

# Severe malaria in children: a proposal for clinical grading

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**Background.** Severe malaria (SM) mortality remains high (10 - 40%) despite treatment. Reports suggest that the World Health Organization-defined SM of 2000 is not a homogeneous group.

**Objective.** To test the hypothesis that SM patients are heterogeneous, identify criteria that could be used for the grading of SM severity, and propose a method for clinically grading SM in children.

**Method.** A retrospective study of children aged 3 months to 12 years who fulfilled the WHO SM criteria and were seen at two Nigerian hospitals during a specified period. The presenting clinical features (PCFs) and their calculated case fatality rates (CFRs) were investigated to identify PCFs with the highest CFRs that could be separated from the rest and classified as major PCFs. Major and minor PCFs were used to develop a three-grade system, with analysis of variance (ANOVA) to compare grades.

**Results.** A total of 8 PCFs were identified in 155 children with SM; impaired consciousness, prostration, convulsions and respiratory distress (in that order) had the highest CFRs (and were designated as major PCFs). The severity grading system was developed using 4 major and 4 minor PCFs as follows: grade I SM - no major, and 1 - 4 minor PCFs; grade II and grade III SM had 1 - 2 and 3 - 4 major PCFs respectively and 1 - 4 minor PCFs ( $p=0.05$ ).

**Conclusion.** The proposed severity grading system requires validation by large prospective studies. It is suited for use at the bedside and has the potential to be used in guidelines that are specific to various grades of disease severity and to reduce unnecessary parenteral antimalarials and hospital admission.

Despite advances in our knowledge of the disease, malaria continues to be a major health problem<sup>1-13</sup> in more than 100 developing countries in the tropics, where over 2 billion people are at risk.<sup>14</sup> Severe (life-threatening) malaria (SM) from *Plasmodium falciparum*<sup>6,12,13</sup> causes 1.5 to 2.7 million deaths in children <5 years of age every year;<sup>4,14</sup> 90% of these deaths occur in sub-Saharan Africa.<sup>2</sup> SM's mortality rate approaches 100% if it is untreated, and remains significant even when optimally treated (10 - 25%),<sup>15,16</sup> with most deaths occurring within 24 hours of admission to hospital.<sup>5,15</sup>

Despite efforts by international organisations and governments, the rates for SM in developing countries remain unacceptably high (10 - 40%).<sup>5,8,13,15,16</sup> The 2000 World Health Organization (WHO) definition of SM did not address the issue of grading the clinical severity of SM in children, which would be particularly useful in resource-poor countries. As a result, the current practice worldwide puts all SM patients into a single severity category, and places them all on the same treatment regimen (full course of parenteral drug therapy) without regard for possible differences in case severity. There are reports suggesting that SM patients may not be a homogeneous group<sup>8,9,17</sup> and that the broader 2000 WHO definition (compared with the stricter one of 1990) might have included in the diagnosis some less severely ill children.<sup>8</sup>

The objectives of our study were to: (i) test the hypothesis that SM patients are not a homogeneous severity group; (ii) identify criteria that could be used for the grading of SM case severity; and (iii) propose a method for grading SM case severity in children.

## Methods

**Study site.** The study was conducted from January 2001 to December 2002 at the 500-bed University of Calabar Teaching Hospital (UCTH), Calabar, Cross River State, and from January 2005 to March 2006 at the 200-bed Federal Medical Centre (FMC), Yenagoa, Bayelsa State. These hospitals are major tertiary health care facilities, each in the capital city of 2 of the 36 Nigerian states, and serving over 1 million people. Consent from patients and ethical clearance were obtained from both hospitals.

**Study design.** The hospital records of 155 children (86 from FMC, 69 from UCTH) consecutively admitted into the paediatric wards of UCTH and FMC within the study periods, with a diagnosis of SM which fulfilled the 2000 WHO criteria<sup>20</sup> for this disease, were analysed retrospectively. The presenting clinical features (PCFs) - symptoms and signs - were extracted for detailed study. The most frequent PCFs associated with the highest case mortality rates were identified and studied.

