

## **Severe malaria in children: Factors predictive of outcome and response to Quinine**

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### **Abstract**

**Objective:** To identify clinical features of severe malaria and their association with adverse outcomes according to recently proposed WHO guidelines and observe treatment failure to Quinine.

**Methods:** This descriptive study was performed at Civil Hospital Karachi from September 2007 to January 2008. Various clinical features and laboratory parameters were analyzed according to the WHO guidelines and treatment failure to anti-malarial drugs was recorded. Mean, frequencies, percentages and chi-square test were used for analysis. Statistical significance was defined as p-value <0.05.

**Results:** Total of 81 patients were enrolled in the study. Mean age of children was 5.5 ± 3.4 years. Type of malaria infections that were seen included falciparum 46(57%), mixed infection 26(32%) and vivax 9(11%). Frequent clinical features included splenomegaly (74%), multiple organ dysfunction (MOD) (70%), cerebral malaria (31%) and malnutrition (27%). Thrombocytopenia (86%) and severe anaemia (42%) were the common laboratory findings. Shock (p<0.001), renal failure (p<0.001), hepatic involvement (p<0.002) and cerebral malaria (p<0.002) emerged as strong predictors of complications. Fourteen out of 81 cases showed early treatment failure to Quinine.

**Conclusion:** Shock, renal failure, hepatic involvement and cerebral malaria are strongly associated with complications in severe malaria. MOD and malnutrition were identified as significant new clinical features present in severe malaria in this study.

**Keywords:** Malaria, clinical features, WHO guidelines, Quinine (JPMA 61:54; 2011).

### **Introduction**

Infection resulting from malaria accounts for more than one million children death globally every year.<sup>1</sup> World Health Organization (WHO) eastern Mediterranean region comprises of twenty two countries, out of which six (including Pakistan) bear 95% of the disease burden.<sup>2</sup> Every year Pakistan is threatened by malaria epidemic in post monsoon seasons resulting in loss of many precious lives, which can be minimized by prompt diagnosis and implementation of correct treatment. In 2004, reported annual parasite incidence of malaria in Pakistan was 5.6% and plasmodium falciparum ratio was 33%.<sup>3</sup> Rural Sindh and Balochistan are the areas having major disease burden in Pakistan and severe malaria is a well known cause of morbidity and mortality in these regions.<sup>4</sup>

Recent WHO guidelines<sup>5</sup> have proposed a classification of severe malaria based on clinical features, thereby, prioritizing malaria cases according to risk factors.

However, these guidelines depend mainly on studies conducted in African children population. To the best of our knowledge, these guidelines have not been studied on children with malaria in Pakistan. We also included additional syndrome of multiple organ dysfunction (MOD) in the list of clinical syndromes as it was found to have a significant relation with malaria mortality in previous literature.<sup>6</sup>

Furthermore data available on treatment failure of antimalarial drugs is not in accordance with WHO proposed guidelines of treatment failure which requires clinical and parasitological follow up for twenty eight days after primary infection.<sup>7</sup> Also Pakistani studies fall short of describing in detail the predictors of morbidity and mortality of severe malaria in children.

This study was, therefore, undertaken to identify clinical features of severe malaria and their association with adverse outcomes according to recently proposed WHO guidelines, and observe treatment failure to Quinine.

## Patients and Methods

This study was undertaken during the malaria epidemic in September 2007 to January 2008 at Civil Hospital Karachi (CHK). CHK is a 1000 bedded University Hospital that caters to patients coming from endemic and hyper endemic malaria regions of Sindh and Balochistan provinces. WHO guidelines<sup>5</sup> were used to establish diagnosis of severe malaria.

Study physician evaluated the enrolled patients and completed predesigned data collection forms which included details of demographic data, clinical features and type of malarial parasite. Clinical features were recorded at initial enrollment and categorized according to WHO criteria.<sup>5</sup> Glasgow coma scale was used to assess level of consciousness. Routine laboratory investigations done in all patients included a complete blood count, haematocrit, blood sugar level, serum urea, creatinine and liver function tests. Identification of malarial parasite and its species were done on thick and thin film peripheral smear stained with Giemsa stain, in cases where peripheral smears were inconclusive rapid antigen tests were used to establish diagnosis of malaria. Some laboratory tests were performed only when required such as cerebral spinal fluid, arterial blood gases, chest x-rays and malarial parasite load. Admission laboratory values were used for data analysis. Viral hepatitis was ruled out in all the patients who showed liver involvement with malaria.

