Short Report: Successful Oral Therapy for Severe *Falciparum* Malaria: The World Health Organization Criteria Revisited

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Abstract. We report a successful treatment of severe *falciparum* malaria in a non-immune adult patient with 30% parasitemia treated with the 6-dose oral regimen of artemether plus lumefantrine combination therapy alone. We have also retrospectively searched our tertiary center's database for similar cases and we have found two additional severe malaria cases, resolved uneventfully with oral regimen. These cases might indicate a need to specifically address the definition of severe and complicated malaria in non-immune patients either in designated guidelines or as an explicit addition to the historical World Health Organization criteria.

INTRODUCTION

Severe malaria may be manifested with rapidly evolving, life-threatening conditions such as coma, metabolic acidosis, severe anemia, hypoglycemia, acute renal failure, or acute pulmonary edema. The World Health Organization (WHO) definition for severe malaria is broad and includes additional criteria, each of which is sufficient to define it, such as hyperparasitemia or failure to feed (Table 1). The main objective of any effective antimalarial therapy for severe malaria is to prevent the patient from dying, although not each severe malaria criterion bears the same prognostic value for death. The mortality in some forms of severe malaria, particularly of untreated cerebral malaria, is nearly 100%.^{1,2}

CASE REPORTS

A 59-year-old Caucasian man presented to our department in June 2011 with a 4-day history of intermittent febrile illness 19 days after returning from Cameroon. The patient had an unremarkable medical history, including any past malaria episodes and was not on any regular medications. He did not take antimalarial prophylaxis during his 2-week stay in Cameroon.

On admission, he was tachycardic and had a decreased saturation on room air (90%), which was improved with oxygen administration. His chest x-ray was normal. He had a marked thrombocytopenia (22,000 platelets/ μ L; normal range: 130,000–440,000 platelets/ μ L). Other laboratory findings of interest were a mild hemolytic anemia with hemoglobin of 11.8 g/dL (normal range: 13.5–17.5 g/dL), slightly elevated aspartate (48 IU/L; normal range: 7–40 IU/L), and alanine (54 IU/L; normal range: 7–45 IU/L), elevated total blood bilirubin (2.34 mg/dL; normal range: 0.1–1.1 mg/dL), and normal blood creatinine level (0.99 mg/dL; normal range: 0.8–1.2 mg/dL). Rapid diagnostic immunoassay for *Plasmodium falciparum* antigen in blood (Binax Inc., Scarborough, ME) was positive.

The standard 3-day oral therapy schedule of artemether-lumefantrine (Coartem, Novartis Pharma AG, Basel, Switzerland) for uncomplicated malaria, with a total of 6 doses, was started. Only at the end of that day, the official result of the malaria

blood film arrived, showing a 30% parasitemia level. This level of parasitemia was far above the 2% cutoff level for severe malaria hyperparasitemia in non-immune patients.¹ At this point we have debated whether to switch to intravenous (IV) therapy and also have considered blood exchange. However, because none of these therapeutic options were available immediately, and in light of the hemodynamic and respiratory stability of the patient, who was monitored continuously, the oral treatment regimen was not changed.

A repeated malaria blood film after 24 hours from the beginning of treatment showed a significant reduction of the parasitemia to < 5%. During the second day he had an episode of hyperpyrexia accompanied with a short episode of confusional state (< 24 hours).

His condition improved during the third day with defervescence, and a complete clearance of parasitemia was observed after 72 hours from treatment initiation. The pathogen was later confirmed as *P. falciparum* also by a real-time polymerase chain reaction assay, which did not identify any other *Plasmodium* species. At the clinic follow-up visit, 28 days after his hospital discharge, the patient was in a good general condition, with no clinical or laboratory sequela (Table 2: patient 1).

Following this case presentation, we retrospectively searched for other *falciparum* malaria patients, who fulfilled the WHO definition of severe malaria,^{1,2} upon admission to the hospital, and who were treated orally in our center in the past decade (January 2000 to December 2010). Briefly, we focused our search in one WHO criterion for severe malaria, in which the patient condition might allow him to tolerate oral therapy; such is the criterion of having clinical jaundice, as we defined by the acceptable threshold of total bilirubin in blood > 3 mg/dL, which is accompanied by dysfunction of other vital organs,¹ particularly the kidneys.

Of the 205 malaria patients, who were hospitalized in the past decade, we have found two patients ($\approx$ 1%); both of them were previously healthy young adult males, who fulfilled the aforementioned severe *falciparum* malaria criterion (Table 2, patients 2, 3). Both of these patients were treated with an oral regimen alone and had an uneventful recovery.

DISCUSSION

We report an uneventful course of severe *falciparum* malaria in a non-immune adult patient treated with the 6-dose

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TABLE 1

Current World Health Organization criteria for severe *Plasmodium falciparum* malaria for immune and non-immune adults and their prognostic values^{1,2}

