



Regional Guidelines for the Management of Severe *Falciparum* Malaria in Small 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
small hospitals.

- (1) Malaria – therapy.
- (2) Malaria, Falciparum – diagnosis – therapy.
- (3) Guidelines.

ISBN 92 9022 280.8

(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: A Township hospital in Myanmar.

Source: WHO Country Office for Myanmar.

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October 2006

List of abbreviations

ABC	Airway, breathing and circulation
ACT	Artemisinin-based combination therapy
ARDS	Acute respiratory distress syndrome
CSF	Cerebrospinal fluid
DIC	Disseminated intravascular coagulation
ECG	Electrocardiogram
HRP-II	Histidine-rich protein II
KVO	Keep vein open
NSAIDs	Non-steroidal antiinflammatory drugs
pLDH	Parasite lactate dehydrogenase
RDT	Rapid diagnostic test

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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.

A handwritten signature in black ink, reading "Samlee Plianbangchang". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

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 one 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.

Some cases of severe malaria can be treated in small hospitals or health facilities while others may require referral to higher levels of health facilities for treatment of life-threatening complications.

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.

Categorization of the small and large hospitals and health facilities is described in Annex 1.

Generic description of small hospitals and health facilities

Small hospitals/health facilities are likely to have fewer than 50 beds. This classification of hospitals on the basis of the number of beds is arbitrary and flexible. Laboratory facilities are minimal and include routine blood examination, urine and stool examination, chest X-ray, electrocardiogram (ECG), and routine cerebrospinal fluid (CSF) examination. Small hospitals should be able to undertake definitive malaria diagnosis by light microscopy or rapid diagnostic test (RDT). There should be trained staff to manage correctly most cases of severe malaria. In some of the facilities, intravenous (IV) fluids can be given although it may not be possible to sustain it due to limitation of biochemical tests and the fact that round-the-clock monitoring of very sick patients may not be possible. Oxygen is generally not available or is in short supply. The range of medicines may be limited but severe malaria cases can be treated with antimalarials recommended by the national treatment policy. First aid treatment like the treatment of convulsions, hyperpyrexia, hypoglycaemia and severe anaemia can be provided but blood transfusion facility may not be available.

Each country has to define the small hospitals and ensure that they have adequate capacity to manage patients according to the prescribed norms.

Role of small hospitals/health facilities in the treatment of severe malaria

Small hospitals/health facilities can contribute substantially to the effective diagnosis and treatment of patients with severe malaria and help in saving many lives through early diagnosis and prompt treatment. Specifically, they can contribute to the following activities:

- Identification of suspected malaria cases based on appearance of fever and by using a standard case definition
- Diagnosis of malaria by light microscopy or RDT
- Treatment of malaria cases using standard treatment guidelines for uncomplicated cases
- Recognition of severe malaria cases and referral to large hospitals or higher levels if facilities are not available in small hospitals

- Organizing therapeutic and logistics support for patients who are being transferred
- Provision of the best possible treatment for complications and continuing antimalarial treatment if the patient cannot be referred.

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 definite 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 present with fever, chills, headache, bodyache, anorexia, and occasionally abdominal pain and diarrhoea, and palpable liver and spleen. In young children there may be irritability, refusal to eat, and vomiting. Often, fever may be the only sign, 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 give a history of residence in a high-risk area for malaria and those who travelled recently to these high-risk areas should also be considered as suspected malaria cases.

3.2 Definitive diagnosis

It is important to make a definitive diagnosis of malaria since the disease mimics other conditions and *P falciparum* is becoming increasingly resistant to commonly used antimalarials. Severe malaria may be confused with some conditions such as meningitis, typhoid fever, septicaemia, influenza, dengue and other haemorrhagic fevers, viral encephalitis, hepatitis and leptospirosis. Efforts should be made in the hospitals and health facilities to establish the diagnosis of malaria rapidly to be able to provide specific treatment.