Initially all the patients received intravenous Quinine injection in a loading dose of 20mg/Kg diluted in 10 ml/Kg of dextrose saline over four hours followed by 10mg/Kg as infusion over two hours, eight hourly. Children were switched to oral Quinine in a dose of 10 mg/Kg, eight hourly, as soon as they were able to tolerate medicine orally. Other treatment modalities offered to patients during the study included blood transfusion for severe anaemia, acetoaminophine for fever, intravenous diazepam for seizures, oxygen for respiratory distress, rehydrating fluids for dehydration and intravenous antibiotics for bacterial infections, where indicated.

Clinical features and microscopic parasite clearance was recorded daily till disappearance of asexual form of parasite (trophozoites) by trained laboratory technicians of Civil hospital. If there was failure of clearance of parasite (trophozoites) or failure of resolution of clinical signs after seventy-two hours of starting Quinine then injection Artemether 3.2mg/Kg/dose was given intramuscularly once followed by injection or tablet Artemether according to the condition of child. Subsequent dose of injectable Artemether was 1.6mg/Kg/dose intramuscularly once daily. Dose of tablet Artemether-lumefantrine (20/120) combination was 1 tablet or two tablets twice daily for children having weight ranges

between 5-15 Kg and 15-25 Kg respectively. Total treatment with Artemether consisted of five days. Patients were followed clinically as well as biochemically for clearance of parasite. After the parasite clearance was achieved patients were discharged and advised for follow up on twenty eighth day of primary infection for final microscopic analysis. Those patients who failed to show up were contacted on phone and reminded of the visit and blood samples were collected on their arrival. Patients who did not complete the follow-up were excluded from the analysis for response to anti-malarial drugs. Patients were categorized as "treatment failure" or "adequate response" according to WHO criteria.<sup>7</sup>

Criteria used to define other clinical features present in the study population are given as follows.

**Morbidity:** Presence of motor weakness, cranial nerve weakness, aphasia, renal failure or encephalopathy.

**Tropical splenomegaly:** Past history of malaria infection with positive laboratory result of malaria along with massive splenomegaly and raised Ig M levels.

**Macrocytic anaemia:** Mean corpuscular volume (MCV) more than 100 fL, peripheral smear showing hypersegmented neutrophils and decreased serum folic acid levels in absence of malnutrition.

**Vertical transmission:** Presence of clinical features of malaria in baby and positive lab report of malaria in mother and baby simultaneously.

**Early treatment failure:** Development of danger signs or severe malaria on day 1-3 in presence of parasitaemia despite of taking anti malarial drug appropriately.

**Late treatment failure:** Development of danger signs or severe malaria after day 3 in presence of parasitaemia without previously meeting any of the criteria of early treatment failure.

**Hepatic involvement:** Presence of clinical jaundice or serum bilirubin >3 mg/dl or hepatic encephalopathy.

### Statistical analysis:

Statistical analysis was performed by using SPSS version 13. Descriptive analysis (frequencies and percentages) were used for demographic data, clinical features and outcome. Chi-square test was used to determine association of clinical features with adverse outcome. P value < 0.05 was considered significant. Haemoglobinuria, arterial blood gases and parasite load were excluded from final analysis because of lack of adequate data.

### Ethical considerations:

Permission from care givers of all the patients were taken prior to enrollment in the study. Records were kept strictly confidential. There was no conflict of interest.

## Results

Data of 84 patients were included in the analysis who met the 2000 WHO criteria for severe malaria. Four patients were excluded from the final analysis as they were found to be suffering from other diseases also, making total number of patients 81. The mean age of children with severe malaria was  $5.5 \pm 3.4$  years. Number of children more than 5 years (54%) were more compared to children less than 5 years (45%). Females were slightly more in number, thirty nine (48%) compared to males, who were forty two (52%). Forty five children were from Sindh out of whom 32 belonged to Karachi. Thirty five children were from Baluchistan of whom 10 were from Hubchoki. One patient came from Peshawar.