**Patients.** Patients aged between 3 months and 12 years, with complete hospital records, who were admitted to the paediatric wards of UCTH and FMC within the study periods and fulfilled the 2000 WHO criteria<sup>20</sup> for the diagnosis of SM, were included in the study. SM was defined as diagnosis of an asexual *P. falciparum* parasitaemia, at least one of the 2000 WHO criteria,<sup>18</sup> and the absence of detectable, non-malarious causes of PCFs, as shown in Table I.

**Clinical management.** All patients were examined by experienced medical doctors, including consultant paediatricians and physicians, who documented the PCFs,

illness history, results of physical examinations (including neurological evaluation), vital signs, laboratory test results and treatments administered. Patients were treated with intramuscular artemether<sup>12</sup> and intravenous quinine dihydrochloride (later orally) in standard doses. Anaemia was corrected with blood transfusion, convulsions were controlled with intravenous diazepam, and hypoglycaemia was corrected with 25 - 50% glucose.

### Laboratory investigations

On admission, the following investigations were done:

- Malaria parasites: thick and thin blood films were stained with Giemsa and examined for asexual forms of *P. falciparum*; the parasite count was per 200 leucocytes. A thick slide was considered negative if no parasites were found after 100 high-power fields were examined. Thin films were used to determine the *Plasmodium* species.
- Blood glucose, full blood count, urea, creatinine and electrolytes. The hospitals had no facilities for blood gas analysis.
- Lumbar puncture was done where indicated, to exclude the diagnosis of meningitis.

### Statistical analysis

Analysis of variance (ANOVA)<sup>20,21</sup> (SPSS statistical software, version 16.0) was used to analyse the SM severity group data. Detailed description of the analysis is included in Table I. Case fatality was calculated (effect; 95% confidence intervals (CI)).

### Results

Of the 155 subjects who fulfilled the 2000 WHO criteria for SM, 89 were male and the balance of 66 were female; their ages ranged from 3 months to 12 years (mean 2.6±2.0 years) and their mean body weight was 11.7±4.4 kg (range 5.4 - 38 kg). A total of 8 PCFs were identified (Table I). Only 25 (16.1%) of the 155 patients fulfilled the WHO criteria for cerebral malaria, i.e. unrousable coma not attributable to any other cause in the presence of asexual *P. falciparum* parasitaemia. The overall SM case fatality rate was 10.3% (95% CI 5.5 - 15.1%; 9 females, 7 males). Impaired consciousness and convulsion were present

among the highest CFRs. The fatality rates for the 8 most common PCFs are shown in Table I. Four PCFs (impaired consciousness, prostration, convulsion and respiratory distress) occurred in the higher CFRs (11.4 - 24.2%) and were classified as major PCFs; the remaining 4 PCFs (cough, vomiting, fever and anaemia, with lower CFRs of 9.0 - 10.7%) were classified as minor PCFs.

We assumed that SM is (i) most severe in patients with the highest number of major PCFs; (ii) moderately severe in those with fewer major PCFs; and (iii) less severe in those with no major PCFs. We then placed the 155 SM patients into three severity groups, based on the number of major PCFs on admission: group I: 41 (26.5%) had no major and 0 - 4 minor PCFs; group II: 82 (52.9%) had 1 or 2 major PCFs, plus 0 - 4 minor PCFs; and group III: 32 (20.7%) had 3 or 4 major PCFs, plus 0 - 4 minor PCFs.

The CFRs were compared in the three groups (Table II). ANOVA was used to compare all three groups (I, II, and III) as well as only the two with major PCFs (groups II and III). The results showed significant differences between the three groups regarding the CFRs and the four major PCFs (F-test statistics: 45.02; degrees of freedom: 2, 6;  $p=0.05$ ), which suggests that groups I, II and III are distinct SM severity groups, and justifies the grading of the four major and minor PCFs in this clinical classification of malaria severity into grade I, grade II and grade III (Table III). Our results show that grade I is clinically less severe, grade II is moderately severe, and grade III is the most severe form of SM, with the highest mortality, and also confirm the non-homogeneity hypothesis.<sup>8,9,22</sup>

### Discussion

Malaria is a major health problem confronting developing countries, with millions of children at great risk. Mortality rates for SM have remained at 10 - 40%.<sup>5,8,10,13,15,16</sup> The situation urgently calls for a review of current management strategies. The data generated by this study have further strengthened the call for a new clinical SM classification, which has implications for management strategy.

