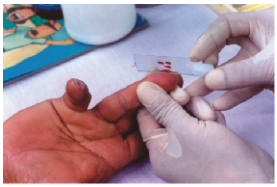
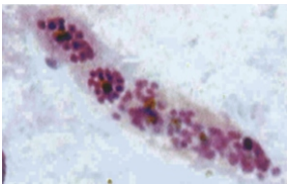
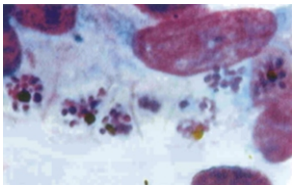
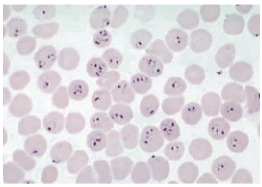

Regional Guidelines for the Management of Severe Falciparum Malaria in Large Hospitals

World Health Organization
Regional Office for South-East Asia
New Delhi

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WHO Library Cataloguing-in-Publication data

World Health Organization, Regional Office for South-East Asia
Regional guidelines for the management of severe falciparum malaria in large hospitals.

(1) Malaria – therapy.
(2) Malaria, Falciparum – diagnosis – therapy.
(3) Malaria – complications – immunology.
(4) Guidelines.

ISBN 92 9022 281.6 (NLM classification: WC 750)

Further publications can be obtained from the Malaria Unit, Department of Communicable Diseases, World Health Organization, Regional Office for South-East Asia, World Health House, Indraprastha Estate, Mahatma Gandhi Road, New Delhi 110002, India.

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Cover Photo: Bangkok Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

October 2006

List of abbreviations

ABC	Airway, breathing and circulation
ACT	Artemisinin-based combination therapy
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
ARF	Acute renal failure
AST	Aspartate aminotransferase
CSF	Cerebrospinal fluid
DIC	Disseminated intravascular coagulation
ECG	Electrocardiogram
G6PD	Glucose-6-phosphate dehydrogenase
GI	Gastrointestinal
HRP-II	Histidine-rich protein II
JVP	Jugular venous pressure
KVO	keep vein open
LP	Lumbar puncture
NSAIDs	Non-steroidal antiinflammatory drugs
pLDH	Parasite lactate dehydrogenase
RDT	Rapid diagnostic test
SIADH	Syndrome of inappropriate antidiuretic hormone secretion

Contents

Annexes

Preface

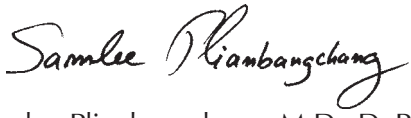
Malaria is a serious disease that causes high morbidity, mortality and enormous economic loss in the South-East Asia Region. The dynamics of the disease, especially the drug resistance patterns, are changing rapidly. There is therefore a need for health personnel to be aware of changing situation, of the availability of new drugs and new combinations as well as proper clinical management of malaria patients in order to save lives and reduce the economic loss due to direct and indirect costs.

These guidelines were developed by the WHO Regional Office for South-East Asia and the WHO Collaborating Centre for the Clinical Management of Malaria, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. The guidelines were peer reviewed in a workshop in June 2005 by a group of experts from Member States in the field of malaria case management. Two regional guidelines were developed simultaneously, *i.e.* the guidelines for small and large hospitals (primary and secondary hospitals/health facilities, respectively). The guidelines are based on a review of current evidence, existing WHO guidelines and experience in the management of malaria in small hospitals/health facilities in the South-East Asia Region. The guidelines primarily focus on clinical management of severe malaria. Management of uncomplicated malaria or preventive uses of drugs are not included as these issues are usually covered in the respective national drug policies.

The guidelines are targeted for use by medical personnel who treat severe malaria patients, referred from lower-level health facilities.

These can, if needed, be further adapted by the Member States in keeping with their needs, especially in terms of the drug resistance situation, the national drug policy, availability of antimalarial drugs and hospital facilities.

I am confident that these guidelines will be most useful in the management of severe malaria in countries of the South-East Asia Region.



Samlee Plianbangchang, M.D., Dr.P.H.
Regional Director

1. Introduction

Malaria is a major cause of mortality and morbidity in the tropical and subtropical regions of the world. An estimated 300-500 million persons suffer from and more than 1 million die of malaria each year. A majority of malaria deaths, particularly those in children under five, occur in sub-Saharan Africa. The South-East Asia Region reports a high number of cases and deaths second only to Africa. Unlike some of the other acute diseases such as encephalitis, meningitis, and most of the chronic diseases, patients of severe malaria can recover completely without any long-term effects if treated promptly and correctly. Therefore, rationalization and standardization of treatment of cases of severe malaria at different levels of health care is important and has several advantages. Deaths can be reduced through effective use of standard treatment. Patients who require hospitalization and those who need intensive care can be identified promptly and treated before complications develop and result in deaths. The adoption of this approach of standard management will contribute to the reduction in the mortality and morbidity from malaria.

Severe malaria is characterized by cerebral malaria; severe anaemia; renal failure; hypoglycaemia; acidosis, *etc* and if not treated promptly and effectively, may lead to death.

Severe malaria is mainly caused by *P falciparum* but not all cases of *P falciparum* are severe. The treatment of this condition requires hospitalization and sometimes institution of intensive care. The signs of severe malaria may be non-specific and can occur in other severe febrile diseases such as meningitis, encephalitis, septicaemia, typhoid fever, leptospirosis and viral infections that are commonly seen in malarious areas. In view of the non-specific presentation it is difficult to recommend a standard clinical case definition for the disease. Furthermore, the treatment of severe malaria involves the use of medicines which may be toxic. Malaria caused by

P falciparum is becoming increasingly resistant to antimalarials. Therefore, it is necessary to use effective drugs only in cases of confirmed malaria. To ensure that effective medicines are used when they are needed, the definitive diagnosis of malaria by microscopy or rapid diagnostic tests (RDTs) is essential.

2. Managing severe malaria at small and large hospitals and health facilities: the rationale

The situation with regard to different categories of hospitals and health facilities in countries of the South-East Asia Region vary widely. Norms, standards and guidelines for the treatment of severe malaria would vary according to the capacity of the hospitals and health facilities to treat the disease. At present, standard treatment guidelines and procedures are not widely available and used. It is difficult to produce many different guidelines to suit the individual needs of the hospitals and health facilities. Therefore, the hospitals and health facilities (private and public) are broadly grouped into three categories based on their capacity to treat severe malaria cases. The descriptions in the present guidelines are generic based on the needs of patients and the existing capacity of hospitals and health facilities. Individual countries should decide about specific categorization based on the existing situation, facilities available (drugs and supplies), presence and capacity of the staff and the policy regarding the treatment of severe malaria. Therefore, the different guidelines that are proposed to be provided can be suitably adapted and made available to the staff in different facilities.

Since cases of suspected severe malaria often need to be hospitalized, only hospitals and health facilities where doctors and nurses are available and hospitalization facilities are present are considered in these guidelines.

Importance of standard guidelines for treatment of severe malaria

For effective treatment of severe malaria to reduce mortality and complications, WHO Regional Office for South-East Asia recommends to countries the use of standard guidelines that are suitable for use in

small and large hospitals. Categorization of small and large hospitals/ health facilities is in the Annex 1. No guideline is proposed for tertiary care hospitals since patients admitted there require specialized care on an individualized basis and every patient has a unique set of problems. Tertiary care hospitals have adequately trained manpower with access to the latest research. Standard guidelines, therefore, are likely to have limited usefulness. Similarly no guidelines are prepared for the staff in health outposts whose role is limited to prompt referral of cases of severe malaria. Guidelines for recognition of malaria and referral are included in the manual for health workers as an integral part of the treatment process.

Description of large hospitals

A large hospital ideally should have the following facilities:

- Round-the-clock coverage by qualified doctors and nurses
- Facilities for intravenous infusion and central venous monitoring
- Microscopy and rapid diagnostic test for malaria
- Routine blood, urine and stool tests, biochemical tests including blood glucose, urea, serum creatinine, bilirubin, electrolytes, arterial blood gas measurement, cerebrospinal fluid (CSF) tests, electrocardiogram (ECG), basic X-ray and microbiology tests
- Blood transfusion
- Oxygen therapy and ventilatory support
- Facilities for doing a lumbar puncture
- Facilities for specialized biochemical, radiological, microbiological tests
- Facilities for intensive care management of critically ill patients
- Facility for peritoneal/haemodialysis

Currently, the availability of these facilities is not uniform in all large hospitals. The government is expected to provide trained staff and facilities to enable these hospitals to offer the standard treatment to patients. Private hospitals should also be encouraged to use the

standard treatment guidelines to help in the reduction of mortality and complications from severe malaria. If they lack laboratory facilities or adequately trained staff, they can be assisted by the government or by other private institutions. Patients who require treatment or investigations for severe malaria should be referred to hospitals where such facilities exist.