**Table-1: Clinical features observed in the study.**

Clinical features	Frequency (n)	Percentage (%)
Thrombocytopenia	70	86
Splenomegaly	60	74
MOD	59	70
Hepatomegaly	46	57
Severe anaemia	34	42
Vomiting	30	37
Cerebral malaria	25	31
Impaired consciousness	26	30
Malnutrition	23	27
Respiratory distress	20	24
Abdominal pain	19	23
Convulsions	19	20
Jaundice	15	17

MOD= multiple organ dysfunction.

**Table-2: Clinical outcome of patients.**

Clinical outcome	Frequency	Percentage (%)
Early treatment failure	14	34
Late treatment failure	0	-
Adequate clinical response	26	63
Resistance	0	0
Mortality	5	12.5
Morbidity	4	10

Results calculated from data of 40 patients who had 28 days follow up.

**Table-3: Clinical features predictive of complications.**

Clinical features	Complication (morbidity +mortality).number (n)	P-value
Shock	3	<0.001
Renal failure	4	<0.001
Hepatic involvement	5	<0.002
Cerebral malaria	7	<0.002
Impaired consciousness	6	<0.007
MOD	9	<0.035
Severe anemia	7	<0.02

MOD=multiple organ dysfunction. Chi square test was used to calculate P-value.

Type of malaria infections that were seen were falciparum 46(57%), mixed infection (falciparum+vivax) 26(32%) and vivax 9 (11%). Spectrum of malaria infection in children coming from Karachi showed 21 cases of falciparum, 8 cases of mixed infection and 3 cases of Vivax. Maximum number of children (13) came from Hawksbay and its adjoining areas.

Maximum number of children, 57(70%) came in the months of October and November 34 and 25 respectively, whereas remaining patients were sporadically distributed in rest of the months. Numbers of patients were 15 in September, 6 in December and 3 in January. The clinical features observed have been shown in Table-1.

Complications were categorized into morbidity and mortality and were seen in 9 out of 81 patients. Mean age of patients with complications was  $4.38 \pm 1.69$  years. MOD was present in all patients with complications. Common overlapping features present in most patients with complications were cerebral malaria, severe anaemia and thrombocytopenia. However jaundice was present only in patients with morbidity whereas renal failure and malnutrition emerged as clinical feature present only in mortality group. Maximum numbers, 8 (57%), of treatment failures were observed in falciparum infections followed by mixed infections in 6 (42%) patients. Clinical outcomes observed in terms of treatment failure, adequate response and complications are given in Table-2.

Shock, hepatic involvement, renal failure and cerebral malaria emerged as significant predictors of complications which have been summarized in Table-3.

Special features noted in the patients included two cases of tropical splenomegaly, four cases of vertical transmission and 6 cases of macrocytic anaemia (after ruling out malnutrition) due to folate deficiency .

## Discussion

In the current study we observed many features similar to previous observations however certain dissimilarities were also noted. The ages of patients in our study ranged from 2 months to 13 years with the mean age of  $5.5 \pm 3.4$  years as opposed to the mean age of two years observed in a study done in year 2000.<sup>4</sup> Majority of children were from Karachi (32), out of which thirteen were from Hawksbay area. Enquires made from residents of Hawksbay revealed poor sanitary conditions and abundance of mosquitoes in those areas.

Maximum number of cases were observed in the months of October and November (72%), the reason could be the fact that these months comprised the post monsoon period in which the ambient climatic conditions favour mosquito breeding. Similar observation were also made by Nizamani,<sup>3</sup>

but malaria outbreaks have also been reported in months of July to September.<sup>8</sup> In Karachi, falciparum infections (66%) were more followed by mixed (25%) infections. WHO also confirms increasing falciparum infections in Sindh with falciparum ratio rising to 46%,<sup>9</sup> however, a recent study conducted in Karachi reported otherwise with vivax infections more compared to falciparum (51% versus 46%).<sup>10</sup>

Thrombocytopenia (86%), splenomegaly (74%), severe anaemia (42%) and cerebral malaria (31%) were the commonest clinical features prevalent in our study and were comparable to other Pakistani studies which have shown 72% thrombocytopenia,<sup>11</sup> 64% cerebral malaria,<sup>12</sup> 20% anaemia and 20% splenomegaly.<sup>13</sup> Certain clinical features emerged different in the present study which included malnutrition, respiratory distress, hepatic involvement, renal failure and MOD. Malnutrition and respiratory distress were mainly present in children under 5 years of age whereas hepatic involvement and renal failure were seen mainly in older children.