The patients' clinical features on admission are more useful to clinicians than laboratory tests for assessing disease severity. In the course of effective treatment, PCFs gradually decrease and then disappear when the patient fully recovers. With this

**TABLE I. PREVALENCE OF PRESENTING CLINICAL FEATURES (PCFS) AND CASE FATALITY RATES (CFRS) IN 155 CHILDREN HOSPITALISED WITH SEVERE MALARIA (SM)**

PCFs	PCF prevalence (N (%))	PCF CFR (N (%))	CFR (95% CI)
Impaired consciousness, including unrousable coma	66 (42.6)	16 (24.2)	13.8 - 34.6%
Convulsion	67 (43.2)	11 (16.4)	7.4 - 25.4%
Prostration	30 (19.4)	6 (20.0)	5.5 - 34.5%
Respiratory distress	44 (28.1)	5 (11.4)	2 - 20.8%
Anaemia (Hb<0.8 g/dl)	133 (85.8)	12 (9.0)	4.2 - 13.8%
Vomiting	84 (54.2)	8 (9.5)	3.3 - 15.7%
Cough	56 (36.1)	6 (10.7)	1.7 - 19.7%
Fever	155 (100)	16 (10.3)	5.5 - 15.1%

Definitions of clinical features (only the 8 PCFs with the highest CFRs are listed in the table): (i) severe anaemia: haemoglobin <5.0 g/dl; (ii) prostration, defined as inability of the conscious patient to sit, drink or eat/breastfeed when he/she would otherwise be able to; (iii) respiratory distress, defined as tachypnoea with sustained nasal flaring, subcostal recessions, or Kussmaul breathing; (iv) multiple convulsions, defined as a respective history within the preceding 24 hours, plus one directly observed convulsion; (v) impaired consciousness, defined as Blantyre score ≤4; (vi) clinical jaundice; (vii) haemoglobinuria, verified by dipstick; (viii) circulatory collapse, defined as systolic blood pressure <60 and <80 mmHg in children aged 5 years and >5 years of age respectively, cool limbs or weak or absent peripheral pulses; (ix) abnormal bleeding; (x) pulmonary oedema.

TABLE II. STUDY GROUPS AND NUMBER OF DEATHS (CASE FATALITY RATES (CFRS))

PCF/study groups	Patients (N (%))	Group CFR (N (%))	CFR (95% CI)
Group I (no major PCFs, 1 - 4 minor PCFs)	41 (26.5)	No deaths (0%)	0%
Group II (1 - 2 major PCFs, 0 - 4 minor PCFs)	82 (52.9)	7 (8.5%)	(2.5 - 14.5%)
Group III (3 - 4 major PCFs, 0 - 4 minor PCFs)	32 (20.7)	9 (28.1%)	(12.2 - 43.8%)

NB: (i) the four major PCFs: impaired consciousness, convulsion, prostration and respiratory distress;  
(ii) the four minor PCFs: cough, fever, vomiting and anaemia.

TABLE III. GRADING SEVERITY OF SEVERE MALARIA IN CHILDREN

SM severity grades: I - III	Abbreviation	Severity group characteristics
Severe malaria, grade I severity	SM, grade I (less severe)	Only minor PCFs; no major PCFs
Severe malaria, grade II severity	SM, grade II (moderately severe)	1 - 2 major PCFs, plus 0 - 4 minor PCFs
Severe malaria, grade III severity	SM, grade III (most severe form)	3 - 4 major PCs, plus 0 - 4 minor PCs

NB: (i) the four major PCFs: impaired consciousness, convulsion, prostration and respiratory distress;  
(ii) the four minor PCFs: cough, fever, vomiting and anaemia.

in mind, we documented the admission PCFs of 155 children with SM and developed a severity grading system for the disease in children, using four major and four minor PCFs. We noted the high prevalence rates of the four major PCFs in our study, similar to those reported in other African studies (Ghanaian<sup>8</sup> and Ugandan<sup>9</sup>), and the observation that most hospital admissions among SM patients were attributed to these major PCFs.