3. Diagnosis of malaria

Severe malaria usually occurs as a result of delay in specific treatment of uncomplicated falciparum malaria. Severe malaria should be suspected in patients with confirmed malaria and who have severe manifestations as described in Section 4. These manifestations can occur solely or, more commonly, in combination in the same patient. Jaundice *per se* is not considered a criterion of severe malaria. This is only a marker of severe malaria when combined with evidence of other vital organ dysfunction such as coma or renal failure. However, jaundice is usually associated with vital organ dysfunction. If the patients with falciparum malaria have jaundice, vital organ complications should be looked for. Also, hyperpyrexia is no longer considered a sign of severity.

The following provide a clinical and definitive diagnosis of malaria. All suspected cases of severe malaria should be blood-tested to confirm if the patients have malaria parasites and subsequently assessed clinical symptoms to recognize severe manifestations (Section 4).

3.1 Clinical diagnosis of malaria

Non-immune malaria patients commonly show signs of fever, chills, headache, bodyache and anorexia and occasionally show signs of abdominal pain and diarrhoea, and palpable liver and spleen. In young children there may be irritability, loss of appetite, and vomiting. Often, fever may be the only sign and it may or may not be of tertian type or accompanied by rigors.

However, in malaria endemic areas, any patient reporting fever, abdominal pain, diarrhoea and vomiting should be suspected of having malaria. Those patients who have a history of residence in a

high-risk area for malaria and those who have travelled recently to these high-risk areas should also be considered as suspected malaria cases.

3.2 Definitive diagnosis

The diagnosis of malaria is essentially made from clinical features and can be confirmed by the demonstration of *plasmodia* by laboratory examination if facilities exist. However, when large hospitals have the laboratory facility to confirm the diagnosis, the diagnosis should not base on clinical studies without laboratory confirmation.

Presence of *Plasmodium falciparum* parasites in the blood can be detected by microscopy or immunological tests for parasite derived proteins (or rapid diagnostic tests: RDTs). Diagnosis by RDTs may be helpful in hospitals where laboratory technicians are not familiar with microscopic diagnosis of malaria by blood films.

Parasitological diagnosis using light microscopy

Giemsa or Field-stained thick and thin blood smears should be examined in all patients suspected with malaria. ***A thick smear should be examined in all suspected cases of malaria*** because of its ability to detect parasites even when the parasitaemia is low. A thin film is used for species and stage identification, and to provide information regarding erythrocytes, leukocytes and blood platelets. High parasitaemia, growing stages of parasites (trophozoites and schizonts) and pigment-laden neutrophils indicate poor prognosis. The doctor should be alerted if any of these conditions are detected. In case of uncertainty in identification of the species in patients with severe symptoms, it should be considered as *P falciparum*.

The laboratory staff in large hospitals should be adequately trained to perform light microscopy. They should be able to prepare proper blood films, stain it correctly and spend adequate time to examine it before a negative report is given. Good management should be ensured so as not to overload laboratory staff since they may commit mistakes if the workload is high and they read too many blood films.

Advantages of light microscopy

Light microscopy is cost effective, fairly sensitive and highly specific. Microscopy can estimate parasite density and differentiate between parasite species, provides information about platelets and leukocytes, and also help diagnose many other conditions. Repeated examinations also provide information on parasite clearance and successful treatment.

Disadvantages of light microscopy

Supervision and quality assurance are absolutely necessary if light microscopy is used. ***False negative results*** may be seen in conditions of very low parasitemia, maturation of sequestered parasites in the broods, partially treated with antimalarials or on chemoprophylaxis, and may also be due to technical factors such as poorly prepared or stained slides, poor quality of microscope, examination of only thin films, inexperienced technicians and the like. ***False positive results*** are also seen due to artefacts which can be confused for malarial parasite by an inexperienced microscopist.

Rapid diagnostic tests (RDTs)

These tests are recommended when microscopy is not available or inconclusive. They are based on detection of *P falciparum*-specific circulating proteins in the whole blood. The commonly used proteins for diagnostic purposes is histidine-rich protein-II (PfHRP-II or HRP-II), and recently developed parasite lactate dehydrogenase (pLDH), which is superior to HRP-II for its shorter shelf life. While pLDH can detect live parasites, HRP-II detects antigen of live and dead parasites. The staff should be properly trained to administer the rapid diagnostic tests for reliable results and quality assurance must be maintained for the results to be reliable. Wherever possible, treatment of severe malaria should be guided by light microscopy.

Advantages of RDTs

The tests are fairly sensitive and specific. The tests are also fast and simple. These tests are particularly helpful in partially treated cases and those with low parasitaemia or when the microscopy gives negative results. The tests can be very useful when the patient reports after the working hours of the laboratory technicians or when microscopic diagnosis can not be conducted for any reason.

Limitations of RDTs

There are many RDTs available in the market with advantages and disadvantages including differing levels of sensitivity, specificity, and stability. The latest advice should be sought when they are being considered for use. HRP-II antigen may continue to be detected in blood for up to 2-4 weeks even when parasites are dead or no more detected in the peripheral blood. Monitoring parasite clearance, quantification of parasite load and stage identification is not possible with these immunological tests while another limitation is its relatively high unit cost.

4. Clinical manifestations of severe malaria

Severe malaria is characterized by cerebral malaria (unrousable coma and also impairment of consciousness which is less marked than unrousable coma); severe anaemia; renal failure; pulmonary oedema or acute respiratory distress syndrome (ARDS); hypoglycaemia; circulatory collapse or shock; spontaneous bleeding from gum, nose, gastrointestinal tract, *etc.* and/or substantial laboratory evidence of disseminated intravascular coagulation (DIC); repeated generalized convulsions; acidaemia or acidosis including hyperlactataemia; macroscopic haemoglobinuria; prostration and hyperparasitaemia. Death may occur when severe malaria patients are not treated promptly and effectively.

Patients with severe malaria if not diagnosed and treated promptly can rapidly develop complications that are commonly associated with the illness. These are listed in Table 1.

Table 1: *Clinical manifestations and laboratory findings in severe malaria*

Clinical manifestations	Recognition	Laboratory findings
Impaired consciousness	Assessment by Glasgow scale (10 or less) or Blantyre scale (3 or less) as appropriate	Normal cerebrospinal fluid (CSF)
Severe pallor	Conjunctiva; tongue, lips and palms are pale	Haemoglobin <5 g/dl (Haematocrit <15%)
Oliguria or anuria/Acute renal failure	Urine output <400 ml/24 hours in adults and <0.5 ml/kg/hour in children	Serum creatinine >3 mg/dl in adults and >1.5 mg/dl in children
Jaundice (combined with evidence of other vital organ dysfunction)	Yellow discolouration of sclera	Serum bilirubin >3 mg/dl
Circulatory collapse, cold extremities, weak peripheral pulse	Cold, clammy and cyanotic skin and extremities, weak peripheral pulse and hypotension (systolic BP <80 mmHg in adults and children over 10 years; <70 mm Hg in children aged 1 month-10 years; <60 mmHg in neonates); core/skin temperature difference of >10°C)	
Metabolic acidosis	Laboured hyperventilation with increased inspiratory effort (often termed respiratory distress) and a clear chest on auscultation (Kussmaul's breathing)	Arterial pH <7.35 or plasma bicarbonate <15 mmol/l; venous lactate level of >5 mmol/l
Pulmonary oedema or acute respiratory distress syndrome	Tachypnoea, dyspnoea and bilateral basal rales	Bilateral infiltration in the lungs on chest film
Multiple convulsions	Jerky limb movements and staring eyes; two or more convulsions in 24 hours	Normal CSF
Spontaneous bleeding	Gums, nose, venepuncture sites, gastrointestinal tract	Blood tests suggestive of disseminated intravascular coagulation (DIC)
Haemoglobinuria	Dark red or black coloured urine	Urine is positive for haemoglobin
Hypoglycaemia	Anxiety, sweating, palpitation, dilatation of pupils, breathlessness, convulsions, alteration of consciousness	Blood sugar <40 mg/dl or 2.2mmol/L
Hyperparasitaemia		Parasite density higher than 250,000/μL blood or infected red blood cells more than 5% in non-immune patients (≥20% in any patient) and appearance of peripheral schizontaemia
Prostration	Unable to feed, sit, stand, walk unaided	

< = less than
> = more than

4.1 Presentation of severe malaria in adults and children

There are considerable differences in the manifestations of severe malaria between adults and children. While severe anaemia is the most common manifestation in very young children, cerebral malaria is the predominant cause of death in older children and adults. Severe malaria in South-East Asia affects all age groups and multi-system involvement is common in adults. The pattern of disease in children is intermediate, for instance the incidence of renal failure is higher than African children but lower than the adults from South-East Asia.

