Problems In Management Of Severe Malaria

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Citation

S Mishra, S Mohanty. *Problems In Management Of Severe Malaria*. The Internet Journal of Tropical Medicine. 2002 Volume 1 Number 1.

Abstract

Malaria has become a major global problem affecting more than 2000 million population and causing 1.5 million deaths annually 1. In India the problem is enormous and almost half of the population is exposed to this dreadful disease. During the last decade, there has been a resurgence of malaria in India which has affected the economic growth by denting the national exchequer as well as causing deaths in thousands2. Malaria in India usually affects mostly patients who are at the prime of their life. It is a matter of great concern that the country is losing these people who could have been saved by prevention of malaria transmission, by early diagnosis or by instituting early therapy. Whenever, a case of malaria is adequately and successfully treated, malaria does not usually have a residual deficit and these patients recover fully.

INTRODUCTION

Malaria, particularly pernicious malaria (falciparum malaria) poses a diagnostic dilemma at early stage as the disease can mimic many other conditions[1]. Even after proper diagnosis, it can pose problem due to associated complications which unless anticipated earlier or diagnosed at proper stage can cause death.

The aim of WHO's Roll Back Malaria programme has been early diagnosis and prompt treatment to reduce the mortality to a great extent. There is a great need for early diagnosis and recognition of the complications of malaria at local centre, and if warranted, to be sent to a higher centre for management of the complications at an early stage to avoid mortality due to complications.

There are certain difficulties in the diagnosis and management of malaria. We like to make a brief review of these issues.

DIFFICULTY IN THE DIAGNOSIS AND TREATMENT OF MALARIA

- Diagnosis is the most important part of management. Diagnosis of malaria may be missed purely for technical reasons 1
    - inadequate smear
        - faulty microscopy
    - faulty staining
        - dirty slides
    - wrong buffer pH
        - contaminated or deteriorating stain
    - inexperienced technical hands
    - inadequate time spent in examining the slide
    - faulty storage of the blood before preparation of slide
    - anticoagulants may interfere in interpretation
- Difficulty in identifying falciparum parasites in mixed infection (vivax and falciparum)
- There may be cleared parasitemia from the peripheral blood due to treatment posing difficulty in establishing diagnosis. In this circumstance immunochromatographic tests may be useful 3.
- If the patients come at a later stage of the disease when there is a peripheral clearance of parasites but complications like acute renal failure or acute lung injury has set in.
- Malaria may be missed clinically in the presence of epidemics of dengue, meningitis, viral hepatitis, in

patients with haemoglobinopathy, heat hyperpyrexia, alcoholic liver diseases etc 1,2.

- At times coexisting conditions like cerebrovascular accidents, pneumonia, aspiration pneumonia, meningitis and hepatic coma , diabetic ketoacidosis can often be missed if one is not careful enough.
- Difficulty in getting the laboratory facility where it is most wanted, like rural or suburban areas; and even if facility is available, the quality of most of the laboratories is questionable.
- Difficulty in getting biochemical test done at odd hours. Non-oliguric renal failure cannot be diagnosed without a biochemical test.
- Failure to take a travel history – this aspect is forgotten by the patients as well as physicians. It can lead to missing the diagnosis of malaria. When a patient goes to a high transmission area from a low one, he is at an increased risk of developing severe malaria. If a person leaves an endemic area for a prolonged period, he is at a higher risk to suffer from severe malaria on return.
- Patients who present to a center without expertise in tropical medicine may receive suboptimal treatment. Improvements in recognition, diagnosis, and treatment of malaria are essential to prevent morbidity and death among travelers 4 .
- At times there is underestimation of the severity of the disease. Anaemia or jaundice are not given due importance, which may lead to fatal outcome. Oral treatment is initiated in a patient having complications. Hypoglycemia, a common complication, is often overlooked unless anticipated. Many patients on road to recovery from malaria lapse into coma have been diagnosed to be cases of hypoglycemia5,6 . Pregnant females and children
- are prone for this complication ,5,7,8. Bedside blood glucose estimation is of immense value when the patient is on intravenous quinine.
- Difficulty in the clinical assessment of recovery and deterioration are also important factors in the management of the severe malaria.