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

Parasitological diagnosis using light microscopy

Giemsa or Field-stained thick and thin blood smears should be examined in all malaria-suspected patients. ***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. If any of these conditions are detected, doctors should be alerted. 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 small hospitals should be adequately trained to perform light microscopy. They should be able to prepare proper blood films, stain it properly and then 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

It is cost effective, fairly sensitive and highly specific. Microscopy can estimate parasite density and differentiate between parasite species, provide information about blood platelets and leukocytes, indicate disease prognosis and help in diagnosing many other conditions. Repeated examinations also provide information on the 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 parasitaemia, maturation of sequestered parasites in the broods, partially treated with antimalarials or on chemoprophylaxis, and may be due to technical factors; (poorly prepared and stained blood films, poor quality microscope, examination of only thin films, inexperienced technician etc). **False positive results** are also seen due to artefacts which can be confused for malarial parasites 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 and when, for any reason, microscopic diagnosis is not available.

Limitations of RDTs

There are many RDTs available in the market with advantages and disadvantages including differing levels of sensitivity, specificity, and stability. When their use is being contemplated, up-to-date advice should be sought. HRP-II antigen may continue to be detected in blood 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. Another limitation is its relatively high unit cost.

4. Clinical manifestations of severe malaria

Severe malaria is characterized by cerebral malaria, 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 hyperlactatemia; macroscopic haemoglobinuria; prostration; 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. These are listed in Table 1.

The staff in small hospitals/health facilities may not have laboratory facilities to diagnose the manifestations but the use of the above table will help them in the early recognition of manifestations. Details of assessment are given in the Annexes. If a patient with severe malaria develops one or more of the above problems, it is necessary to refer the patient to a higher-level hospital. The staff working in

Table 1: Clinical manifestations of severe malaria

Clinical manifestations	Recognition
Impaired consciousness	Assessment by Glasgow scale (10 or less) or Blantyre scale (3 or less) as appropriate (Annexes 2a, 2b)
Severe pallor	Conjunctiva, tongue, lips, palms pale
Oliguria or anuria	Urine output <400 ml/24 hours in adults and <0.5 ml/kg /hour in children
Jaundice (combined with evidence of other vital organ dysfunction)	Yellow discoloration of sclera
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 mmHg in children aged 1 month-10 years; <60mmHg in neonates), core/skin temperature difference of >10°C)
Metabolic acidosis	Laboured, deep hyperventilation with increased respiratory effort (often termed respiratory distress) and a clear chest on auscultation (Kussmaul's breathing)
Pulmonary oedema or acute respiratory distress syndrome	Tachypnoea, dyspnoea and bilateral basal rales
Repeated or prolonged convulsions	Fits comprising of tonic or clonic convulsions followed by loss of consciousness or abnormal behaviour
Abnormal bleeding	Significant bleeding and haemorrhage from gums, nose, venipuncture sites, gastrointestinal tract
Haemoglobinuria	Dark red or black coloured urine
Hypoglycaemia	Anxiety, sweating, palpitation, dilatation of pupils, breathlessness or oliguria.

< = less than

> = more than

small hospitals should have a list of large hospitals (secondary level) and higher-level hospitals (tertiary level) so that the patient can be referred to an appropriate facility without delay.

The patient should be referred to a large hospital/health facility if the staff at the small hospital feel that the following facilities are required:

- Specialized biochemical, radiological or microbiological tests
- Intensive care management and round-the-clock monitoring to deal with the critical illness e.g. comatose cerebral malaria
- Ventilatory support, particularly volume ventilator
- Dialysis
- Blood transfusion

There may be a need to refer the patient to a large hospital/health facility if there is a variation in the diagnosis.

5. Treatment of severe malaria

Severe malaria is caused by *P falciparum*. Due to the problem of multi-drug resistant *falciparum*, it should be treated with drugs known to be effective in local situations. Severe malaria should always be treated with parenteral antimalarials because gastrointestinal absorption of oral drugs may be unpredictable. Oral drug administration can be given only after patients are able to tolerate oral medication.

If parenteral drug administration is not possible, then the rectal route can be chosen. The intravenous route is preferred if the facilities exist. Patients should be monitored clinically and biochemical tests like blood electrolytes, blood sugar and electrocardiogram (ECG) should be done whenever possible. The treatment should be given for the prescribed dosage and duration (Table 2). Whenever feasible, referral should be considered for patients failing to respond to treatment or when developing complications which can not be managed by the existing facilities. It is advisable to keep the patients in the hospital/health facility while they are being given parenteral/intrarectal drugs which will ensure compliance during the first 3-4 days.