Table 2: *Difference between severe malaria in adults and children*

Signs or symptoms	Adults	Children
Anaemia	Common	Very common
Convulsions	Common	Very common
Pre-treatment hypoglycaemia	Less common	Common
Metabolic acidosis	Less common	Common
History of cough	Uncommon	Common
Cerebral malaria	Common	Common in older children
Jaundice	Very common	Uncommon
Renal failure	Common	Less common
Pulmonary oedema, Acute Respiratory Distress Syndrome (ARDS)	Less common	Rare
Duration of illness before severe features	Longer (5-7 days)	Shorter (1-2 days)
Resolution of coma	Longer (2-4 days)	Shorter (1-2 days)

5. General management of severe malaria

The following steps should be considered:

5.1 Initial assessment

History

The following history is very essential for all malaria patients:

- Area of residence or travel
- History of previous malaria infection
- Treatment with antimalarials or other drugs before admission

- Urine output in the last 8-12 hours
- Recent or past history of convulsions
- History of blood transfusion
- Pregnancy
- G6PD-deficiency status

Clinical assessment

It should include:

- Temperature, pulse, blood pressure, rate and depth of respiration, hydration
- Weight (in children determine weight for age)
- Level of consciousness [assessed using modified Glasgow Coma Scale for adults, (Annex 2a) and Blantyre coma scale for children (Annex 2b)]
- Anaemia
- Fundus examination if possible
- Clues for alternative diagnosis, *e.g.* meningitis, encephalitis, *etc.*

5.2 Laboratory investigations

The following investigations should be performed:

- Examination of peripheral blood films, parasite density and immunological test for parasite protein if microscopy is inconclusive/not done
- Hb, WBC, blood platelet count, blood group, blood glucose, liver and renal function tests, and serum electrolytes
- Lumbar puncture (LP) for cerebrospinal fluid (CSF) analysis in unconscious patients if meningitis is highly suspected. CSF analysis is very useful in differentiating cerebral malaria from meningitis, particularly in children.
- ECG, Chest X-ray if clinically indicated
- Blood culture and sensitivity and other serological tests, if available

5.3 General management

- Maintain airway, breathing and circulation (ABC of critical care, Annex 3)
- Monitor temperature, pulse, respiration and other vital signs every 4-6 hours
- Insert a urethral catheter in those with reduced urine output using a sterile technique and attached to a closed urinary drainage system or as otherwise indicated
- Insert a nasogastric tube to prevent aspiration pneumonia, to look for gastro-intestinal (GI) tract bleeding and for administration of medicines and nutrients
- Change intravenous sites every 72 hours to prevent infection and thrombophlebitis
- Cover eyes with pad to prevent corneal ulcers
- Mouth care should be done to prevent parotid gland infections
- Back care is needed to prevent bedsores
- Fluid intake and output chart should be maintained and reviewed regularly

In addition, the following complications should be managed:

- Convulsions
- High fever
- Hypoglycaemia and electrolyte imbalance
- Anaemia/bleeding
- Breathing difficulty if present, and,
- Dehydration and shock

If parasitological confirmation is likely to be delayed, specific antimalarial therapy should be started based on the clinical diagnosis. If there is suspicion of bacterial infection, antibiotics in appropriate doses should also be administered.

6. Specific antimalarial chemotherapy in severe malaria

All patients of severe malaria should be treated with parenteral artemisinin derivatives or quinine due to presence of widespread chloroquine-resistant *P falciparum* in South-East Asia.

Table 3: *Dosage of antimalarial drugs in severe malaria*

Antimalarial drug	Dosage and administration
Artemisinin derivatives	**Artesunate**: 2.4 mg/kg body weight (bw) IV or IM on admission (time=0), followed by 2.4 mg/kg at 12 and 24 hours, followed by once daily for seven days. Once the patient can tolerate oral therapy, treatment should be switched to a complete dosage of artemisinin-based combination therapy (ACT) for three days as recommended in the national treatment guidelines for uncomplicated malaria. **Artemether**: 3.2 mg/kg bw IM on the first day followed by 1.6 mg/kg bw daily for seven days. Once the patient can tolerate oral therapy, treatment should be switch to a complete dosage of an ACT. **Arteether:** 3.2 mg/kg bw IM on the first day, followed by 1.6 mg/kg bw for the next 4 days. Once the patient can tolerate oral therapy, may switch to a complete dosage of an ACT.
Quinine	***Loading dose:*** Quinine dihydrochloride 20 mg salt/kg bw diluted in 10 ml/kg bw of 5% dextrose or dextrose saline administered by IV infusion over a period of four hours. ***Maintenance dose:*** Quinine dihydrochloride 10 mg salt/kg bw diluted in 10 ml/kg bw of 5% dextrose or dextrose saline administered by IV infusion. In adults, the maintenance dose is infused over a period of four hours and repeated every eight hours. In children, it is infused over a period of two hours and repeated every eight hours (calculated from the beginning of the previous infusion) until the patient is in a position to swallow. An oral medication

	can be given following this to complete the seven-day treatment. The amount of fluid for infusion of quinine should be considered keeping in mind the hydration status of the patient. For instance, if the patient has volume overload or pulmonary oedema, quinine in 10 ml/kg IV fluid may be harmful. Therefore, the calculation of fluid for quinine infusion should be made accordingly. For choice of oral drugs for follow-on treatment, it is recommended to prescribe a combination therapy: three days of ACT according to the national treatment guidelines. If ACT is not in use in the country, quinine should be administered in combination with tetracycline or doxycycline or clindamycin, to complete the seven-day treatment, except for pregnant women and children under eight years of age for whom tetracycline/doxycycline is contraindicated.

Remarks:

- Artemisinin derivatives are safe, effective, have a wider therapeutic window, can be administered intramuscularly and should be considered a safer alternative to quinine.
- A loading dose of quinine should not be given if (i) the patient has received or suspected to have received quinine, quinidine or mefloquine within the preceding 12 hours, and (ii) facilities for controlled rate of flow of quinine infusion are not available. In areas where a 7-day course of quinine is not curative (such as Thailand), a course of oral tetracycline of 4 mg/kg bw to be taken four times daily, or doxycycline 3 mg/kg bw once daily, may be added except for children below the age of eight and pregnant women. Alternatively, clindamycin 10 mg/kg bw may be added twice daily for 3-7 days.
- If there is no clinical improvement after 48 hours of parenteral therapy, the maintenance dose of parenteral quinine should be reduced by one third to a half (*i.e.*, 5-7 mg/kg bw of quinine dihydrochloride). The total daily dose

of quinine in patients requiring parenteral therapy beyond 48 hours is as follows:

Adults: Day 0: (first day of treatment) 30-40 mg salt/kg of body weight

Day 1: 30 mg salt/kg of body weight

Day 2 and subsequent days: 15-21 mg salt/kg of body weight.

Children: Day 0: (first day of treatment) 30-40 mg salt/kg of body weight

Day 1: 20 mg salt/kg of body weight

Day 2 and subsequent days: 10-14 mg salt/kg of body weight.

- Intravenous quinine should be administered at recommended dosage for the first 48 hours even if acute renal failure (ARF) or severe jaundice is present.
- Quinine is **not** contraindicated in pregnancy.
- Pulse and blood pressure should be monitored ideally every hour and at least once in six hours while the patient is on quinine, particularly for those with underlying heart disease or taking anti-arrhythmic drugs.
- Patient should be kept in bed while on parenteral quinine to avoid severe postural hypotension.
- Volume of infusion fluid for administration of quinine can be reduced to half (Quinine dihydrochloride 10 mg salt/kg bw diluted into 5 ml, or 1 mg of quinine salt/0.5 ml of fluid) if volume overload is suspected. However, the duration of infusion should be the same.
- Quinine can be given by IM injections in the same dosages if IV infusion is not possible. It should be diluted in normal saline to a concentration of 60-100 mg salt/ml, the dose divided equally and administered in the two anterior thighs (not in the buttocks).

An uncomplicated *P falciparum* malaria patient may progress to a severe and complicated state if not treated early and appropriately.

7. Management of severe complications

7.1 Cerebral malaria

Cerebral malaria is the most dreaded complication of *P falciparum* malaria and is responsible for most of the deaths caused by the disease. The death rate increases significantly when it is associated with other complications such as ARF, jaundice, or ARDS.

