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Treating Severe Plasmodium falciparum Malaria in the United States: Historical Trends and Current Challenges

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Introduction

Malaria, a parasitic disease transmitted by the Anopheles mosquito, remains a cause of great morbidity and mortality worldwide. Numbers of reported cases from the most recent report on malaria surveillance in the United States (US) shows a continual drop in the burden of malarial disease nationally (1,727 and 1,725 in 2013 and 2014 to 1,517 in 2015)[a] [1-4]. *Plasmodium falciparum* constituted 67.4% of infections and a reported 17.1% of malaria infections were classified as "severe illnesses"[3]. Despite reports of dropping incidence over the last few years, the number of malaria deaths in the United States in 2015 was actually higher (11 deaths) than the average over the years 2000-2014 (6.1 deaths per year)[3]. This brief report discusses the current trends in the treatment of severe malaria in the US. Articles were found in pub-med indexed journals by a team of investigators.

Early Stage of the Disease

While this article will focus on the treatment of severe malaria (described below) in the US, it is critical to understand the early stages of the disease in an effort to prevent progression to the severe form of malaria. The early symptoms of malaria are very nonspecific, and so returning travelers often hesitate to seek medical counsel. Initially, headache, malaise, muscle aches, and abdominal discomfort may be experienced, followed by a characteristic irregular fever[4]. However, there is no specific set of symptoms for malaria, and the disease can present variably[4, 5]. Mild anemia, hepatosplenomegaly, and mild jaundice may also accompany these early symptoms[4]. When uncomplicated malaria is diagnosed and treated quickly and appropriately, mortality rates are extremely low[4]. In addition to serum antibody testing, diagnosis is obtained through examination of thick and thin blood films by an expert trained to determine speciation of the parasite and current parasite load[5]. Early hospitalization is recommended. Initial treatment differs by country. In the United Kingdom (UK), the initial treatment for uncomplicated malaria is Artemether-lumefantrine with dihydroartemisinin-piperaquine as an alternative therapy[b] [5]. In the US, the first line treatment is chloroquine phosphate or hydroxychloroquine according to the 2013 Centers for Disease Control (CDC) Guidelines for Treatment

[a]The most recent report on malaria surveillance in the United States available on PubMed is the 2015 report. Final publication of these reports typically lags three years behind collection of data.

[b]Both of these medications are artemesinin derived therapies, in stark contrast to first line medication in the US

of Malaria[6]. This difference in initial treatment is a major point of distinction between treatment of malaria in the UK and the US, as we will explore when we discuss the treatment of severe malaria.

Progression to "Severe Malaria"

If initiation of treatment is delayed or not completed soon enough and parasite burden progresses, uncomplicated malaria can develop into severe malaria[4, 7, 8]. The clinical syndrome of severe malaria constitutes a series of clinical signs and laboratory values indicating worsening illness and end-organ dysfunction[4]. Clinical symptoms consist of prostration, confusion or agitation, coma, respiratory distress, convulsions, shock (prolonged capillary refill time >2 s), pulmonary edema, abnormal bleeding, jaundice, anuria, and repeated vomiting[4]. Laboratory values seen in severe malaria include hemoglobin <8 g/dl, hemoglobinuria, hypoglycemia <40 mg/dl, acidosis (base deficit >8 meq/L or plasma bicarbonate <15 mmol/L), acute kidney injury (creatinine >3 mg/dL or urea >20 mmol/L), and asexual parasitemia >10% of infected red blood cells[4]. Once progression to severe malaria has occurred, intravenous (IV) antiparasitic agents must be administered. Consensus on choice of treatment in the UK is Intravenous artesunate (2.4 mg/kg per dose hours 0, 12, and 24; then every 24 h) [4, 5, 9]. Artesunate is also the treatment of choice in Germany[10].

History of Treatment of Severe Malaria in the US

A review article published in 1972 noted that roughly 3,000 cases of malaria were reported annually in the US. That article describes the same clinical course for severe malaria seen today, with renal, cerebral, pulmonary, and hematologic complications. For uncomplicated cases, quinine was the treatment of choice[8]. For severe malaria, 650 mg of quinine dihydrochloride diluted in saline solution and administered intravenously was considered the first line treatment[8]. In 1991, the CDC issued a guideline for the treatment of severe malaria recommending the treatment of *Plasmodium falciparum* malaria with IV quinidine gluconate[11]. A stereoisomer of quinine, IV quinidine gluconate at a dose of 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hrs, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hours remains the first line treatment for severe *Plasmodium falciparum* malaria in the US[6]. Administration of this drug should be accompanied by cardiac and blood pressure monitoring for widening of the QRS complex and/or lengthening of the QTc interval and hypotension respectively[6]. For severe malaria, IV quinidine gluconate should be accompanied with one of the following adjunct treatments: doxycycline: 100 mg po bid x 7 days, tetracycline: 250 mg po qid x 7 days, or clindamycin: 20 mg base/kg/day po divided tid x 7 days[6].

Current Treatment Protocol in the US

No article which specifically outlines the treatment protocol of severe malaria in the United States has been published. The most recent review article published on the treatment of malaria in general in the United States dates from 2007. The authors write: "The artemesinin derivatives clear parasites very rapidly, are now a key component of malaria treatment worldwide, and have been shown to reduce mortality in severe malaria compared with parenteral quinine. These drugs are not yet available in the United States, but the CDC hopes to make intravenous artesunate available under an Investigational New Drug protocol in 2007"[7].

