Introduction
Despite efforts at vector control, malaria still remains a major public health problem and Plasmodium falciparum infection is associated with a mortality in excess of two million individuals per year. Most of this mortality occurs as a result of complications associated with organ dysfunction due to parasite vascular sequestration. Severe and complicated malarial syndromes must be rapidly identified and aggressively managed in an efficient and well-equipped ICU if mortality is to be reduced.

Epidemiology
Malaria remains one of the world’s most prevalent infectious diseases. 300-500 million cases occur annually in tropical regions with an estimated 1.1-2.7 million deaths yearly. Official data from the National Malaria Eradication Programme in India estimates the incidence as 2.5-3.0 million cases with 1000 deaths annually. This represents significant underreporting in this author’s opinion. In the non–immune individual, fatality rates are as high as 20% for primary P. falciparum infection. The mortality and prevalence of P. falciparum infections has increased as a result of widespread resistance of the parasite to chloroquine and sulpha-pyrimethamine compounds. Mortality rates for patients with cerebral malaria and other severe complications in India vary from 10% in South India to a high of 32% in Rajasthan and 20% in other parts of the country. The mortality of cerebral malaria in pregnant women can be as high as 40%.

In a recent study in Mumbai 70% or more of P.falciparum was resistant to chloroquine and similar increases have been reported from around the country. The vector anopheles spp has also become resistant to standard insecticides and the vitality of the early malaria eradication programmes undertaken in the 1950’s and 1960’s has waned. Similarly, large increases in resistant falciparum malaria were reported from the North East of India where high-grade multi drug resistance was acquired from nearby Myanmar. In the last few years there have been explosive outbreaks of resistant P.falciparum infection in Rajasthan due to extensive breeding of mosquitoes in newly laid irrigation canals. In general, malaria in India is a seasonal disease with outbreaks during and after the monsoons.

In recent years, there seems to have been a shift away from classical cerebral malaria as the main cause of mortality with a greater proportion of adults with severe and complicated malaria now presenting...
with renal and hepatic manifestations. Until a vaccine is developed it seems malaria will remain endemic in tropical regions with regular outbreaks when multi-drug resistant strains are encountered.

**Pathophysiology and Life Cycle**

Human malaria is caused by four varieties of the protozoan plasmodium, an obligatory intracellular parasite that multiplies within red blood cells by asexual reproduction, and completes its life cycle by sexual reproduction within the foregut of the female anopheles mosquito.

Following a bite by an infected female anopheles mosquito, sporozoites are released into the blood stream and are rapidly extracted by hepatocytes within which they multiply to form merozoites. These mature over a period of six to fourteen days after which they rupture into the blood stream, and infect human erythrocytes. Within the erythrocytes, ring forms of plasmodia enlarge to form trophozoites, which enlarge further to form multinucleated schizonts then undergoing fission and in the process causing erythrocyte rupture and the release of further merozoites. Such merozoites go on to infect a fresh round of red cells by attaching themselves to red cell chemokine receptors by means of parasite surface proteins encoded for by a family of plasmodial genes. It is this process of erythrocyte infection and rupture that is responsible for the clinical malarial febrile paroxysms. This entire process has enormous potential for amplification. A single sporozoite may produce over 10-15,000 hepatic merozoites and each erythrocyte releases 10-20 merozoites each of which is capable of infecting more red cells. After a period of time some of the trophozoites mature into male and female gametocytes, which are extracted during the blood meal of a mosquito where further multiplication occurs completing the life cycle. It is notable that gametocytes per se are incapable of causing clinical illness and their persistence on blood films after successful treatment is common and should not be mistaken for resistant malaria.

*Plasmodium falciparum* differs significantly from the other three species of malaria viz *P. vivax*, *P. ovale* and *P. malariae*. Only *P. falciparum* causes mortality by inducing severe and complicated malarial syndromes such as cerebral malaria, renal failure, adult respiratory distress syndrome etc. This is partly because of its capacity to infect red blood cells of any age therefore causing disastrous levels of parasitaemia. As a rule, any non-immune individual with a parasitaemia in excess of 10% will be considerably ill.