Clinical features

Cerebral malaria is defined as unrousable coma (non-purposeful response or no response to a painful stimulus) in falciparum malaria. The above definition should only be used for identification of patients for the purpose of research and publication. However, ***every patient of malaria with altered sensorium should be treated for cerebral malaria*** until proved otherwise. The altered sensorium may manifest as abnormal behaviour in a conscious patient in its mildest form to deep coma in its most severe form. In between these extremes various stages of altered sensorium such as delirium, drowsiness, stupor and unconsciousness with purposeful motor response to painful stimulus can be observed (Annex 2). The onset of coma may be gradual after an initial stage of confusion or may be abrupt after seizures. The unconsciousness of the post-ictal state is usually short and persistence of unconsciousness beyond 30 minutes after convulsion should be considered as cerebral malaria. If the cause of unconsciousness is in doubt, other locally prevalent encephalopathies such as bacterial or viral meningoencephalitis should be excluded.

Neurological manifestations

One or several of the following neurological manifestations may be present.

- Diffuse symmetrical encephalopathy (focal neurological signs are rare)
- Focal or generalised convulsions.
- Muscle tone may be increased or decreased.

- Tendon reflexes are variable; plantar reflex may be flexor or extensor.
- Teeth grinding and clenching (bruxism) may be observed.
- Motor abnormalities such as decerebrate rigidity and decorticate rigidity (arms flexed and legs stretched) may be present.
- Change of behaviour such as agitation, confusion, aggression, *etc.*
- Mild neck stiffness may occur but frank signs of meningitis in the form of neck rigidity, positive Kerning's and photophobia are rare. However, in suspected cases meningitis should be ruled out by doing a lumber puncture examination.
- Cerebrospinal fluid (CSF) is clear with fewer than 10 white cells per µl; the protein is often slightly raised.

Ocular manifestations

Dysconjugate gaze (divergent eyes) may be common but cranial nerve involvement is rare. Convergent gaze, nystagmus, subconjunctival and retinal haemorrhages may be seen. Retinal haemorrhages indicated poor prognosis.

Management of cerebral malaria

Principles of management consist of (1) care of the unconscious patient (2) symptomatic management (3) specific antimalarials (4) management of associated complications.

Care of the unconscious patient

Airway, breathing and circulation (ABC) care of unconscious patients (Annex 3) should be practised in all patients of cerebral malaria in addition to meticulous nursing care.

Symptomatic treatment

Convulsions and body temperature should be controlled:

- ***Control of body temperature:*** Body temperature may be controlled by tepid sponging and fanning. If the fever is not controlled then appropriate antipyretics (paracetamol) may be used.
- ***Control of convulsions:*** Convulsions can be controlled with intravenous diazepam of 5-10 mg injected slowly. The dose can be repeated every 15 minutes if the convulsion persists but the total should not exceed 20 mg in an hour. This regimen can be repeated once every 2-4 hours up to a maximum dose of 100 mg in 24 hrs.

  Intramuscular injection of paraldehyde (0.2 ml/kg bw) or 0.4 ml/kg intrarectally is safe and an effective anti-epileptic drug. It carries a minimal risk of respiratory depression and may be given in repeated doses, even to children who have already received diazepam.

  For repeated and uncontrolled seizures, phenytoin 15-20 mg/kg bw (administered by slow intravenous injection, the rate not exceeding 0.5 mg/kg bw/min) can be used. The drug should not be diluted with dextrose-containing fluids as it precipitates easily. Maintenance, if necessary, is to be executed with 5 mg/kg bw every 12 hours.

Administration of specific antimalarial drugs

The antimalarial drug should be administered parenterally to achieve quicker and predictable blood concentrations. Artemisinin derivatives or intravenous quinine can be administered (Table 3).

Management of associated complications

The following conditions (in addition to convulsions and hyperpyrexia mentioned earlier) may also cause impaired consciousness. Appropriate recognition and management of these conditions will help reduce mortality and to differentiate impaired consciousness due to cerebral malaria from other associated conditions:

- Hypoglycaemia;
- Severe anaemia;

- Acidosis;
- Electrolyte imbalance;
- Other associated infections, and
- Use of sedative drugs.

The following drugs have been used or suggested for the treatment of cerebral malaria but are now considered of no beneficial effect and should be avoided:

- Corticosteroids;
- Other anti-inflammatory agents;
- Agents given for cerebral oedema (urea, mannitol);
- Low molecular weight dextran;
- Epinephrine (adrenaline), and
- Heparin.

Mortality is significantly higher in patients of cerebral malaria when associated with other complications such as acute renal failure, acute respiratory distress syndrome, jaundice, *etc.* Therefore, cerebral malaria patients with multiple complications should be referred to intensive care.

7.2 Severe anaemia

Anaemia of varying degree is a common accompaniment in severe malaria. Severe anaemia is defined as haemoglobin lower than 5g/dl or haematocrit lower than 15%. Severe life-threatening anaemia is less common in adults of low transmission areas though it may be witnessed in children. Pre-existent iron deficiency may be present in many malaria patients.

Clinical features

The signs and symptoms of anaemia in malaria depend on the degree of anaemia and rate of decrease of blood haemoglobin concentration. Sudden fall in the haemoglobin concentration may lead to cerebral anoxia and may even manifest as cerebral malaria. Malaria patients having pre-existent severe iron deficiency anaemia may present with

manifestations of heart failure. Anaemia decreases oxygen carrying capacity of the blood and severe anaemia may lead to tissue hypoxia and lactic acidosis. Haemoglobin level in finger-prick samples may be lower than venous blood due to serum oozing during squeezing the finger by finger prick.

Management of severe anaemia

The blood haemoglobin level is likely to fall after fluid replacement and it should be re-estimated after dehydration is corrected to review the requirement of blood transfusion.

- Indications of blood transfusion:
  - (a) ***Based on blood haemoglobin:*** (1) when fall of haemoglobin is by 20% or more per day (2) haemoglobin concentration of <7.0 g/dl with symptoms of severe malaria (signs of hypoxia, severe metabolic acidosis with no other apparent cause) or features of heart failure, or (3) haemoglobin concentration of <5.0 g/dl with or without symptoms.
  - (b) ***Based on clinical criteria:*** Anaemic patients with (1) hyperparasitaemia, in whom a large drop in haemoglobin is anticipated; (2) impaired consciousness, which might be exacerbated by reduced oxygen supply secondary to anaemia; (3) ARF where haemodialysis is required; (4) disseminated intravascular coagulation (DIC), and (5) high output cardiac failure.
- Transfusion of pathogen-free compatible fresh blood, preferably packed cells or settled cells should be given.
- Small intravenous doses of furosemide (adult: 20-40 mg; children: 1 mg/kg) may be given during the blood transfusion to avoid circulatory overload, provided that the patient's renal function is adequate. In patients with ARF, only packed or settled cells should be transfused. The volume of transfused blood should be included in calculation of fluid balance.
- Haemoglobin or haematocrit should be monitored daily during treatment.

- Iron or iron containing tonics should be prescribed only if the cause of anaemia is iron deficiency after recovery from acute malaria. Anaemia due to infection may present in the form of mild to moderate anaemia. In such conditions it is better to estimate blood haemoglobin after four weeks or before hospital discharge (and without parasitaemia) and if anaemia is still present it should be treated with haematinics.

7.3 Acute renal failure

Pre-renal azotaemia is an abnormally high level of nitrogen-type waste in the bloodstream. It is caused by conditions that reduce blood flow to the kidneys. It is rapidly reversible upon restoration of renal blood flow. More severe hypoperfusion may lead to ischaemic injury of renal parenchyma and intrinsic renal azotemia. Thus, pre-renal azotemia and ischaemic ARF are part of a spectrum of manifestations of renal hypoperfusion. ARF as a complication of malaria is more common in adults than children. Acute renal failure by itself is less severe than when associated with other complications (cerebral malaria, jaundice, pulmonary oedema/ARDS). Malarial ARF is catabolic in type characterised by rapid rise of plasma urea and creatinine. The cause of established ARF is due to acute tubular necrosis or as part of multi-organ dysfunction.

