Artesunate treatment of severe pediatric malaria: A review of parasite clearance kinetics and clinical implications

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Severe malaria causes an estimated 1.24 million deaths every year, mostly in children in sub-Saharan Africa (1). Canadian pediatric infectious diseases practitioners may encounter life-threatening malaria among children emigrating from or returning from travel to the tropics. There were 195 reported cases of severe malaria in Canada between 2001 and 2012 (2), and the recent death of a malaria-infected adult in Alberta provided a reminder of the potential severity of the disease. Two large, multicentre, randomized controlled trials conclusively demonstrated a mortality benefit for the use of artesunate over quinine, the centuries-old standard, for children and adults with severe malaria (3,4). As a result, intravenous artesunate is now the treatment of choice for severe malaria, as reflected in guidelines from the WHO and the Canadian Committee to Advise on Tropical Medicine and Travel (5,6).

Severe malaria in children most often manifests as either a single, or a combination of three clinical syndromes: severe malarial anemia, cerebral malaria and/or respiratory distress. In addition, patients with a high parasite density are at elevated risk for progression to severe disease and death. In travellers from low-transmission settings, such as Canada, the parasitemia threshold suggested for close monitoring, hospitalization and parental therapy is >2% (6). It should be emphasized that circulating parasites represent only a fraction of the sequestered parasite biomass in severe malaria, such that this threshold is imprecise.

Artesunate is a water-soluble, semi-synthetic derivative of artemisinin, the active antimalarial component of the herb Artemisia annua (qinghaosu). Its use in clinical practice is expanding in malaria-endemic areas of Africa and Asia, replacing quinine as the mainstay of severe malaria treatment (7). It is available across Canada, 24 h per day, through the Canadian Malaria Network and Health Canada’s Special Access Program (8). If, despite national efforts to ensure its accessibility, artesunate cannot be obtained in a timely manner for a patient with severe malaria, alternative agents (eg, atovaquone-proguanil or quinine) should be initiated pending arrival of artesunate.

Although the weight of evidence and international consensus favour artesunate treatment, some countries continue to list quinine or quinine for severe malaria as they await regulatory approval of artesunate (9,10). Clinicians consulting widely available online (9,11) or print (10,12) treatment guidelines for severe malaria may be puzzled by the United States (US) Centers for Disease Control and Prevention’s listing of quinine as first-line therapy in the US, or quinine in the United Kingdom (Table 1). WHO-prequalified artesunate (Guilin Pharmaceutical, China) was used in major clinical trials with excellent results, development of coma) was lower (3,4). Artesunate is, therefore, preferred not only for its superior efficacy over quinine, but also its lack of acute toxicity.

As artesunate use expanded to include nonimmune returning travellers with severe malaria, reports emerged of hemolytic anemia occurring weeks after treatment (13). This late sequela of artesunate treatment was not reported in earlier studies because they only had a three-day median for follow-up of hemoglobin levels (14).

Anemia with malaria is multifactorial, and can be due to parasite and host factors, in addition to antimalarials. For example, severe anemia (hemoglobin <50 g/L) is the most common pediatric presentation of severe malaria (15), and severe acute intravascular hemolysis (‘blackwater fever’) occurs in the acute phase in both quinine- and artesunate-treated patients (3). During recovery, protracted anemia was observed in up to 7% of patients even before the introduction of artesunate (16), which may be caused by bone marrow suppression and/or hemolysis due to autoimmune and nonimmune processes (17-19).

Drug-induced hemolytic anemia related to glucose-6-phosphate dehydrogenase (G6PD) deficiency may also contribute to anemia. PADH has recently been recognized as a clinically and mechanistically distinct entity that only occurs in patients with severe malaria treated with artesunate. PADH occurs well after parasite clearance and resolution of clinical symptoms, and is not consistently associated with markers of autoimmune hemolysis (eg, positive direct antiglobulin test)
or erythrocyte susceptibility to oxidative stress (eg, G6PD deficiency) (20,21). Although artesunate may cause reversible bone marrow suppression, this mechanism likely contributes minimally to postartesunate anemia (22). Instead, PADH involves a distinct mechanism of hemolytic anemia, discussed below (22).