In like manner it is only *P. falciparum* that can undergo the phenomenon of vascular sequestration or cytoadherence and thereby cause severe organ dysfunction. In order to sequester within the circulation and avoid the culling effects of circulation through the splenic sinuses, *P. falciparum* has acquired the evolutionary capacity to attach itself to the endothelium of capillaries and post capillary venules by the formation on the RBC surface of “knobs” which are rich in histidine containing proteins. Another important binding ligand, which has been identified, is *P. falciparum* infected erythrocyte-binding protein (PfEMP-1). Within the PfEMP-1 region there is considerable variation in antigenic expression, which is coded for by between 50-150 genes thus allowing the parasite to effectively evade the immune process. Numerous molecules within the endothelium are responsible for attachment to PfEMP-1 such as ICAM1, CD36, VCAM1, ELAM1 and thrombospondin. The expression of these endothelial receptors is upregulated by the presence of TNF alpha liberated during erythrocyte lysis. TNF alpha production is important in the pathogenesis of cerebral malaria as it appears that the presence of a TNF alpha receptor on tissue cells is necessary for the induction of lethal cerebral malaria and similar studies of raised levels in Indian patients have indicated prognostic value.

The net result of this vascular sequestration and cytokine release is a dysfunction of the involved organ system as a result of the local ischaemia and hypoglycaemia that occurs. The hyperparasitaemia that may ensue as a result of *P. falciparum* infection contributes to morbidity and mortality not just by destruction of a large quantity of the body’s total RBC mass but also by a greater degree of cytoadherence, hypoglycaemia and lactic acidosis caused by parasite metabolism. Previous theories...
regarding an increase in tissue permeability, decreased cerebral perfusion, immune mediated cerebral damage and mechanical RBC sludging are still a matter of investigation and debate but these appear to have given way to the belief that the phenomenon of cytoadherence and now cytokine activation as studied by immunohistochemistry of brain tissue leads ultimately to disruption in axonal transport, causing the ultimate pathological derangements in cerebral malaria. With the advent of recent studies in Africa showing high CSF opening pressures in a large number of children with cerebral malaria implying cerebral oedema, it seems that our understanding of the overall pathophysiology of this condition is somewhat incomplete. The fact that there is no suitable animal model impairs studies considerably.

Host Immunity
There is no true protective immunity in malaria and persons who have suffered a clinical infection may continue to present with clinical disease with each fresh infection. Immunity in malaria is only partial which is why the term semi-immunity is used. The spleen serves to prevent levels of parasitaemia from reaching disastrous levels by its function as a filter of non-deformable erythrocytes and splenectomised patients may rapidly develop hyperparasitaemia with a mild infection. No increase in the incidence or severity of malaria has been noted in children or adults with immune suppression due to HIV infection. Immunity in malaria is not only species but also strain specific as was ascertained by experiments in the early 1900s when malarial parasites were injected into patients with tertiary syphilis as “fever therapy”. Patients who are semi immune develop milder symptoms and tolerate higher levels of parasitaemia. Studies have shown the association of severe malaria is significantly higher in patients with certain HLA- alleles and the HLA-DR13 allele was highly associated with severe malaria. Historically semi-immunity from repeated infections has served to protect local populations from the advancing armies of non-immune aggressors. The Romans held out against the armies of Hannibal while they were devastated by malaria and in the 1970’s in Vietnam, more combat days were lost by US soldiers due to malaria than due to battle injuries. In general a person who resides outside an endemic area loses his semi-immunity within two years, a fact to be remembered when dealing with issues of prophylaxis in returning residents. Strangely patients infested with Ascaris lumbricoides appear to have a definite protection against cerebral malaria.