Clinical features

- ARF may present as oliguric or non-oliguric renal failure and even anuria in severe cases.
- The diagnosis of ARF is suspected when urine output decreases to 400 ml or less in 24 hours or 20 ml/hour (<0.5ml/kg bw per hour for children), which fails to improve after rehydration.
- The diagnosis is confirmed when the serum creatinine exceeds 3 mg/dl (265 µmol/l) in adults and 1.5 mg/dl (130 µmol/l) in children. Oliguric phase usually lasts about a week but may vary from a few days to a few weeks.
- Pre-renal azotemia usually presents with clinical signs of severe dehydration. However, prolonged anuria or oliguria

may lead to inevitable volume overload because of diminished salt and water excretion. The distinction between pre-renal and established ARF is important for the correct clinical management, which can be differentiated by the simple measurement of urine specific gravity. In pre-renal azotemia it may be more than 1.020 while in established ARF it may be less than 1.010 due to loss of urine concentration ability of the kidneys.

Management of acute renal failure

Fluid replacement

The patient should be examined for hydration status. Signs of fluid overload should be monitored closely (raised jugular venous pressure, basal crepitations and reduced urine volume) during transfusion of blood or fluids because of the vulnerability of ARF patients towards post-transfusional volume overload.

Supportive therapy

There has been an argument to use diuretics and vasoactive drugs in an effort to improve blood pressure and renal blood flow. Many of these pharmacological approaches are of uncertain efficacy although theoretically reasonable.

- Loop diuretics (furosemide) can convert an oliguric renal failure to non-oliguric renal failure. Though this does not usually affect the progress of the disease process and serum creatinine may continue to rise in spite of adequate urine volume, conversion of oliguric to non-oliguric renal failure reduces the risk of volume overload. Therefore, the use of loop diuretics may be restricted to the following conditions:
  - Intravenous furosemide 40 to 250 mg IV should be titrated given in conditions of volume overload.
  - In oliguric patients, increase in urine volume with diuretics may mislead in assessing renal status where the monitoring of renal function is done by urine volume alone. In conditions where a diuretic is administered (or has already been administered before patient reached

hospital) renal function should be monitored by serum creatinine and other clinical and biochemical indicators.

- Diuretics are of little help, and may be hazardous in complete anuric patients.

- Nephrotoxic drugs should be avoided when ARF is suspected or anticipated.

The following drugs should be avoided in malaria patients because of their adverse reactions on renal function:

- **Angiotensin-converting enzyme inhibitors (ACEI) and cyclooxygenase inhibitors and non-steroidal antiinflammatory drug (NSAID) should not be given as they may precipitate pre-renal azotemia to ischaemic ARF.**

Assessment of renal function using measurement of urine volume should not be done in patients receiving diuretics.

Associated conditions requiring urgent attention:

Hypervolaemia, shock, hyperkalaemia, severe acidosis, and severe anaemia should be treated on priority.

Indications for dialysis

(a) Clinical indicators

- Uremic symptoms: Nausea, vomiting, hiccup, flapping tremor, muscle twitching and convulsions.
- Symptomatic volume overload: As shown by examination of jugular venous pressure (JVP) and pulmonary oedema.
- Pericardial rub
- Persistence of acidotic breathing even after rehydration.

(b) Laboratory indications

- Hyperkalaemia with no response to medical treatment.
- Uncorrectable metabolic acidosis by non-dialysis treatment.

- Hypercatabolic states as follows:
  BUN increases > 20 mg/dl per day
  Cr increases > 2 mg/dl per day
  serum K increases > 1 mmol/L per day
  serum HCO3 decreases > 2 mmol/L per day
  Uric acid increases > 1 mg/dl per day.

7.4 Fluid and electrolyte disturbances

Hypovolaemia and circulatory overload are both extremely dangerous. Correct assessment of hydration status, management of fluid and electrolyte balance is, therefore, of considerable importance.

7.4.1 Hypovolaemia

Hypovolaemia is a common accompaniment in severe malaria. Severe dehydration may be caused due to persistent fever, profuse perspiration, inadequate fluid intake and, in some cases, vomiting and loose motion. Untreated hypovolaemia may lead to hypotension, shock, and underperfusion of the kidney, brain and other vulnerable organs. Hypovolaemia may also lead to tissue hypoxia resulting in lactic acidosis.

Clinical features

The usual manifestations are those of dehydration such as increased thirst, orthostatic dizziness, orthostatic hypotension (drop in blood pressure of more than 10 mm Hg when the patient sits up from supine position), tachycardia, reduced JVP, decreased skin turgor, dry mucous membranes, reduced axillary sweating, oliguria with high urine specific gravity.

Management of hypovolaemia

- Dehydration should be corrected with 0.9% saline or 5% dextrose saline by IV infusion. Excessive administration of isotonic dextrose solutions can induce hypoosmolality and hyponatremia. If severe, it may lead to cerebral oedema and neurological abnormalities, including seizures.

- Monitor blood pressure, urine volume, and JVP every hour to assess hydration status.
- Improve oxygenation by clearing airway and oxygen therapy.
- Avoid administration of sodium bicarbonate unless associated with severe life threatening acidosis.

Avoid circulatory overload, which may lead to fatal pulmonary oedema.

7.4.2 Hyponatremia

Many patients with hyponatremia are dehydrated and salt-depleted. It is often 'depletional' on account of losses in sweat, vomitus and diarrhoea or 'dilutional' if the patient is drinking large quantities of plain water or by use of intravenous dextrose solution alone. Hyponatremia may also be attributed to inappropriate secretion of antidiuretic hormone (SIADH). Isotonic saline (0.9% normal saline) infusion is an appropriate replacement for hyponatremia.

7.5 Shock/circulatory collapse

Circulatory collapse occurs due to severe malaria. It may also be associated with severe dehydration, gram-negative septicaemia, massive gastrointestinal haemorrhage and ruptured spleen. Possible sites of infection could be the urinary tract (especially if there is an indwelling catheter), intravenous lines, lung (*e.g.* pneumonia), *etc.* Patients may have concomitant or superimposed bacterial infection during severe malaria.

Clinical features

Circulatory collapse is diagnosed when one or more of the following features are present:

(1) Having systolic blood pressure in supine position:

Lower than 80mm Hg in adults, adolescent and children aged over 10 years,

Lower than 70 mm Hg in children aged 1month-10 years,

Lower than 60 mm Hg in neonates, and

(2) Having cold, clammy and cyanotic skin, constricted peripheral veins, and rapid and feeble pulse or core-skin temperature difference >10 °C

Management of shock/circulatory collapse

- Correct hypovolemia with an appropriate fluid, e.g. normal saline or 5% dextrose saline.
- Look for the possible sites of infection (lung, urinary tract, IV injection sites).
- Take a blood culture and start broad-spectrum antibiotics, e.g. third-generation cephalosporins.
- If patient does not respond to adequate fluid therapy, administer inotropics agents, e.g. dopamine/dobutamine 5-20 µg/kg /min.

7.6 Metabolic acidosis

Metabolic acidosis is a common feature in severe malaria. Severe dehydration is the most important contributor to it. Blood lactate level rises due to tissue hypoxia and increased body metabolism. Failure of the hepatic clearance of lactate leads to loss of bicarbonate and culminates in metabolic acidosis.

Clinical features

Severe metabolic acidosis may present itself with hyperventilation, Kussmaul's breathing and acidotic breathing, but chest signs are usually absent. Presence of chest signs (crepitations and/or rhonchi) is indicative of pulmonary oedema/ARDS or associated pneumonia. Estimation of arterial pH and plasma bicarbonate will confirm the diagnosis.

Management of metabolic acidosis

- Rehydrate the patient, but care must be taken not to overhydrate.
- Treat severe anaemia with blood transfusion.

- Now most authorities either do not administer sodium bicarbonate at all or give it only once in severe acidosis (*e.g.* arterial pH <7.15).
- Haemofiltration or haemodialysis may be used to control acidosis.

7.7 Jaundice

Although jaundice *per se* is not considered as severe malaria, it indicates a severe degree of the disease when combined with other vital-organ dysfunction. Jaundice in severe malaria is more commonly found in adults than in children. A tender enlargement of the liver and spleen are common in malaria. Mild jaundice may be due to haemolysis but a considerable rise in bilirubin levels is usually associated with hepatic dysfunction. The dose of liver enzymes aspartate amino transferase (AST) and alanine amino transferase (ALT) may be increased, but rarely more than 10 times the normal. Other causes of jaundice should be excluded if the enzyme levels are found to be very high. Jaundice in malaria patients may not be fatal on its own but mortality is increased significantly when high bilirubin values are associated with renal failure and cerebral malaria. Clinical signs of liver failure with hepatic encephalopathy are rare. Hepatic dysfunction may lead to altered handling of antimalarial drugs.

No specific treatment is required for jaundice.

7.8 Hypoglycaemia

Hyponglycaemia is an important complication of falciparum malaria. Vulnerable groups are pregnant women, either on admission or following quinine treatment; patients with severe disease, especially young children; and patients on quinine therapy due to quinine-induced hyperinsulinaemia leading to hypoglycaemia.