PROBLEMS IN THE MANAGEMENT OF MALARIA

- If repeated blood smear examinations are negative, there may be a delay in starting treatment on clinical suspicion only, as the phobia of COPRA lurks in the mind of a doctor. But treatment should be initiated early on strong clinical suspicion. However, one should not deter from attempt for confirmation of diagnosis by resorting to antigen capture tests (viz. ParasightF, Paracheck, Malacheck etc), QBC test, other serological tests, if available3.
- There is an unfounded fear of quinine toxicity in the minds of many doctors while instituting this potent drug in pregnant women 8, in patients with jaundice or in the presence of hypoglycaemia.
- There is always a difficulty in weighing the patient. The visual assessment will be good enough to institute a proper dose of quinine. In case of small children, weight should always be recorded prior to institution of antimalarials and anti convulsants.
- Inadequate dose, viz. giving a reduced dose of 5 mg/ kg of body weight will not be able to reach the MIC, even in the presence of hepatic or renal complications. The dose need to be modified only after the initial 48 hours of therapy. 9
- In rural areas, where facility for a venous access is lacking, antimalarials given by oral or nasogastric route may be considered before transferring the case to a higher centre.
- The rate of infusion of quinine is very important. It is always advisable to infuse each dose of quinine over a period of four hours. A slow infusion will fail to reach the desired MIC, and a faster infusion can lead to toxicity, as quinine has a very narrow safety margin.
- Cessation of therapy: at times a prolonged period of more than 7 days may be necessary.
- Delay in starting dialysis due to non availability, or a delay in deciding for dialysis may lead to avoidable deaths. Similarly delay in recognising early respiratory distress invariably leads to late institution of ventilator support and ultimate death.

- There may be a difficulty in treating severe malaria in pregnant women. Apart from the fear of abortion due to quinine therapy, there may be a dilemma for termination of pregnancy, and starting peritoneal dialysis when facility of HD is lacking.

In many dedicated and advanced centres, it has been seen that despite institution of proper therapy for severe and complicate malaria, the death rates are high as many of these patients are brought to hospital quite late in irreversible state. In cerebral malaria, if acute renal failure sets in, the mortality is approximately 40% and in the presence of acute lung injury, it reaches almost 80 to 90% even in most advanced centres [1] .

Prevention of ARDS by prophylactic artificial respiratory support is still controversial.[10] .

At times, despite early diagnosis and institution of prompt therapy, patients proceed to have MODS with disastrous outcome. Most of the complications can be anticipated, viz. anaemia in presence of haemolysis, ARDS in presence of ARF etc. But there is no marker or scale to predict the complications. The estimation of TNF, thromboxane B orIL-6 may be raised in the severely ill patients; but in most centres these facilities are not available, and if available it cannot be repeated frequently due to prohibitive cost factor.

Considering the above facts, it can be said that the therapeutic challenge can be met with institution of proper agent at proper dose, proper route of administration, rate of infusion, duration of therapy, correction of electrolytes, calories, antibiotics and supportive therapy as indicated. Anticipation, close monitoring with recognition of the complications at an early stage will be of immense value.

There are certain differences in the presentation of severe malaria in the children [1],[2],[10],[12]

Figure 1

Table-1 :Differences in adult and children

Symptoms and signs	Adults	Children
Cough	Uncommon	Common in early stage
Convulsion	Indicates cerebral malaria or hypoglycemia	Indicates cerebral malaria, hypoglycemia but may be non specific consequence of fever.
Duration of symptoms	Several days	Usually 1-2 days only
Jaundice	Common	Uncommon
Anaemia	Not so common	Common
Pulmonary oedema	Common	Rare
Acute renal failure	Common	Rare
Hypoglycemia	Common in pregnant women, or with quinine therapy, sometimes may be present without quinine therapy	Common before treatment
Seizure	Less common	Frequent
Development of unconsciousness	Insidious	Rapid
Coma recovery time	Slow, usually 2 – 4 days	Rapid (usually 1-2 days)
CSF pressure	Usually normal	Variable, raised
Neurological sequelae	Uncommon	Occurs in about 10% cases

CLINICAL FEATURES OF SEVERE MALARIA IN PREGNANT WOMEN

Pregnant women are more prone to develop multiple complications of malaria. There are several factors that make pregnant women more vulnerable to malaria and its complications including mortality[7],[8],[13],[14]:

Malaria parasites are preferentially sequestrated in the placenta,

1. Acquired immunity against malaria is known to decline during pregnancy.

2. During the second half of pregnancy, there is a transient immuno-suppression due to high levels of adrenal steroids, chorionic gonadotrophin, alpha-fetoprotein and depression of the role of lymphocytes. Therefore the incidence of malaria relapses, recrudescence & severe malaria is more common during pregnancy.

3. Frequency of heavy parasitemia is more during pregnancy than in the non-pregnant state. Primigravidae are at higher risk of morbidity & mortality from malaria.