Clinically, several patterns of anemia following artesunate treatment of severe malaria are observed, including a ‘rising’ hemoglobin profile following early nadir, ‘persistent’ anemia and late-onset extravascular hemolysis beyond day 8 (PADH pattern) (22). To distinguish PADH from the myriad causes of anemia in severe malaria, a specific case definition of PADH has been proposed, and includes: a nonrecurring hemolytic episode occurring >7 days after initiation of treatment, with artesunate associated with a >10% decrease in hemoglobin level; haptoglobin <0.1 g/L; and either an increase in lactate dehydrogenase to >390 IU/L or a >10% rise (23).

The incidence of PADH is difficult to quantify with currently available data because of the variability in case definitions used in the literature since its relatively recent description. A systematic review of the literature up to 2014, revealed 37 cases of hemolysis and estimated an incidence rate of 13% among patients with severe malaria treated with artemisinin derivatives. However, this report did not use the optimized case definition of PADH; application of the more specific case definition would result in a lower incidence rate (22,24). The majority of these cases involved nonimmune adult returning travellers receiving intravenous artesunate. Reports of PADH from North America are surprisingly uncommon relative to Europe (24). The incidence among children with severe malaria in an endemic area has been estimated to be 7%; however, the reduction in hemoglobin in this report was <10 g/L in all but one patient (25). Again, applying the more specific definition of PADH would result in a lower incidence rate estimate.

The severity of anemia in reports of PADH is variable. In a systematic review of mostly adult cases, the median reduction in hemoglobin level was 60 g/L, and 73% of patients required blood transfusions (24). One study involving children revealed a median reduction in hemoglobin of 8 g/L, although one patient was noted to have a decrease of 42 g/L (25). No fatal outcome has been reported in the literature to date.

The mechanism of PADH has been elucidated in recent studies. Malaria parasites killed by artesunate are removed from erythrocytes by the spleen, leaving behind once-infected erythrocytes (o-iE). These o-iEs have a ‘pitted’ appearance, remaining in circulation with a considerably decreased life span of seven to 21 days (26,27). This reduced life span correlates with the timing of the onset of PADH, and may account for the higher risk for PADH among patients with higher initial parasite densities in whom higher numbers of o-iEs were observed. Therefore, PADH is a predictable consequence related to the life-saving effect of artemisinins: patients with high parasite burden rapidly cleared with artesunate, who may otherwise have succumbed to the acute infection, are left with high numbers of residual short-lived pitted erythrocytes.

**TABLE 1**

Guideline confusion: summary of recommendations for treatment of severe malaria from several national guidelines

| Country         | Source                                                                 | Statement                                                                                     |
|-----------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| United Kingdom  | World Health Organization (6)                                          | Treat adults and children with severe malaria with parenteral artesunate. (Strong recommendation, high quality evidence) |
| United States   | Canadian Committee to Advise on Tropical Medicine and Tropical Medicine and Travel (CATMAT) (2) | “Parenteral artesunate is recommended as first-line treatment for severe Plasmodium falciparum malaria, with parenteral quinine as an alternative.” (Good evidence from at least one properly randomized controlled trial) |
| United States   | United States Centers for Disease Control and Prevention (9)          | “Since 1991, quinine gluconate has been the only parenterally administered antimalarial drug available in the United States.” |
| United Kingdom  | Public Health England British Infection Association (11)              | “In the UK, the treatment of choice for severe or complicated malaria is currently an infusion of intravenous quinine.” |