Clinical Manifestations
Severe and complicated malaria may present to the clinician in a variety of guises depending on the predominant organ system affected by the cytoadherence phenomenon. WHO has defined severe and complicated disease according to the criteria listed in Table 1.

In clinical practice, most patients with severe falciparum infections present with cerebral malaria,

Table 1: Some WHO Criteria for defining severe malaria

- Cerebral Malaria [unarousable coma]
- Severe normocytic anaemia [haemoglobin<5.0gms, haematocrit <15%]
- Renal failure [urine output <12ml/kg/24hours or elevated serum creatinine>3.0mgs%]
- Pulmonary oedema
- Hypoglycaemia [blood sugar <40mgs%]
- Circulatory collapse [systolic blood pressure <50mmHg and cold extremities]
- Spontaneous bleeding and disseminated intravascular coagulation
- Repeated generalized convulsions
- Acidaemia [arterial pH<7.25] or acidosis [plasma bicarbonate <15mEq/L]
- Malarial haemoglobinuria [not drug induced]
which is a diffuse bihemispheric neurological dysfunction characterized by drowsiness, disorientation, coma and convulsions. In severe cases of cerebral malaria patients may have extensor posturing and bipyramidal signs. Fever is the cardinal clinical manifestation among all patients with malaria and malaria should be definitely excluded as the cause of any untoward febrile clinical illness in an endemic area. Thus fever and jaundice may be due to falciparum malaria as may be fever with seizures, fever with oliguria, fever with ARDS and fever with anaemia. In patients with cerebral malaria seizures may occur in up to 50% of patients and are largely generalized. Papilloedema and exudates are seen less frequently than retinal haemorrhages, which occur in up to 15% of individuals and to a greater degree in cerebral malaria than in non-cerebral severe malaria. Though these appear to have no prognostic significance in the Indian setting, many workers consider retinal haemorrhages a useful reflection of the pathophysiological processes in the brain. In all cases of cerebral malaria neurological manifestations of hypoglycemia, which may occur de novo, or as a result of quinine therapy must be suspected and excluded.

Severe anaemia in P. falciparum infections correlates well with parasitaemia, schizontaemia, total serum bilirubin and creatinine concentrations. Patients with severe anaemia and severe jaundice must be suspected to have had an intravascular hemolysis caused by G6PD deficiency the levels of which should be estimated. Jaundice as a manifestation of severe malaria is common and is caused by a combination of RBC haemolysis and hepatic dysfunction due to parasite vascular sequestration in the liver. Liver enzymes are invariably elevated but never more than tenfold or to the levels seen in viral hepatitis. Features of hepatic encephalopathy such as aps are almost never seen. In the jaundiced patient with cerebral manifestations, differentiation between fulminant hepatic failure due to viral hepatitis or leptospirosis may be difficult. Subconjunctival haemorrhages are commonly seen in P falciparum infections but clinical bleeding is uncommon and if present tends to be associated with concomitant renal and hepatic dysfunction and thrombocytopenia. Acute renal failure is a common manifestation of severe malaria and is often the cause of mortality. Patients may be anuric, oliguric, or non-oliguric with a steadily rising creatinine. In many patients prolonged dialysis is needed as the kidneys may be the last organ to recover. A significant proportion of patients with cerebral malaria will have elevated levels of the serum creatinine and these patients are more likely to have prolonged coma, jaundice and hypoglycaemia. Pulmonary oedema may occur early in the course of the disease in patients and in these instances is often a manifestation of over enthusiastic hydration in patients with leaky alveolar capillaries and a normal pulmonary capillary wedge pressures. In many patients pulmonary oedema develops late when patients have recovered from other manifestations of severe malaria and these patients will require prolonged ICU management with invasive and non-invasive ventilation. Cardiovascular abnormalities are uncommon and in patients with evidence of an unstable blood pressure investigations to exclude bacterial sepsis should be excluded. Patients in the ICU may develop multiple nosocomial infections and these should be identified and managed accordingly.