Clinical features

In conscious patients, hypoglycaemia may present with classical symptoms of anxiety, sweating, palpitation, dilatation of the pupils, breathlessness, alteration of consciousness, a feeling of coldness,

tachycardia and light-headedness. The condition if untreated may worsen leading to impaired consciousness, coma, generalised convulsions, extensor posturing and shock. The diagnosis can be mistaken because of the similarity of clinical features with cerebral malaria but blood sugar estimation will easily differentiate between the two.

In malaria patient suffering from unconsciousness, the cause of unconsciousness may not be cerebral malaria alone. Differential diagnosis of cause of unconsciousness in malaria patients is important.

Management of hypoglycaemia

- In all suspected cases of hypoglycaemia, a 50-ml 50% glucose solution should be given, to be followed by an intravenous infusion of 5% or 10% dextrose.
- Blood glucose levels should be monitored to regulate the dextrose infusion.

7.9 Pulmonary oedema/Acute respiratory distress syndrome (ARDS)

Pulmonary oedema is a grave complication of severe malaria which entails a high mortality rate. It may develop early after one or two days of treatment or may appear late in the course of the disease when the patient's general condition is improving. Fluid overload may be an important contributory factor, but in some patients pulmonary oedema may develop even with normal or negative fluid balance. Malaria patients with ARF, severe anaemia and pregnant women – particularly after delivery – are vulnerable for pulmonary oedema/ARDS.

Clinical features

The first indication of impending pulmonary oedema is usually an increase in the respiratory rate in the absence of metabolic acidosis and anaemia. Bilateral basal crepitation, raised JVP, hilar congestions

with bilateral diffuse infiltrations in the chest radiogram with reduced arterial pO_2 are invariably present. Hypoxia may cause convulsions and deterioration in the level of consciousness. In most cases it is difficult to differentiate between pulmonary oedema and ARDS.

Table 4: *Comparison of metabolic acidosis, pulmonary oedema/ ARDS and pneumonia*

Clinical features	Metabolic acidosis	Pulmonary oedema/ ARDS	Pneumonia
Respiratory rate	High/Low in late stages	High	High
Depth	Deep Kussmaul's breathing	Shallow	Variable
Effort of accessory respiratory muscles	Indrawing of lower chest wall, mostly in children	Increase effort of accessory respiratory muscle (e.g. sternocleidomastoid)	Variable, mostly seen in gross hypoxia
Bronchial breathing	Absent	May be present in the late stages	Present
Crepitations	Usually absent	Mostly present in bases.	Present on the site of pneumonia
Rhonchi	Absent	Present	Usually absent
Cyanosis	Mostly absent	Usually present in late stage	May be present in severe hypoxia
Jugular venous pressure	Not raised	Raised with volume overload; not raised in ARDS	Not raised
Chest X-ray	Clear	Bilateral interstitial infiltration, hilar vessels prominent	Consolidation in the affected part of the lung

Management of pulmonary oedema/ARDS:

- Keep the patient semi-upright, raise the head end of the bed, nurse the patient at 45°.
- Give a high concentration of oxygen by any convenient method available.
- Give diuretics, IV furosemide, if there is volume overload.
- Reduced all intravenous fluids or give IV fluid as ***kvo*** (keep vein open).

7.10 Abnormal bleeding and disseminated intravascular coagulation (DIC)

Bleeding gums, epistaxis, petechiae, bleeding from injection sites and subconjunctival haemorrhages may occur in patients of severe malaria. DIC may lead to hematemesis or melena. Asymptomatic thrombocytopenia is very common in falciparum malaria, which usually reverts to normal after recovery from the disease.

Management of abnormal bleeding and DIC

To manage abnormal bleeding and DIC, fresh blood, blood clotting factors or blood platelets may be transfused. The following conditions are not indication for platelet transfusion in patients with thrombocytopaenia and mild bleeding symptoms:

- Ecchymosis of skin, and
- Subconjunctival haemorrhage.

7.11 Macroscopic haemoglobinuria (Black water fever)

Black water fever associated with malaria is relatively uncommon. It may present itself in adults as a severe disease accompanied by anaemia and renal failure and occasionally with circulatory collapse. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are vulnerable for this complication but patients with normal G6PD activity may also suffer, particularly those with massive haemolysis. The mortality rate from black water fever is highest when it is associated with severe malaria and other evidence of vital organ dysfunction.

Continue appropriate antimalarial treatment if parasitaemia is present and **do not** withdraw quinine doses if the patient is receiving it. Transfuse screened fresh blood if needed. Black water fever is often not associated with significant renal impairment. It is usually transient and resolves without complications though renal failure may develop in severe cases. In case of renal failure, the patient must be referred to a dialysis centre.

8. Special clinical features and management of severe malaria in children

Management of severe malaria is essentially the same in both adults and children though certain manifestations and drug dosage are different in children.

8.1 Cerebral malaria in children

Clinical features

- The early symptoms of cerebral malaria in children are fever (37.5 °C-41°C), inability to eat or drink and vomiting. The history of symptoms preceding coma may be very brief - one or two days in most cases.
- Convulsions are common before or after the onset of coma. Occasionally their presentation may be very subtle such as intermittent nystagmus, salivation, and minor twitching of a single digit or corner of the mouth and an irregular-breathing pattern.
- In children with profound coma, corneal reflexes and "doll's eye" movement may be abnormal.
- In some children opisthotonus may be observed, which may lead to a mistaken diagnosis of tetanus or meningitis.

Management of cerebral malaria in children

- Convulsions are common in children and can be treated with intravenous diazepam, 0.3 mg/kg bw (rate not exceeding 2 mg/minute) or as slow bolus ("push") or 0.5 mg/kg bw administered intrarectally. Alternately, paraldehyde 0.2 ml/kg bw may be administered by deep intramuscular injection or 0.4 ml/kg bw intrarectally.
- In case of repeated convulsions, the following are recommended:

  (a) Phenytoin sodium 0.5 mg/kg bw/minute in a non-glucose-containing fluid, preferably in isotonic saline.

It should be administered slowly (1 mg/kg bw/minute), followed by 5 mg/kg every 12 hours,

or

(b) Phenobarbitone intravenous or intramuscular loading dose of 10-15 mg/kg bw and maintenance dose of 3-5 mg/kg bw/day in divided doses twice daily.

In any child with convulsions, hyperpyrexia and hypoglycaemia should be excluded and if present treated.

- The management of cerebral malaria in children is the same as in adults, including the modalities of careful nursing and monitoring of the unconscious patient.
- The child with cerebral malaria may also suffer from anaemia, respiratory distress (acidosis) and hypoglycaemia. These problems have to be managed accordingly.
- If hypoglycaemia cannot be excluded by blood glucose examination, then all unconscious patients of malaria should be treated with intravenous glucose.

8.2 Severe anaemia in children

Anaemia is more common in children than adults. Children with severe anaemia may show signs of acidosis such as deep and laboured breathing and grunting, hypoxic cerebral signs such as confusion, restlessness and coma, and cardiopulmonary signs such as tachycardia, dyspnoea, gallop rhythm and pulmonary oedema.

Management of severe anaemia in children

Indications of blood transfusion in anaemic children are the same as that for adults. Some children may require urgent blood transfusion (10 ml packed cells or 20 ml whole blood per kg body weight). A diuretic may not be indicated if the child is hypovolaemic, but many of the severely anaemic children may be in a hyperdynamic circulatory state. In such cases, furosemide 1-2 mg/kg body weight should be given intravenously before blood transfusion.

8.3 Metabolic acidosis in children

Rapid and deep breathing with recession of the bony structures of the lower chest wall suggests metabolic acidosis. Metabolic acidosis commonly accompanies cerebral malaria or anaemia but it may develop in a child without impaired consciousness. The risk of death is increased in either case. Its management consists of correction of all reversible causes of acidosis such as dehydration or severe anaemia as mentioned.

8.4 Hypoglycaemia in children

Hypoglycaemia is particularly common in children under three years of age and in those with convulsions or hyperparasitaemia, or in profound coma. ***It is easily overlooked clinically because the manifestations may be similar to those of cerebral malaria.***

Unconscious children should be given dextrose regularly to prevent starvation hypoglycaemia. It is most conveniently provided as 5% dextrose in saline infusion, but if volume overload is anticipated 25% dextrose diluted in an equal volume of normal saline or 10% dextrose may be infused intravenously. If this fails, 25% dextrose or any sugary solution may be given through a nasogastric tube at a dose of 1 ml/kg of body weight.