5. Severe malaria poses a special problem as placental parasitemia is often associated with pregnancy rather than peripheral parasitemia. They usually have a multitude complications viz. severe anemia, hypoglycemia, acute renal failure, acute pulmonary oedema, ARDS.

6. Risk of mortality is nearly three times higher than

nonpregnant women.

7. Associated infections: e.g. Urinary tract infections and respiratory tract infections, septicaemia are more common in the gravid state. 1

Anaemia : In India, women have a lower haematocrit because of dietary habits, frequent pregnancies, folate deficiency etc. Malaria increases the incidence of anemia. Mild anaemia doesn't influence the mortality but moderate or severe anaemia is associated with increased morbidity & mortality in pregnant women. It is associated with an increased risk of perinatal mortality, maternal morbidity, PPH and pulmonary oedema.

Cerebral malaria- Although incidence of cerebral malaria is same as that of non-pregnant women, however once they develop cerebral malaria, the mortality is three times higher in pregnant women.

Hypoglycemia - This may be present in pregnant women at the time of admission or may develop after quinine infusion. Commonly it is asymptomatic. Abnormal behaviour, sweating & sudden loss of consciousness are the usual manifestations. It may be missed if blood glucose estimation is not done. It should be treated with intravenous 50% glucose 50 ml or 25% dextrose 100ml; followed by IV infusion of 10% dextrose. Continue monitoring blood glucose levels is desirable. If glucose infusions are not available, glucose solutions can be given through mouth or nasogastric tube. It may be associated with lactic acidosis, a dreaded accompaniment with mortality upto 70%. Women in second or third trimester of pregnancy may develop hypoglycemia even with low parasitemia.

Pulmonary oedema : This is a serious complication. It may be present on admission, may develop unexpectedly several days later or may develop immediately after childbirth.

Premature labour: In non immunised females, foetal distress and premature labour is common and may occur at the height of fever. Foetal prognosis with premature labour is invariably poor. In endemic areas, pregnant women tolerate heavy parasitemia better than the pregnant women from non endemic areas.

Septicaemia: Pregnancy increases susceptibility to pneumococcal infections and may lead to pneumonia or meningitis. Septicaemia following bladder catheterisation is common in pregnant women with heavy parasitemia [1] .

SAFETY OF ANTIMALARIALS DURING PREGNANCY

1. Quinine does not cause abortion in therapeutic dose. The uterine contraction is related to the height of the fever and heavy parasitemia. Hence intravenous and oral quinine can be safely used in all trimesters of pregnancy 8 .
2. Artimisinin derivatives are not recommended at present, since extensive trials have not yet been conducted in pregnant women.
3. Chloroquin is safe in all trimesters of pregnancy.
4. Mefloquin is safe during pregnancy
5. Sulfa containing drugs are contraindicated.
6. Tetracycline and primaquin are contraindicated in pregnancy.

MANAGEMENT OF VARIOUS COMPLICATIONS IN SEVERE MALARIA

Cerebral malaria is the most important complication of severe malaria. These patients need close monitoring and meticulous management. This can lead to death if left untreated, and 15 to 30% die even with treatment. The patrasitemia may clear, but still the patient can die. Hence there is a need to understand the pathophysiology of cerebral malaria. The prognosis becomes worse in the presence of MODS. Prophylactic use of anticonvulsants is debatable. Use of steroids in this situation has not been without side effects. [15]

SEVERE ANAEMIA IN MALARIA IS DUE TO

1. Rupture of parasitised erythrocytes.
2. Rupture of non parasitised erythrocytes mediated though cytokines and reactive oxygen species (ROS).
3. Bleeding from different sites
4. Bone marrow depression
5. Disseminated intravascular coagulation (DIC).
6. Auto immune haemolytic anaemia (rarely).

Anaemia due to acute malaria is usually normochromic normocytic in nature. The presence of microcytic

hypochromic anaemia indicates either iron deficiency, nutritional anaemia or hemoglobinopathies; which are not uncommon in tropical countries. The preexisting anaemia due to nutritional deficiency or haemogloboinopathy may be aggravated in malaria. Severe anaemia (Haemoglobin below 5 g/dl) or a rate of fall of more than 2g in 24 hrs may induce cerebral anoxia and cardiac failure. Patients with heavy parasitemia, pregnancy or delivery, and children are vulnerable to develop severe anemia.

INDICATIONS OF BLOOD TRANSFUSION IN SEVERE MALARIA

The presence of severe or rapidly progressing anaemia in malaria needs prompt treatment, as it is associated with poor prognosis.