5.1 Specific antimalarial treatment

Table 2: Schedule of antimalarial drugs recommended for the treatment of severe malaria

Drug	Route of administration	Schedule
Artesunate*	Intravascular (IV) (preferable) or Intramuscular (IM)	2.4 mg/kg bw IV or IM given 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, parenteral treatment should be switched to a complete treatment course of an artemisinin-based combination therapy (ACT) as recommended in the national treatment guidelines for uncomplicated malaria.
Artemether	IM	3.2 mg/kg bw on the first day, followed by 1.6 mg/kg bw daily for a minimum of 3 days until the patient can take oral treatment. Give a complete treatment course of an ACT as recommended in the national treatment guidelines for uncomplicated malaria.
Quinine**	IV (preferable) or IM	20 mg/kg bw dihydrochloride salt as loading dose by intravenous infusion over four hours, followed by 10 mg/kg bw over four hours every eight hours until the patient can swallow, prescribe quinine tablets 10 mg quinine salt/kg bw every eight hours in combination with doxycycline or clindamycin to complete 7 days treatment or preferably a full course of an ACT as recommended in the national treatment guidelines for uncomplicated malaria. If quinine is given IM, the dose should be split and injections given in the anterior part of the thigh.
Artesunate suppository	Intrarectal	200 mg intrarectally at 0,4, 8,12,24,36,48 and 60 hours followed by an oral ACT.
Artemisinin suppository	Intrarectal	40 mg/kg bw intrarectally then 20 mg/kg bw at 4, 24, 48 and 72 hours followed by oral administration of an oral ACT.

*Artesunic acid 60 mg is dissolved in 0.6 ml of 5% sodium bicarbonate diluted to 3-5 ml with 5% dextrose administered immediately by intravenous bolus injection.

**** 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, oral medication should be administered to complete the seven-day treatment.

The amount of fluid for infusion of quinine should be based on 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.

The loading dose of quinine should not be used if the patient has received quinine, quinidine or mefloquine within the preceding 12 hours. In areas where a seven-day course of quinine is not curative (e.g. Thailand), add a course of oral tetracycline 4 mg/kg four times daily or doxycycline 3 mg/kg once daily except children under eight years of age and pregnant women. Alternatively, clindamycin 10 mg/kg bw may be added twice daily for 3-7 days.

Remarks

- Member countries may have their national treatment guidelines; please refer to them accordingly.
- Quinine administered intravenously is preferable. It may be administered intramuscularly if intravenous injection is not possible. However, IM injection carries the risk of necrosis at the injection site and the injection is very painful. **If quinine is administered intravenously it should never be given as a push. An extremely slow drip of quinine is not effective. Therefore, a continuous and uniform flow of IV quinine in dextrose solution should be maintained over a period of four hours.** Patients on IV treatment require monitoring of pulse, blood pressure, and blood glucose. Patients should be kept flat on a bed while on IV quinine treatment.
- Quinine is **not** contraindicated during pregnancy and in children.

- Artemisinin derivatives are safe, effective, have a wider therapeutic window, can be administered IM, IV, or intrarectally and provide an alternative to quinine.
- Artemisinin derivatives are **not** recommended in the first trimester of pregnancy and for children below one year of age.

5.2 General supportive management

In addition to the specific treatment of severe malaria, general supportive measures of good quality are important and help early recovery and prevent complications. This comprises of maintaining hydration by administration of fluids. Oral fluids should be given if the patient is conscious and can swallow. In unconscious patients (Annex 2) and in those who have persistent vomiting, IV fluids are needed. If the patient requires IV fluids for a sustained period of time, biochemical monitoring of electrolytes becomes important. Such patients should be referred. The patient should also be encouraged to eat food. Food and appropriate nutritional supplements should be given by mouth. It is advisable to give energy-rich food frequently so as to maintain the nutritional status of the patient. If the patient is on quinine, it is important to provide a sugar-rich solution to prevent hypoglycaemia. A 10% glucose solution is recommended but if this is not available, sugar solution should be given. High fever should be reduced by the use of oral paracetamol and other supportive measures like increased fluid intake and tepid water sponging to reduce the high fever. Non-steroidal antiinflammatory drug (NSAID) is not recommended to reduce fever due to risk of gastrointestinal bleeding.

Management of unconscious/comatose patient is important (Annex 3).