9. Special clinical features and management of severe malaria in pregnancy

Women developing malaria during pregnancy or post-partum period are at higher risk of developing severe complications than non-pregnant women. Mortality in pregnant women is 2-10 times higher than non-pregnant patients. ***The clinical manifestations of malaria in pregnancy may vary greatly according to the level of immunity***. Non-immune pregnant women are more likely to develop cerebral and other complications such as hypoglycaemia and acute pulmonary oedema. They also run an increased risk of abortion (in cases of severe malaria), stillbirth, premature delivery and low infant birth weight. Uterine contractions may be induced, the frequency and intensity of which appear to be related to the degree of the fever.

9.1 Management of malaria in pregnancy

- Pregnant women with severe malaria should be transferred to an intensive care unit for careful monitoring because of the higher risks involved.
- Hypoglycaemia should be treated as described earlier in this report.
- If volume overload condition develops, treat as described earlier.

9.2 Antimalarial drugs for malaria in pregnancy

Quinine is safe during pregnancy in doses advocated for the treatment of life-threatening malaria. It has been shown that the initial intravenous infusion of quinine in women who are more than 30 weeks pregnant is not associated with uterine stimulation or foetal distress. Its major adverse effect is hypoglycaemia. Artesunate and artemether should not be used in the first trimester of pregnancy.

Pregnant women are susceptible to

- ***severe anaemia***
- ***hypoglycaemia***
- ***Pulmonary oedema and ARDS***

Quinine is not an abortifacient in therapeutic doses. It is safe in all trimesters of pregnancy.

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10. Common errors in management

10.1 Failure to diagnose malaria infection

- Index of suspicion of *falciparum* malaria at the earliest is the hallmark of diagnosis.
- Malaria may not be diagnosed because of similar clinical presentation of several diseases such as viral encephalitis, meningitis, hepatitis, enteric fever, leptospirosis, dengue, influenza and other viral diseases which are commonly seen in tropical countries.

- The condition may also be wrongly diagnosed if the history of recent travel to an endemic area is not properly elicited, particularly for those living in low transmission or malaria-free areas.

10.2 Failure to diagnose associated or complicating conditions

- Failure to detect hypoglycaemia in severe malaria patients is a common error due to gaps in the clinical presentation. Therefore, bedside blood glucose examination should be conducted in all unconscious patients. In places where this facility is not available, the patient should be assumed to be hypoglycaemic and treated accordingly.
- Gram-negative septicaemia should be suspected in patients developing shock and treated with effective antibiotics.

10.3 Errors in antimalarial chemotherapy

- ***Delay in starting treatment:*** Mortality is higher in severe malaria patients who have not received any antimalarials before hospitalisation than those who have received the same.
- ***Unjustified withholding/inadequate dosage:*** An antimalarial drug should not be withheld for exaggerated fears of toxicity. It should also not be discontinued for minor adverse reactions during the course of treatment. Quinine dosage should not be altered in the first 48 hours even in case of renal failure or jaundice.
- ***Dangerous route of administration*:** Quinine if given rapidly through the IV route (intravenous push) may cause serious cardiovascular complications and even lead to death. Intramuscular quinine may cause severe local reaction and chloroquine may lead to fatal hypotension because of its erratic absorption in severe malaria. Therefore, these drugs can be administered through the intramuscular route only when the intravenous access is not available.

- ***Failure to control the rate of intravenous infusions:*** Too rapid or too slow infusion of quinine is harmful. These errors are common where the facility for controlled flow of quinine infusion is not available. A common occurrence is an initial slower rate of infusion due to wrong eye assessment of rate of flow or blockage of IV lines. If this is followed by a higher rate of infusion to complete the drip within the stipulated four hours, it may lead to fatal consequences.
- ***Early ambulation of patients under quinine therapy:*** Fatal hypotension may occur if severe malaria patients receiving IV quinine are allowed to walk or stand for a longer time.

10.4 Errors of fluid and electrolyte replacement

Many patients with severe malaria may be grossly dehydrated and will need rapid fluid replacement. However, some patients with renal impairment - particularly those who have received fluids before admission - may present with volume overload. Any error in fluid replacement of these patients may lead to irreversible pulmonary oedema. A large volume of hypertonic fluids, bicarbonate, mannitol or blood may precipitate fluid overload.

11. Referral of patients with severe malaria to the tertiary care hospital

It is extremely difficult to frame rigid guidelines for referral because of non-uniformity in availability of facilities in large hospitals and financial constraints of the patient. However, following are a few guidelines to help the doctor in taking a decision.

Indications for referral if facility at large hospital/health facility is not available for management:

(1) Patients requiring hemofiltration or dialysis.

(2) Patients requiring artificial ventilation.

(3) Severe anaemia requiring multiple transfusions.

(4) Severe malaria in pregnant and post-partum women.

(5) Multi-organ failure.

(6) Active bleeding.

(7) Cerebral malaria not responding to treatment in 48 hours.

The following measures should be taken while referring a patient to the tertiary care hospital:

- Endotrachial intubation in unconscious patients to prevent aspiration during referral. Oxygen tank and ambu-bag should be available in ambulance.
- Maintain IV access and infusion of IV fluids to correct dehydration.
- Provide life support system and guidance to the person accompanying the patient.
- Start the administration of appropriate antimalarial drugs and other essential drugs required till the patient is admitted.
- Insert a urethral catheter in patients with reduced urine output.
- Provide a referral note (Annex 4).
- Patient's attendant or relative, nurse or doctor (if possible) should accompany patient in ambulance during referral to the tertiary care hospital.

Bibliography

(1) Fairhurst RM, Wellems TE. Plasmodium species (malaria). In: Mandell, Douglas. *Bennett's principles and practice of infectious diseases*. 6th edition, Philadelphia, Elsevier Churchill Livingstone, 2005. p. 3121- 44.

(2) White NJ. Malaria. In: Cook GC, Zumla AI (eds). *Manson's tropical diseases*. 21st edition, London: WB Saunders, 2003. p. 1205-95.

(3) White NJ, Breman JG. Malaria and babesiosis: diseases caused by red blood cell parasites. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL (eds). *Harrison's principle of internal medicine*. 16th Edition, McGraw Hill, 2005. p. 1218-32.

(4) World Health Organization, Communicable Diseases Cluster. Severe falciparum malaria. Trans R Soc Trop Med Hyg 2000 Apr; 94 (suppl 1): S1/1-90.

(5) World Health Organization. *WHO Expert Committee on Malaria: twentieth report*. WHO Technical Report Series no.892. Geneva, 2000.

(6) World Health Organization. *Management of severe malaria: a practical handbook*. 2nd edition, Geneva, 2000.

(7) World Health Organization. *The use of antimalarial drugs*. Geneva, 2001.

(8) World Health Organization. *Guidelines for the treatment of malaria*. Geneva, 2006.

Annex 1

Categorization of hospitals and health facilities for the treatment of severe malaria

This classification on the basis of the number of beds and facilities available is arbitrary and flexible and may differ from country to country. Each country has to define the level of health facilities and hospitals.

Small hospitals include basic health unit in Bhutan (in these facilities there are no doctors but health workers are expected to diagnose and treat illnesses); upazila health complexes in Bangladesh; community health centres and sub-district (tehsil) hospitals in India; Category-D hospitals at district level and health centres with in-patient services at sub-district level in Indonesia; station hospitals and township hospitals in Myanmar; district hospitals in Nepal, and district hospitals in Sri Lanka and Thailand. Private nursing homes can also be included in this category.

Small hospitals have fewer than 50 beds. Laboratory facilities are minimal, with provision for routine blood examination, microscopy, urine, stools, X-ray chest, CSF examination and ECG. However, biochemical tests and microbiology are not available. These facilities have trained staff but no specialists, and IV treatment can be initiated but generally not maintained because of lack of biochemical support. Oxygen, though available, is not very reliable. Round-the-clock monitoring of patients is also difficult to implement. The range of medicines available for the treatment of complications of malaria is limited.

Large hospitals are medium-sized hospitals. These generally include district hospitals in the Member countries of the WHO South-East Asia Region. This category includes private hospitals. In many countries large hospitals are present in the provincial or zonal level because of the small size of their districts as administrative units.

Large hospitals generally have more than 50 beds. Here, trained doctors and nurses are available and some of them are specialists. Round-the-clock monitoring of the patients is also done. Laboratory

facilities include routine blood, urine and stool examination, biochemical tests, radiology and microbiology. Pathology services may be available, though not of a very advanced nature. Treatment facilities include a wide range of medicines to treat a variety of problems that cases of severe malaria may suffer from, including blood transfusion, oxygen and IV fluids.