Blood transfusion of whole blood or packed cell is indicated when haemoglobin is below 5 g/dl; a rate of fall of > 2g in 24 hrs; haematocrit < 20 or in patients with features of cerebral anaoxia.

Volume overload must be avoided by giving only packed cells. Injection furosemide 20-to 40 mg should be administered prior to blood transfusion when impending cardiac failure is suspected or already present.

Jaundice as such is a not a grave complication, unless very severe. It is a non fatal complication when occurs alone. It however accompanies other severe complications like cerebral malaria, anaemia, renal failure etc. Usually jaundice is mild to moderate; infrequently the serum bilirubin may go beyond 20 mg %. It is predominantly unconjuagated hyperbilirubinemia, occasionally associated with marginally raised liver enzymes. Liver cell failure due to malaria is relatively rare. [20]

No specific management is needed to reduce hyperbilirubinemia. However when associated with very high bilirubin levels (> 28 mg/dl) in children, exchange transfusion is needed. Severe haemolysis may lead to consequent anaemia, which may need blood transfusion, if severe. [21]

DOSE MODIFICATION IN SEVERE MALARIA IN THE PRESENCE OF JAUNDICE?

- Do not reduce the dose of quinine in the first 48 hours of therapy in presence of jaundice.
- If the alanine aminotransferase (or SGPT) is very high, the dose can be reduced to 2/3rd after 48 hours.

Renal failure increases the mortality three fold. The institution of dialysis is needed at an early stage; and not when the acute renal failure is established or when ARDS has set in. Biochemical parameters need to be checked at least 12 hourly. Urinary estimation of sodium (Na) is required to establish ATN.

Blackwater fever a rare complication . It is suspected when patient passes of black or cola colored urine resulting from massive haemolysis. Urine examination reveals haemoglobinuria without RBC. It may be associated with acute renal failure or DIC.

The management of this rare complication is maintenance of good hydration, blood transfusion, if associated with severe anemia or thrombocytopenia. If associated with renal failure, consider for haemodialysis or peritoneal dialysis. Quinine should not be discontinued or reduced in the first 48 hours of therapy.

Patients with G6PD deficiency are prone to this complication when on quinine therapy.

The newer antimalarials are quite effective and useful in both uncomplicated and complicated malaria.[16,17] . However, it should be used with caution, as these have neurological and cardiovascular side effects [18,19] . It may have deleterious effect in pregnancy and infancy.

Severe P. vivax malaria usually does not cause much problem other than haemolysis and anaemia. But acute complications include splenic rupture and at times hepatic dysfunction. Though cerebral malaria has been described in P vivax malaria, the authenticity of these reports is questionable. Probably mixed infections with P falciparum were missed.

Figure 2

Table-2: Check list for management in severe malaria

Principle: Early diagnosis and prompt treatment	
1.	Check airways and nurse on side
2.	Quick clinical assessment, Weigh the patient (if possible)
3.	Collect blood for MP, Urea, Creatinine., RBS, electrolytes
4.	Start IV line - fluid/Quinine/Symptomatic drugs like antipyretics
5.	Check Urine intake output - pass a catheter SOS.
6.	Decide fluid requirement, avoid fluid overload, CVP preferably.
7.	Avoid hypoglycemia.
8.	LP to rule out other CNS infections
9.	Consider the need for antibiotics, anticonvulsant etc.
10.	CVP monitoring, chest x-ray and blood gas analysis
11.	Consider the need for blood transfusion

Figure 3

Table-3: Conditions mimicking malaria 1,2

Fever	Enteric fever, viral fever
Hyperpyrexia	Heat stroke, sepsis , pontine haemorrhage
Jaundice	Viral Hepatitis, leptospirosis, drug-induced or toxic hepatitis, acute haemolysis: haemoglobinopathy, G6PD ddeficiency, autoimmune haemolytic anaemia, drug induced haemolysis
Hypoglycemia	Severe septicemia, liver failure, Reye's syndrome,
Gastrointiestinal symptoms	Gastroenteritis, salmonellosis, shigellosis, traveler's diarrhoea
Abnormal bleeding	Hepatic failure, poisons, viral hemorrhagic fever leptospirosis, Dengue
Convulsions	Febrile convulsion, epilepsy, cerebrovascular diseases (CVD)
Encephalopathies	Viral encephalitis, bacterial meningitis, poisoning, eclampsia
Hypotension and shock	Gastroenteritis, pneumonia, septicaemia

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