Indicators of poor prognosis in patients with severe malaria include deep coma, renal failure, pulmonary oedema and bleeding. Patients who have hyperparasitaemia (>5% of RBCs parasitised) schizontaemia or acidosis also have a poor outcome.

Investigations
The diagnosis of malaria is established with the demonstration of P.falciparum parasitaemia in any of the clinical settings described above. Well-prepared thick and thin smears prepared at numerous intervals over a 24-hour period inevitably demonstrate malarial parasites and though “smear negative cerebral malaria” has been described in older textbooks of medicine, it is rare. Quantification of the percentage parasitaemia is important in establishing a baseline to assess response to therapy and the goal should be complete clearance of parasites from the peripheral blood smears within 48 hours. Antigen assays by dipstick methods are often useful where quality smears are unavailable but cannot
Severe and Complicated Malaria

quantify the ongoing infection and may be insensitive in patients with low-grade parasitaemias. Patients with cerebral malaria may have low or normal haemoglobin levels. The leukocyte counts are normal or low and platelet counts are reduced but rarely to disastrous levels or to the point where clinical bleeding occurs. Other investigations relating to biochemical and metabolic parameters reflect the presence of co-morbid organ dysfunction such as renal failure, ARDS and hepatic decompensation. In children, hyponatraemia appears to be frequent and due to an excess of ADH secretion. CSF studies are not indicated in cerebral malaria except to exclude other CNS infections. A mild rise in protein content with no hypoglycoracchia or pleocytosis is the usual picture.

The imaging findings in cerebral malaria are varied, differ between children and adults and are important due to their prognostic value. In one study the CT findings included normal scans, diffuse cerebral oedema with bilateral symmetric non-enhancing thalamic and/or cerebellar hypodensities. It was found that the CT findings correlated well with the severity of the disease, a normal scan indicating a favourable outcome, whereas cerebellar hypodensities have a poor prognosis. Diffuse petechial haemorrhages found on post-mortem examination were not identified on CT scans of patients. Thalamic and cerebellar lesions seen on CT are better appreciated on the MRI.

Management

The management of the patient with cerebral malaria aims for a rapid reduction in parasitaemia with effective drug therapy and careful management of all existing and potential complications.

While the management of the uncomplicated case of P falciparum malaria may be undertaken with oral agents, severe and complicated malaria and in particular cerebral malaria requires the administration of parenteral therapy. As a result of widespread resistance to chloroquine, the drugs of choice are intravenous quinine or parenteral artemether compounds [Table 2]. Intravenous quinine is administered as a slow infusion in a dose of 10mg/kg body weight but should not to exceed a total dose of 600mg. This is given in a 5 or 10% dextrose infusion over 4 hours and such drips are repeated eight hourly. In general intravenous quinine therapy is safe and does not require continuous ICU monitoring except in the elderly and those with pre-existing cardiac disease. In these patients the QTc interval should be monitored and therapy discontinued if there is widening which exceeds 25% of basal values. Intravenous quinine is generally continued in this fashion until parasitaemia clears and the patient defervesces. After this the drug may be given orally in the same doses eight hourly to complete 5-7 days of therapy. Workers in the West and Africa prescribe a loading first dose of 20mg/kg body weight. This appears unnecessary in India where no significant quinine resistance has been reported and patients have often received antimalarial therapy with chloroquine or mefloquine, which tends to elevate quinine levels and enhance cardiotoxicity. Quinine is generally well tolerated in patients with cerebral malaria, however patients do manifest hypoglycaemic episodes on account of the known quinine induced hyperinsulinism. In an unconscious patient hypoglycaemia may go undetected unless suspected and tested for regularly. Cinchonism consisting of tinnitus and partial deafness is common and easily reversed by reducing the dose from q8hourly to q12hourly. In some patients given quinine for more than five days a drug fever has been noted.