The 2000 WHO<sup>18</sup> definition of SM is a widely used, simplified tool for the rapid diagnosis of SM, especially in resource-poor countries, and helps in the identification of high-risk children. It is sensitive, easy to use, but less specific than the stricter 1990 WHO criteria.<sup>8,22</sup> The criteria also allow direct comparisons between research studies.<sup>5</sup> However, in recent years, clinicians and researchers using the criteria have concurred<sup>5,8,18,23-25</sup> with the opinion of the authors of the 2000 WHO criteria and guidelines, in that no single definition of severe disease would be satisfactory or relevant in all situations.<sup>5</sup> Of particular interest to us were reports<sup>9,17</sup> stating that the broader 2000 WHO definition of SM might have included in the diagnosis some less severely ill children with malaria, a situation that might have led to a lowering of mortality (but not from better management),<sup>8,9,17</sup> increased hospitalisation or referral to intensive care units,<sup>9</sup> and providing less severely ill patients with the full course of emergency parenteral drug therapy.

We have demonstrated that SM patients are not a homogeneous severity group, and consist of both severely ill and less severely ill patients. A report<sup>17</sup> from Dakar also found that less severely ill children in that series required fewer therapeutic interventions during the course of treatment. In our series, patients with 3 or 4 major PCFs were the most severely ill, with a higher CFR; patients with 1 or 2 major PCFs were moderately ill, with fewer deaths; and those with no major PCFs were the least ill, with no recorded deaths. Similarly, a Ghanaian study<sup>8</sup> reported that CFRs increased with the number of symptoms defining SM.

The evolution of malaria diagnostic technology recently prompted the Special Programme for Research and Training in Tropical Diseases (TDR), Roll Back Malaria and USAID to sponsor an international conference<sup>26</sup> in Geneva, entitled 'Malaria Diagnostics at the Turn of the Century'. The participating experts came to the following conclusions: (i) rapid diagnostic tests (RDTs) are costly, but simple and rapid

to use, and reliably detect *P. falciparum*; the tests do not indicate severity of malaria, and do not discriminate between sexual and asexual stages of the parasite; (ii) RDTs at present cannot replace microscopic diagnosis of malaria; and (iii) the search for new and more sensitive methods of diagnosis of malaria and its severity should be a priority.

Currently, in hospitals worldwide, microscopic examination of blood films is the standard laboratory method<sup>27</sup> for the diagnosis of severe malaria; the greater the parasite density in the peripheral blood, the higher the likelihood that severe disease is present or will develop, especially in the non-immune. Microscopy, although a valuable diagnostic tool, may at times produce results that conflict with the patient's clinical picture,<sup>27</sup> as follows: (i) some individuals develop severe and even fatal malaria with very low peripheral parasitaemia; (ii) very rarely, the blood film may actually be negative in a patient who is then proved at autopsy to have intense tissue sequestration of malarial parasites; and (iii) there may be a marked difference between the number of parasitised cells in the peripheral blood and the number sequestered.

In an attempt to address some of the drawbacks of existing diagnostic methods, the WHO, in the year 2000, re-defined SM, using a set of laboratory and clinical criteria. All the above methods (the 2000 WHO criteria, RDTs and microscopic examination of blood films) are useful in the diagnosis of malaria, but they provide no system of clinically grading disease severity in individual patients.

**This proposed grading system  
is simple, robust, independent  
of laboratory protocols  
and suited for use at the  
bedside. It can also be  
used to monitor response  
to treatment.**



The inclusion of clinical severity grading in the WHO's definition may put to rest calls<sup>4,5,28</sup> for stricter WHO definitions and may help to redirect energies towards the development of more effective treatments for SM, based on validated treatment guidelines, that are specific for various grades of disease severity (grades I - III SM). The ultimate aim is to reduce mortality, hospitalisation of mild cases and the indiscriminate use of parenteral antimalarials (and drug resistance). We used PCFs in designing a system for grading disease severity in children who fulfilled the 2000 WHO criteria for SM. This proposed grading system, when and if validated, may further strengthen the 2000 WHO definition of SM. The method is simple, robust, independent of laboratory protocols and suited for use at the patient's bedside; it can also be used to monitor response to treatment.

In conclusion, although this proposed clinical severity grading system still requires validation by means of large studies, it has the potential to identify less severely ill patients, encourage development of appropriate guidelines that will take into account disease severity, and reduce drug resistance, hospital admissions and unnecessary use of parenteral antimalarials.

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