**EU European Union**

PEDIATRIC PHARMACOKINETICS AND DOSING

Inspection of artesunate-clearance half-life across clinical studies illustrates slower parasite clearance in children relative to adults (Table 2). Quantitative measures of parasite clearance are affected not only by parasite genetics and drug susceptibility (28,29), but also by host determinants including patient age, organ function, drug metabolism and immunity. Therefore, lack of acquired partial immunity (premunition) in pediatric cohorts and/or age-dependent pharmacokinetic differences (30) may explain, at least in part, the slower parasite clearance in children relative to adults (31,32). Differences in pharmacokinetics, leading to lower exposure to the active metabolite dihydroartemisinin, has led to revised dosing recommendations in the 2015 WHO Guidelines for the Treatment of Malaria (6): children weighing <20 kg should receive 3.0 mg/kg/dose of artesunate, rather than the dose for larger children or adults of 2.4 mg/kg/dose (30,33).

EMERGING ARTEMISININ RESISTANCE

Artemisinin-resistant Plasmodium falciparum has recently emerged and spread in Southeast Asia, threatening the efficacy of first-line treatment regimens for severe and uncomplicated malaria worldwide (34-37). Resistance to artemisinins manifests as a slower parasite clearance rate in vivo (28,34,38). The parasite-clearance half-life, derived from the log-linear decline in parasite density during treatment, is now widely accepted as the best pharmacodynamic index of sensitivity to artemisinins (39-43). Parasite clearance time and clearance half-life are compared across studies in Table 2. Nonsynonymous single-nucleotide polymorphisms in the propeller domain of a kelch (K13) gene are generally accepted as the major genetic determinant of artemisinin resistance in P. falciparum (35,40,43,44). The mechanism involves increased expression of unfolded protein response pathways (eg, chaperone complexes), as well as decreased expression of proteins involved in DNA replication among mutant parasites. These K13 polymorphisms have emerged independently in multiple geographic locations in Southeast Asia, suggesting that selection pressure may drive the selection of resistant isolates as artemisinin treatment is distributed worldwide (44). To date, only limited numbers of infections with K13 mutants have been detected in Africa (45-47). One report has linked K13 mutations to delayed parasite clearance in African children treated with artesunate for severe malaria (48).

Artemisinin resistance has alarming implications for malaria control globally. Artemisinin combination therapy is the first-line agent for uncomplicated falciparum malaria, and parenteral artesunate is the
treatment of choice for severe malaria, highlighting our current reliance on this drug class. Alternative effective and safe agents are limited, and artemisinins are believed to be have contributed to the decline in malaria deaths globally over the past decade.

Nonetheless, clinicians managing patients with severe malaria acquired in Southeast Asia should continue to use artesunate for the time being. Safety advantages of artesunate over quinine favour its continued use in clinical practice. It should be emphasized that the phenotype of resistant P. falciparum clones described to date is delayed parasite clearance, rather than nonresponse or increased mortality. Slow-clearing parasites may require longer courses of therapy or alternative antimalarial regimens. Serial quantitative determination of parasite density (eg, daily peripheral blood smear), which is the standard of care in P. falciparum infection, will reflect parasite response to treatment. Note that the presence of gametocytes (sexual-stage parasites) alone in a peripheral smear does not imply treatment failure because this stage is less sensitive to artesunate and is not associated with symptoms or disease.

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CONCLUSION
We have summarized three relevant or emerging practice points for pediatric infectious diseases clinicians managing children with severe malaria using artesunate. First, as an unintended consequence of rapid parasite killing, clinicians should monitor for delayed hemolysis, with hemoglobin measurement weekly, up to four weeks after treatment. Second, pediatricians should be aware of the need for a higher weight-based dose in young children due to pharmacokinetic differences in artesunate metabolism, resulting in slower parasite clearance in young children. Third, artemisinin resistance associated with slow parasite clearance is emerging in Southeast Asia; nonetheless, clinicians should continue to use artesunate while monitoring for parasite clearance with serial blood smears.

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