The artemether compounds are remarkably safe and effective drugs with equivalent potency that produce a rapid reduction in parasitaemia. The most commonly recommended preparation is Artesunate, which is given as a bolus of 2.4mg/kg body weight intravenously or intramuscularly, followed by doses of 1.2mg/kg body weight 12 hourly for a further 5-7 days. Arteether is prescribed in an intramuscular dose of 150mg od for three days and Artemether though effective is not easily available in India. Side effects with these drugs are almost unknown.
Either of the above regimes should produce a marked improvement in clinical symptoms and a sharp fall in parasitaemia within 48 hours. Both quinine and artemether compounds are equally effective in the Indian population in whom there is no significant resistance to these drugs. It is our practice to favour the artemether compounds in view of their relative safety and ease of administration. The simultaneous or sequential use of doxycycline or a sulpha-pyrimethamine compound does little to speed up parasite clearance, but they may be useful in shortening quinine therapy and preventing late recrudescence from small numbers of residual parasites that occur with the use of quinine or artemether compounds as monotherapy. In patients with a parasite count in excess of 20%, exchange transfusions have been recommended though in practice obtaining 5-10 litres of cross matched pathogen free blood and undertaking the exchange transfusion without haemodynamic instability may be difficult. Alternatively, low volume or automated exchanges with a cell separator can be given, as reports of its benefits are promising.

In the management of severe and complicated malaria, parasite clearance remains only one aspect of the overall management. Patients die despite parasite clearance on account of coma with its attendant complications especially aspiration pneumonia. Acute respiratory distress syndrome (ARDS), renal failure, convulsions, severe anaemia, hypoglycaemia, disseminated intravascular coagulation (DIC) and shock are common and may all contribute significantly to mortality. These concomitant manifestations of severe disease in patients with P. falciparum malaria will require their own individual management in a well-staffed and well-equipped ICU. In our own experience the high mortality of severe malaria in India is due to the lack of ICU and blood bank resources and less due to poorly chosen or delayed drug therapy. Ancillary therapies such as steroids, heparin, pentoxyphylline and low molecular weight dextran have been proven to be of no benefit and may in fact be deleterious. In children with cerebral malaria, phenobarbital 20 mg/kg provides highly effective seizure prophylaxis but is associated with an unacceptable increase in mortality. Mannitol appears to produce transient improvements in the sensorium and in light of the fact that studies on African children have shown high CSF opening pressures in patients with cerebral malaria, the role of this drug should not be discounted.

**Conclusion**

The mortality from severe and complicated malaria remains high and patients with the various manifestations of this common disease must be identified rapidly and treated effectively to reduce their

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**Table 2 : Recommended antimalarial medications for patients with severe malaria**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading Dose</th>
<th>Maintenance dose</th>
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<tbody>
<tr>
<td>Quinine dihydrochloride –i.v. diluted in 5 or 10% dextrose</td>
<td>20 mg/kg of the salt * [maximum, 600 mg] over 4 h</td>
<td>10 mg/kg over 4 h, q8h</td>
</tr>
<tr>
<td>Artesunate</td>
<td>2.4 mg/kg first dose</td>
<td>1.2 mg/kg at 12 and 24 h, then 1.2 mg/kg/d for 7 days</td>
</tr>
<tr>
<td>Artemether</td>
<td>3.2 mg/kg first dose</td>
<td>1.6 mg/kg/d od for 7 days</td>
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</tbody>
</table>

*Loading doses of quinine compounds should not be used when the patient has previously received oral quinine, mefloquine or chloroquine*
parasite burden while supporting them in a well equipped ICU until organ dysfunctions recover and hematological abnormalities are corrected. Few patients recover with any residual sequelae and the effort expended in treating these patients is always worthwhile.

Reference
28. Patankar TF, Karnad DR, Shetty PG, Desai AP, Prasad SR. Adult cerebral malaria: prognostic importance of
imaging findings and correlation with postmortem findings. Radiology 2002; 224(3):811-816.