The relationship between malaria and nutritional status has been the subject of debate for many years, recently studies have not only shown increased risk of malaria in malnourished children<sup>6,14</sup> but have also shown that combined vitamin A and Zinc supplementation decreases this risk.<sup>15</sup> In present study malnutrition was present in 23 children out of which nineteen were severely malnourished. Literature search of Pakistani data has not shown renal failure and MOD as complications of malaria in children, whereas in our study they stood out as key predictors of morbidity and mortality in severe malaria. Acute renal failure due to malaria has also been reported in older children in other parts of the world and possible explanation offered for this complication is mechanical obstruction of renal tracts by infected erythrocytes and immune mediated pathology.<sup>16</sup>

MOD was present in 70% of children and resulted in higher morbidity and mortality when overlapped with cerebral malaria and renal failure. Combinations of MOD and cerebral malaria have also been recognized as important terminal sequel in adults with cerebral malaria from Dakar, Senegal.<sup>17</sup> Similar observation in children of our study points towards complex pathogenesis of this disease and to the fact that similar spectrum of symptoms can be seen in wider age group.

Hepatic involvement was seen in 17% patients, one child developed hepatic encephalopathy, and rest of the children recovered completely with no residual liver disease. The fact that hepatic involvement has been identified in two separate studies of Pakistan prompt for more studies to determine overall picture of this complication. Pulmonary manifestations in malaria have been recognized for more than 200 years especially in the form of pulmonary oedema.<sup>18</sup> We also observed respiratory distress in 24 children, all the

children had clinical and radiological picture of pneumonia and all of them recovered completely. Pulmonary oedema was not seen in any patient.

In our series MOD, renal failure shock and cerebral malaria emerged as four major predictors of mortality, although shock and cerebral malaria have been implicated as a risk factor for mortality in children<sup>18</sup> in our part of the world but renal failure and MOD have not been described before.

Mortality was 12.5% in our study which is comparable to Tariq's study done in Lahore, which reported mortality of 5%,<sup>19</sup> four patients (10%) developed neurological sequelae as opposed to 22% sequelae seen in a previous local study.<sup>18</sup> Three children developed transient aphasia while one developed transient motor weakness.

We observed treatment failure to Quinine in 14 patients. All cases were seen within three days of starting treatment which is contrary to the finding of Stepniew who has reported Quinine resistance in the third week<sup>20</sup> of treatment. In the current study drug levels and parasite count were not performed to determine drug resistance, therefore, fourteen cases of treatment failure to Quinine in our study merely represent treatment failure and not resistance because to establish therapeutic efficacy of a drug, its serum concentrations and parasite counts are required to ensure that adequate drug levels and parasite clearance has been achieved. To demonstrate drug resistance it is necessary to show that malaria parasite is surviving or multiplying despite adequate drug administration. This is not the same as treatment failure which is defined as failure to clear malaria or resolve clinical symptoms despite administration of antimalarials.<sup>7</sup> Treatment failure in our study could be due to uncontrolled confounding factors and documented reasons like poor drug quality, interaction with other drugs or individual variations in pharmacokinetic properties.

A study from the province of Sind has shown 5% resistance to Quinine,<sup>21</sup> however, the methodology they used to establish drug resistance were not adequate or standardized. In the light of these facts and to the best of our knowledge it can be stated that currently no study with proper guidelines to establish Quinine resistance has yet been done across Pakistan.

It is possible that we did not capture the full burden of malaria and all clinical manifestations in our hospital setting. Population based surveillance are required for precise measurement of these variables.

## Conclusion

Our study has shown that besides shock, cerebral malaria and severe anaemia which have been implicated even in the past as predictors of complications in severe malaria, additional manifestations like hepatic involvement, renal

failure and MOD also have significant impact over the course of the disease. We also observed treatment failure to Quinine in some cases.

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