict case definition as employed in the prospective study in African children is therefore necessary and should be employed in future clinical reports and prospective studies on this topic. In addition, a number of other potential reasons for haemolysis, including blood transfusion-related haemolysis or haemolysis induced by concomitant medication, may further blur our understanding of this phenomenon. A uniform case definition and complete reporting of clinical data will therefore allow comparison of data and will assist in disentangling potential confounding factors.

5.1. Hypotheses for the underlying pathophysiology of artemisinin-associated haemolysis

Currently there are a number of potential pathophysiological mechanisms to explain the phenomenon under discussion (Table 4). To date, and based on the features of published cases, several of these proposed hypotheses can be refuted as the main underlying reason. Firstly, late onset haemolysis has predominantly been described after the use of intravenous artesunate, but it is definitely not restricted to the use of parenteral artesunate, since case reports have been published for both intramuscular artemether as well as for oral artemether–lumefantrine when used for the treatment of severe malaria.[21,23,24,26] It must therefore be assumed that late onset haemolysis is a class phenomenon of all artemisinin derivatives and all routes of administration. It is also evident that haemolysis may occur following the use of pharmaceutical products of several global companies, minimizing the possibility of a manufacturing problem as the sole explanation for this finding. Increased reticulocyte counts during haemolysis contradict the hypothesis of direct bone marrow suppression by artemisinin drugs. Glucose-6-phosphate dehydrogenase (G6PD) deficiency has repeatedly been ruled out in reported cases, however other haemoglobinopathies and enzyme deficiencies have not been investigated consistently. Finally, autoimmune haemolysis is unlikely to serve as the uniform underlying mechanism since auto-antibodies were detected only in a minority of clinical cases. Similarly, blackwater fever – a syndrome of haemolysis, haemoglobinuria, and renal insufficiency associated with the use of quinine treatment – may be discerned from the reported phenomenon in artemisinin-treated patients based on the differences in timing of haemolysis.

To date, the feature of hyperparasitaemia at initiation of treatment remains the most consistent finding in patients experiencing late onset haemolysis. As parenteral artesunate is the treatment of choice for this patient population, this feature explains the predominance of case reports with delayed haemolysis associated with intravenous artesunate. This hypothesis is further supported by the fact that oral artemether–lumefantrine therapy – an antimalarial used safely on a very large scale in uncomplicated malaria – may lead to haemolysis when used in hyperparasitaemic patients. The observation of a much higher proportion of so-called 'pitted erythrocytes' following the treatment of patients with artesunate compared to quinine may therefore provide an attractive direction for further investigation of the underlying pathophysiology of haemolysis.[30,31] Pitted erythrocytes have been described as previously parasitized erythrocytes that have apparently been cleared from intracellular parasites by a process leaving the erythrocyte intact and in circulation. It is hypothesized that these circulating pitted erythrocytes may decompose following a lag period after the treatment of hyperparasitaemic patients within a relatively short period of time – potentially due to an invariably reduced lifespan.[32] Although this explanation is appealing for various reasons, it is currently unable to explain why only a subgroup of hyperparasitaemic patients will ultimately experience haemolysis. Additional features including host genetics, drug

Table 4
Potential causes of haemolysis following the treatment of severe malaria with artemisinin derivatives

Hypothesis	Comment	Conclusion
Restricted to special patient populations (e.g., returning travellers or adult patients)	Cases have been reported both in returning travellers in Europe and Japan, as well as in African children.	Refuted
Late toxicity due to a manufacturing problem of a single producer	Cases have been reported for IV artesunate produced by a Chinese company, as well as for a GMP-compliant preparation from the USA. The occurrence has also been reported following intra-rectal artesunate by another producer and oral artemether–lumefantrine produced by a GMP facility with EMA approval.	Refuted
Exclusively associated with parenteral use of artemisinin derivatives	Cases have been reported following the use of artemether–lumefantrine when used for the treatment of hyperparasitaemic severe malaria patients.	Refuted
Direct suppressive effect of artemisinins on bone marrow. Total dose is increased due to follow-on treatment of IV artesunate with oral ACT	Reticulocyte counts are consistently increased indicating adequate production capacity of the bone marrow. Cases have been reported with relatively low doses of artesunate and with non-ACT follow-on therapy.	Refuted
Auto-immune-mediated haemolysis triggered by the use of artemisinin derivatives	Coombs testing has been negative in the majority of cases. Consistent resolution of haemolysis without the use of corticosteroids.	Unlikely to be the main underlying mechanism. A potential explanation for a subset of patients?
Differences in pharmacokinetics based on metabolism, drug transporters, and other host factors	Artemisinins have a short plasma half-life of only a few hours, which is inconsistent with the late onset of haemolysis.[33,34] There is currently no experimental evidence to support this hypothesis.	Unlikely
G6PD deficiency, other haemoglobinopathies, or enzyme defects and other host factors	G6PD deficiency has been ruled out in all case reports. Investigations for other haemoglobinopathies and enzyme defects have not been reported consistently.	Potential explanation
Consequence of synchronous decomposition of previously parasitized erythrocytes ('pitted erythrocytes')	Available experimental evidence supports this hypothesis. However, it is unclear why haemolysis only occurs in a subset of hyperparasitaemic patients.	Potential explanation

IV, intravenous; GMP, good manufacturing practice; EMA, European Medicines Agency; ACT, artemisinin combination therapy; G6PD, glucose-6-phosphate dehydrogenase.

metabolism, and synchronicity of *P. falciparum* infections may play an important role in this context.[33,34] Further research is therefore needed to improve our understanding of this phenomenon and to better identify those patients most at risk of this serious safety concern.

5.2. Implications for clinical practice

Currently, there is uniform agreement that intravenous artesunate should remain the treatment of choice for severe *P. falciparum* malaria based on the survival benefit demonstrated in prospective randomized controlled clinical trials. The surprising failure to identify this important safety issue of haemolysis in these large clinical trials (at least with hindsight) is most likely due to a rather low mean parasitaemia in both studies (39 850/μl and 47 922/μl for SEAQUAMAT and AQUAMAT, respectively) and to an effective end of follow-up for most participants in these clinical trials occurring prior to the median time of onset of haemolysis. This failure highlights the necessity of conducting state of the art clinical phase III studies for the registration of GMP-compliant drugs with stringent international regulatory authorities before their inclusion in international treatment recommendations. This was not the case for parenteral artesunate and a repetition of this failure should be avoided in future drug development studies.

The most important clinical implication of these findings is that treating physicians should be instructed of the existence and nature of this potentially life-threatening late adverse reaction following the treatment of severe malaria with artemisinin-containing drugs. It is recommended that patients be informed of this safety concern and that follow-up visits be attended at least once weekly for 4–6 weeks. Clinical examinations and haematological assessments, including haemoglobin (and LDH and haptoglobin wherever possible), should be performed to detect cases of delayed haemolysis. Currently there is no evidence of a benefit of once-daily versus twice-daily dosing of artemisinins on the prevalence of delayed haemolysis. Late onset haemolysis must be regarded, at the same time, as an adequately manageable complication in high-resource settings as well as a serious threat to patient management in resource-constrained regions lacking adequate logistics for weekly follow-up, repeated laboratory investigations, and availability of safe blood transfusions. It is this patient population that attracts most of our attention for the potential clinical implications of artemisinin-associated haemolysis.

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Conflict of interest: The authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2014.09.007.

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