Severe malaria criteria ^{1*}	Prognostic value ²
Clinical	
Impaired consciousness or coma	++
Prostration	Data not available
Failure to feed	NQ
Multiple convulsions: more than 2 episodes in 24 h	++
Deep breathing, respiratory distress (acidotic breathing)	+++
Circulatory collapse or shock, systolic blood pressure < 70 mm Hg	+++
Clinical jaundice plus evidence of other vital organ dysfunction	+
Hemoglobinuria	+
Abnormal spontaneous bleeding	++
Pulmonary edema (radiological)	+++
Laboratory	
Hypoglycemia (blood glucose < 40 mg/dL)	NQ
Metabolic acidosis (plasma bicarbonate < 15 mEq/L)	NQ
Severe normocytic anemia (Hb < 5 g/dL, packed cell volume < 15%)	+
Hemoglobinuria	+
Hyperparasitemia (> 2%/100,000/μL in low intensity transmission areas or > 5% or 250,000/μL in areas of high stable malaria transmission intensity)	Depends on age and background immunity
Hyperlactatemia (lactate > 45 mg/dL)	NQ
Renal impairment (serum creatinine > 3 mg/dL)	NQ

*Any one of the clinical or laboratory criteria is sufficient to define severe malaria.^{1,2}
 NQ = not quantified in the World Health Organization guidelines.²

oral regimen of artemether plus lumefantrine combination therapy alone. Our patient, despite being of older age, a known risk factor for severe malaria in non-immunes,³ did not show the clinical or laboratory features of either severe malaria or its prognostic predictors for death upon admission, and we therefore began the oral regimen. Eventually, the patient was recognized as having severe malaria caused by extreme hyperparasitemia. However, his continued stable condition and the rapid decline in parasitemia were for the clinical call to continue the oral treatment protocol until his uneventful rapid recovery.

Because severe malaria may often be accompanied by findings that may limit oral absorption of drugs, the administration of parenteral, particularly IV antimalarials, is currently and historically the initial regimen in any severe malaria treatment protocol, for 24 hours at the minimum before giving the oral follow-up regimen. This is recommended regardless of the baseline or an early ability of the patient to tolerate oral therapy. Remarkably, this treatment plan has been recommended by the WHO for several decades based on the consensus of experts' opinions and rooted in the pre-artemisinin-based combination therapy age.^{1,2,4,5}

The current WHO guidelines¹ for treating severe falciparum malaria further recommend that after the initial parenteral treatment, and given that the patient can tolerate it, an effective full oral antimalarial course of an artemisinin-based combination therapy or quinine (plus clindamycin or doxycycline) should be administered without delay.

The 6-dose oral regimen of artemether plus lumefantrine combination therapy was found by a Cochrane review⁶ to be more effective than most other non-artemisinin derivative regimens for treating uncomplicated falciparum malaria in endemic countries. A high parasitological cure rate (96%) was also observed among non-immune travelers.⁷ Nevertheless, the regimen has not been studied for the treatment of severe malaria,⁸ including patients who would potentially tolerate oral therapy such as in some cases of renal impairment, severe anemia, or hyperparasitemia, as in our patient.

Another Cochrane review⁹ has recently concluded that parenteral artesunate therapy was superior over the standard treatment of parenteral quinine in both adults and children with severe falciparum malaria in endemic areas of Asia and Africa.

Parenteral artesunate, however, despite being the drug of choice for severe falciparum malaria in endemic countries, is currently not licensed in North America or Europe, and thus is not readily available for treating returning travelers in these regions. Although, IV artesunate may be obtained in the United States under Investigational New Drug protocol (IND) sponsored by the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html) and in Canada through the Canadian Malaria Network (<http://www.phac-aspc.gc.ca/tmp-pmv/quinine/>) under the Special Access Program. In both countries the supply of IV artesunate (as well as quinine in Canada) is upon request and on an emergency basis.

TABLE 2

Characteristics of severe falciparum malaria patients treated with oral regimen alone

Patient	Age	Sex	Admission month/year	Hospitalization duration (days)	Severe malaria criteria ¹	Treatment regimen, duration	Outcome
1	59	Male	06/2011	5	30% parasitemia	Artemether plus lumefantrine, 3 days	Uneventful recovery
2	24	Male	01/2006	7	Br: 3.4 mg/dL Cr: 1.50 mg/dL	Quinine plus doxycycline, 7 days	Uneventful recovery
3	25	Male	03/2006	4	Br: 3.3 mg/dL Cr: 1.25 mg/dL	Atovaquone/proguanil, 3 days	Uneventful recovery

Br = total serum bilirubin; Cr = serum creatinine.

Notably, the efficacy of orally administered artemisinin and its derivatives is characterized by both an immediate onset of action and rapid reduction of parasitemia.¹⁰ Therefore, the 6-dose artemether plus lumefantrine combination oral regimen, which is now easily available and proved to be highly effective, could possibly allow some variations of the historic WHO guidelines, which mandate initial parenteral treatment in all forms of severe malaria for all patients, regardless of the patient's oral tolerance ability. In addition, the guidelines originally addressed the populations of endemic areas, mainly children and, to a lesser degree, adults and thus might not be completely applicable for the growing non-immune adult traveler population.

Finally, as evident from Table 1, not every severe malaria criterion is also a major prognostic predictor. Furthermore, other previously recognized predictors of severity and death, such as older age in non-immune travelers,³ were not included per se in the criteria. Therefore, it might be helpful to present distinctively the definitions and accompanying guidelines for severe malaria according to their purpose, whether for epidemiological research or for therapeutic use in defined populations.

In summary, this report might implicate the possible therapeutic option of the oral artemether-lumefantrine regimen in some forms of severe malaria. However, it is currently explicitly contraindicated for treating any form of severe malaria.^{1,2,8} If it could be unequivocally proved efficacious in future randomized controlled trials, it might serve as an important therapeutic alternative in both developing and developed countries.

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