6. Treatment of severe malaria in special situations

6.1 Treatment of severe malaria in children

The treatment of severe malaria in children is similar to the treatment in adults. The early symptoms of the disease in children are high fever, failure to eat or drink and vomiting. The symptoms of severe

malaria can progress rapidly in children and therefore the risk of death is increased if the case is not diagnosed and treated early. Convulsions are common in children and can be treated with IV diazepam 0.3 mg/kg bw (rate not to exceed 2 mg/min) or a slow bolus “push” or 0.5 mg/kg bw given intrarectally. Alternatively, paraldehyde (0.2 ml/kg bw) can be given by deep intramuscular injection or 0.4 ml/kg bw intrarectally. If control cannot be achieved with diazepam or paraldehyde, phenytoin may be given by intravenous infusion at a rate not exceeding 0.5 mg/kg /min. The drug should not be diluted with dextrose-containing fluids as it precipitates easily. Maintenance, if necessary, is with 5 mg/kg bw every 12 hours. Precise calculation of fluid and electrolyte replacement is important in children.

The problems of convulsions, severe anaemia and hypoglycaemia are more common in children than in adults and these should be suspected. If present these need to be treated appropriately. Because of the higher risk of complications of severe malaria in children, staff in the small hospitals are advised to refer the patients to a higher level with specialized facility after initiating the antimalarial treatment and supportive management of the patient. At a small hospital, diazepam and glucose or dextrose solution for injection are usually available. If children have repeated convulsions and phenytoin is not available, the children should also be referred to a higher level facility hospital. A blood bank is usually not available at a small hospital. If the patient needs a blood transfusion, he/she should be referred to a higher facility hospital.

6.2 Management of severe malaria during pregnancy

Women who develop severe malaria during pregnancy or in the postpartum period are at a higher risk of developing severe complications than non-pregnant women. Mortality is 2-10 times higher in the pregnant and postpartum women than in non-pregnant women. The signs of severe malaria depend on the immune status of the patient. In non-immune pregnant women, cerebral complications, hypoglycaemia and pulmonary oedema are common. They have increased risk of abortions, stillbirths and low birth weight babies. Due to high fever, uterine contractions can be induced and their severity could depend on the intensity of the fever. Pregnant women

can be given quinine safely and the risk is not higher than in non-pregnant women. Severe malaria during pregnancy and the postpartum period may have to be treated at a small hospital. However, when the complications are beyond the facilities available in a small hospital, the patient should be referred. The staff at a small hospital are advised to refer them to a higher facility after starting the antimalarial treatment and providing supportive treatment. Severe malaria in pregnancy that can be treated at a small hospital include:

- Hypoglycaemia (whole blood glucose concentration is lower than 40 mg/dl or 2.2mmol/L)
- Macroscopic haemoglobinuria (if the patient has no renal failure or severe anaemia requiring blood transfusion)
- Hyperparasitaemia (*i.e.* in non-immune patients who have infected red blood cell $\geq 5\%$ or $\geq 250,000$ parasites/ μL with appearance of peripheral schizontaemia). The relation of parasitemia to severity of illness is different in different populations and age groups, but, in general, very high parasite densities are associated with increased risk of severe malaria.

The other complications of malaria (Table 1) such as cerebral malaria, severe anaemia, renal failure, pulmonary oedema, shock, spontaneous bleeding, repeated generalized convulsions, acidemia or acidosis are not safe to be treated at small hospital due to lack of facility and should be referred to higher facility hospital.

7. Referral of patients with severe malaria

Referral of patients with severe malaria is advised for several reasons. Patients should be referred if they have any one or more of the complications of severe malaria as described above which can not be managed. Patients with severe malaria who do not respond to antimalarials or those who worsen despite treatment should be referred. Pregnant women, postpartum women and children below five years who have severe malaria can be treated at a small hospital according to the facilities available but if the need is beyond available facilities, the patients should be referred. This is because they have a high risk of complications. Doctors should consider safe referral transport, e.g. patients should not be referred during shock.

The need for referral and to obtain agreement

The staff in the small hospital should explain to the patient's attendants the need for referral of the patient to a higher level hospital. Discuss why this is important and urgent. Most patients will get convinced and will agree for referral. An agreement should be reached with the patient's relatives where the patient is proposed to be transferred. There are some who are reluctant. In such cases identify the problems and try to overcome the concerns and worries of the patient/attendant. If required, support from some influential members in the community can be obtained.