Tertiary hospitals include most hospitals attached to medical and nursing schools, large city hospitals, regional hospitals, some infectious disease hospitals, research institutions and large private hospitals mainly in the cities.

Tertiary hospitals generally have more than 200 beds with trained doctors and nurses and many specialists. Round-the-clock services are available. These hospitals are able to conduct specialized tests, undertake dialysis for acute renal failure, provide ventilation to patients with respiratory failure, and render intensive care to critically ill patients. These hospitals also undertake research and the library facilities are adequate.

Annex 2a

Modified Glasgow coma scale for adults

Eye opening	Spontaneously To speech To pain No response	4 3 2 1
Best verbal response (Nonintubated)	Oriented and talks Disoriented and talks Inappropriate words Incomprehensible sounds No response	5 4 3 2 1
(Intubated)	Seems able to talk Questionable ability to talk Generally unresponsive	5 3 1
Best motor response	Verbal commands Localizes to pain Withdraws to pain Decorticate Decerebrate None	6 5 4 3 2 1
Total score		3 – 15

Total score = eye opening score + verbal (intubated or nonintubated) score + motor score

Total score ranges from 3 to 15; unrousable coma reflected in a score of <9.

This scale can be used repeatedly to assess improvement or deterioration.

Annex 2b

Blantyre coma scale for children ("Blantyre coma scale")

Eye movements	Directed (e.g. towards mother's face) Not directed	 1 0
Verbal response	Appropriate cry Inappropriate cry or moan None	2 1 0
Best motor response	Localises painful stimuli Withdraws limb from pain Non specific or absent response	2 1 0
Total score		0 – 5

Total score can range from 0-5; 2 or less indicates unrousable coma.

This scale can be used repeatedly to assess improvement or deterioration.

Annex 3

ABC of coma management

A: Airway

Maintain the airway by keeping airway clean, *i.e.* free from saliva, vomitus, *etc*.

- Unconscious patients should be nursed on their side, preferably left lateral position on a flat surface without a pillow. This reduces incidence of aspiration of gastric contents.
- Keep changing the side every 2 hours.
- Insert a nasogastric tube to prevent aspiration pneumonia and aspirate stomach contents.
- Oral or oropharyngeal airway should be used to prevent the tongue from falling back and to keep the airway clean.
- If facilities exist endotracheal intubation should be done in a coma patient if needed.

B: Breathing

Patient may need oxygen inhalation and ventilatory support if tachypnoea, laboured respiration, acidotic breathing is present or develops in the course of the treatment. It should be referred to centres with facilities for intensive care.

C: Circulation

Check for dehydration by examining the pulse rate, blood pressure, skin elasticity, jugular venous pressure, moisture of the tongue, urinary volume and colour.

- If dehydration is present, infuse intravenous fluids.
- Frequently check the rate of infusion to prevent overhydration.
- If patient has overhydration, stop or restrict IV fluids and give intravenous diuretics (furosemide).
- Suspected infection must be treated with antibiotics. Keep an accurate record of fluid intake and output (strict intake and output chart should be maintained). Normal urine output is approximately 1 ml/min.

Annex 4

Patient referral form

Name: ..... Age: ..... Sex: .....
Address: .....
Contact Person(s): .....
Date and time of admission: ..... Date and time of referral: .....
Chief complaint: ..... Pregnancy status .....
Present illness: .....
Past history/co-morbidity: .....

Physical Examination:

Vital signs	BP (mmHg)	PR (bpm)	RR (/min)	Temp (°C)
Upon admission (date & time)				
Upon referral (date & time)				

GCS/BLANTYRE: upon admission (date and time): .....
upon referral (date and time): .....

Events in hospitals

Events	Observations	Events	Observation
❑ witnessed convulsions		❑ hypoglycaemia	
❑ presence of bleeding		❑ blood transfusion	
❑ oliguria		❑	
❑ respiratory distress/ pulmonary oedema		❑	
❑ shock		❑	

Antimalarial(s):

	Dosage	Start		Last dose	
		Date	Time	Date	Time
1.....					
2.....					

Other medication(s):

	Dosage	Start		Last dose	
		Date	Time	Date	Time
1.....					
2.....					

Intake and Output:

Date					
Intake					
Output					

Malaria Density:

Date					
Density					

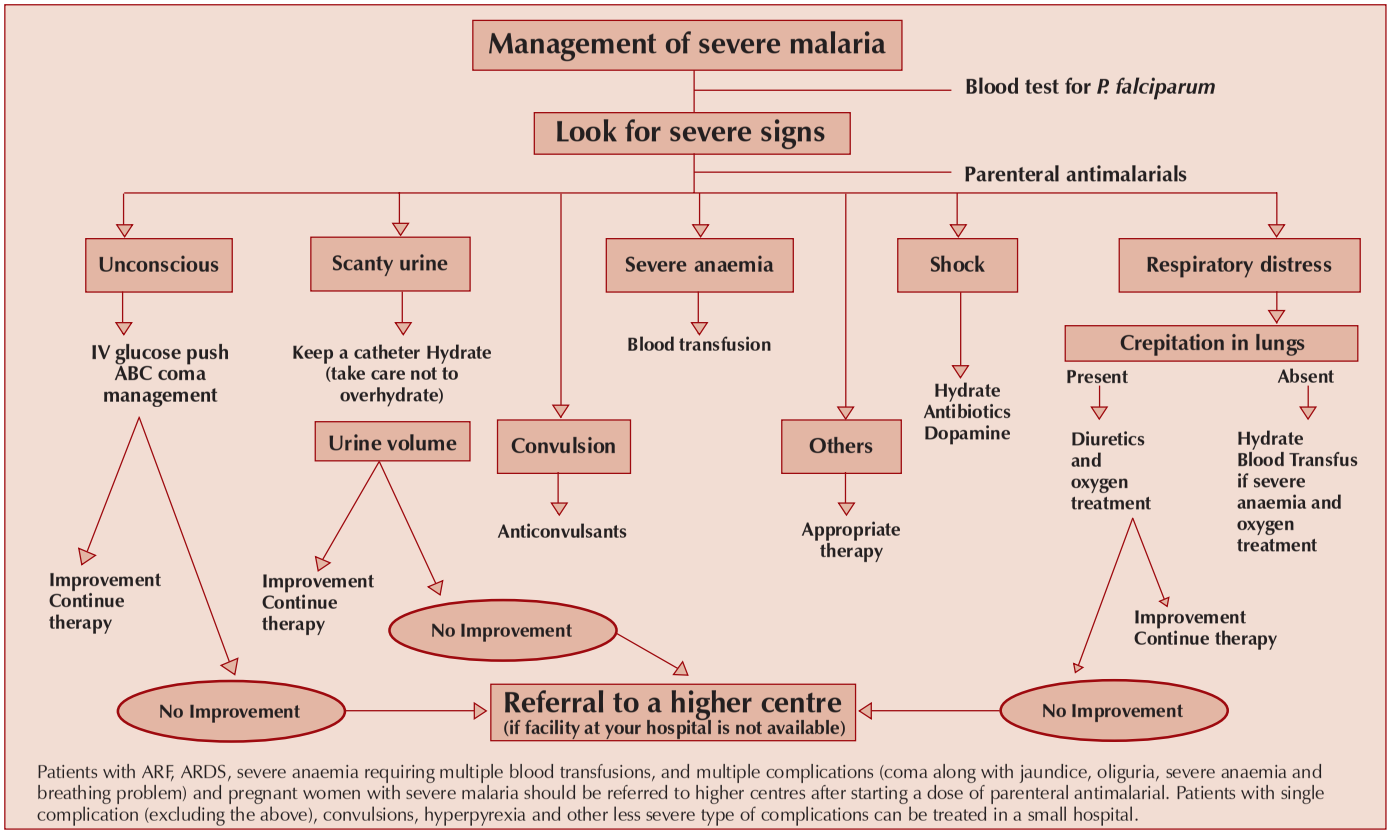
Other investigations:

	Date and time	Result
CXR		
12-lead ECG		
Other(s).....		

Reason(s) of referral:.....
Signature and name of the treating doctor: ..... Tel/Mobile: .....Fax: .....E:mail: .....
Name and address of referring hospital.....

Annex 5

Chart on management of severe malaria in large hospitals/health facilities



Patients with ARF, ARDS, severe anaemia requiring multiple blood transfusions, and multiple complications (coma along with jaundice, oliguria, severe anaemia and breathing problem) and pregnant women with severe malaria should be referred to higher centres after starting a dose of parenteral antimalarial. Patients with single complication (excluding the above), convulsions, hyperpyrexia and other less severe type of complications can be treated in a small hospital.

Annex 6

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