In 2018, over 10 years after this review article was published, quinidine gluconate remains the first line treatment for severe malaria[6], despite growing bodies of evidence that assert the superiority of artemesinin derived antiparasitics[4, 12-15]. The CDC did hold true to their promise, however, and artesunate is currently available as an investigational drug from designated CDC outposts throughout the country. Many reports of the favorable use of artesunate in the US exist, but the drug is still unavailable on hospital formularies[15-17]. Obtaining a waiver from the CDC and arranging for transportation of the medication would delay initiation of artemesinin therapy leading to potential progression of the disease, perhaps explaining rising malaria death rates in 2015, especially as resistance to quinine escalates among returning travelers[18-22].

Why has the US lagged behind other countries in widespread adoption of artemisinin based for treatment of severe malaria? Several reports of delayed hemolysis after use of artemesinins exist. This phenomenon presents 1-3 weeks after artemesinin-containing antiparasitics are begun and manifests as a decline in hemoglobin potentially severe enough to warrant transfusion[23-27]. A review article published in 2015 reports rates of 7-21% for development of post artemesinin delayed hemolysis (PADH) [28]. Recent reports of PADH show full recovery after diagnosis. In a Canadian case report, 2 returning travelers developed PADH. Both were treated with transfusion of packed red blood cells (pRBCs) and their anemia resolved[23]. Paczkowski *et al.* report 2 cases in the US between 2012 and 2014 in addition to the 18 cases identified internationally by the CDC. Of the patients who could be reached for follow up of these 20 cases, all experienced full recovery although several received transfusion of pRBCs[26]. the authors conclude that artesunate remains a safe and effective option for severe malaria[26]. Additionally, researchers have identified a test which can predict potential for development of PADH. The histidine-rich protein 2 (HRP2) predicted subsequent PADH with 89% sensitivity and 73% specificity[29]. This lab test could identify patients at risk for PADH in addition to recommended screening for at least 4 weeks after

discharge to detect symptomatic hemolysis[28]. Artesunate is a safe and effective therapy for severe malaria, but, as with any medications appropriate precautions should be maintained.

Supplemental Therapy to Prevent Organ Failure

While antiparasitic agents formulate the backbone of treatment for severe malaria, controlling deterioration of organ function via other supportive therapies is critical to reduce mortality in life-threatening illness. First off, careful investigation should be undertaken to ensure end-organ dysfunction is the result of a malaria infection and not a concomitant infection by another organism. Endovascular dysfunction leading to microvascular occlusion is thought to be the main cause of end-organ dysfunction in severe malaria, although precise pathogenesis and additional mechanisms are a topic of much research[30-35]. Cerebral malaria, severe anemia, hypoglycemia, pulmonary edema, and kidney dysfunction constitute the primary manifestations of end-organ damage in severe malaria[4]. An in-depth management guide for each of these critical pieces in malaria management is outside the scope of this brief article, but several critical interventions should be pursued should such conditions present in the patient with severe malaria.

Cerebral malaria presents as neurologic dysfunction and eventual loss of consciousness. While no specific consensus protocol exists on the treatment of this condition, prompt anti-malarial therapy as well as attention to management of hypoglycemia, acidosis and hypovolemia is beneficial[36]. Lumbar puncture should be performed to rule out bacterial meningitis and MRI should be performed to rule out cerebral edema or bleed[7]. A number of experimental therapies have been proposed with mixed results[36-39]. Severe anemia from repeated bouts of malaria in pregnant women and children is a major issue in endemic countries. Due to transfusion carrying a risk for HIV transmission in countries where malaria is endemic, transfusion for anemia related to malaria is a topic of current debate[40, 41]. While the CDC does not recommend exchange transfusion for treatment of malaria, in areas where risk of HIV transmission through blood transfusion is lower, transfusion has been used successfully in some case reports[42, 43].

Hypoglycemia can be masked by the symptoms of cerebral malaria, and so regular monitoring of blood glucose is indicated[7]. This entity can be induced by hyperinsulinemia following administration of quinidine[7]. Appropriate fluid replacement and renal replacement therapy is the mainstay of treatment for acute kidney injury from severe malaria[44, 45]. Special care must be taken to avoid nephrotoxic drugs and vasodilators appear to have no survival benefit[44]. Pulmonary edema is either the result of impaired kidney function or development of acute respiratory distress syndrome in severe malaria[7]. Keeping the patient euvolemic is imperative and if needed, the use of endotracheal intubation and positive end-expiratory pressure ventilation should be considered[7, 46].

Conclusions

Severe malaria is a rare but treatable condition that affects a slowly declining number of returning travelers in the US. The majority of the world uses artemesinin derived antiparasitics as the first line treatment for severe malaria, but the US uses IV parenteral quinidine accompanied by an antibiotic. Artesunate is available from the CDC for use as an experimental agent. Post artemesinin delayed hemolysis is a recognized clinical entity, and patients should be followed up appropriately for development of this condition, but this phenomenon should not preclude the use of artemesinin derived antiparasitics. Supportive treatment to prevent end-organ damage should be initiated when necessary in cases of severe malaria.

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