The common reasons for reluctance to go to the hospital and their possible solutions are identified in Table 3.

Table 3: Common problems in utilizing the referral facility and possible solutions

Problems	Possible solutions
Attendant is not convinced about the seriousness of the illness.	The harm that can occur if treatment is delayed must be explained. Local examples of patients with similar illness who suffered from complications or died because of delay in going to the referral hospital may be cited. Some examples of those who went and got better may also be given.
Attendant/patient is scared of the treatment and tests that are carried out in the hospital.	The attendant/patient should be told what to expect. It should be explained clearly that the treatment is to help the patient get better. The injections, IV treatment and some of the tests do cause some pain but are helpful in the recovery of the patient.
Attendant/patient does not have faith in the services provided at the hospital. They have heard of bad outcomes in other patients with similar illness.	Local examples of the patients who have recovered fully following a timely referral may be given. It must be emphasized that the purpose of referral is to try to provide the best possible treatment that is in the best interest of the patient.
The attendant/family has heard that the staff in the hospital is rude and they do not care.	The attendant should be told that a referral card will be given to them. This will help the patient get prompt attention. If the staff in the hospital is known, then a telephone call can be made. Someone in the community who knows someone in the referral facility can also be useful.

Problems	Possible solutions
<p>The attendant/ family is worried about the expenses in the hospital for diagnostic tests and treatment and those incurred on transport and food.</p>	<p>It should be explained that the charges depend on the family's capacity to pay. Poor patients can get free treatment or may be charged very nominally. The likely expenses should be estimated. It is also important to discuss how funds can be arranged. If needed, credit may be arranged. Some hardship is bound to occur but it has to be borne in the best interest of the patient.</p>
<p>The attendant/patient is worried about who will look after the children and other members of the family if the attendant/patient were to be shifted to a hospital.</p>	<p>The possibility of another family member or a neighbour looking after those who are left at home should be discussed. In the absence of relatives, help from neighbours or the community may be sought.</p>
<p>The attendant/patient asks why the patient needs to be referred and why it is not possible to manage the patient in the small hospital itself.</p>	<p>The staff in the facility can treat many patients but not all of them. There are limitations like lack of facilities for blood transfusion, oxygen, keeping a watch on the patient throughout the day and night and for doing some advanced laboratory tests.</p>
<p>There are difficulties in transporting the patient</p>	<p>The staff in the health facility should provide assistance to the extent possible. Community support can be requested for rendering help. Transport may be provided free or on payment. The payment may be deferred if possible to reduce the hardship on the family.</p>

In helping the patient for referral, the support of the community and of a local NGO can be substantial. This should be requested whenever possible.

Pre-referral treatment

Pre-referral treatment means provision of all treatment (specific and supportive) to the patient before referral. Patients who are seriously ill should be checked for responsiveness. A patient who is non-responsive should be quickly assessed and managed. This includes

assessment of the airway, breathing and circulation. Staff at the small hospital should be able to maintain airway, provide assisted breathing and manage shock if required. The principles of managing a non-responsive patient are the same irrespective of its cause. Detailed description of this is beyond the scope of this document.

Before referral, it is important to identify all specific treatment for the patient. For severe malaria this means antimalarial drugs that have been described in an earlier section of these guidelines. The antimalarial medicines should be given as per the dose schedule and continued until the patient reaches the referral facility. After that, the treatment is continued or altered according to the local policy of the hospital. Arrangements have to be made to continue the treatment while the patient is being transferred to the hospital. Time should not be wasted on assessing or treating the patient for non-essential disease conditions/health problems.

Convulsions should be managed with diazepam or phenytoin given by appropriate route and anticonvulsants should be continued until the patient reaches the referral hospital. High fever should be brought down with appropriate doses of paracetamol. Aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) should not be given. Other supportive measures to bring down high fever include tepid water sponging and administration of plenty of fluids. If the patient is dehydrated and acidotic, appropriate IV fluids should be given. However, if the patient has oliguria/anuria the advice on fluid restriction should be specific so as to prevent complications like pulmonary oedema.

During transfer make sure to advise the attendant about the position in which the patient is to be transported. Continue to provide all supportive treatment. This means continuing IV fluids if the patient is unable to drink or giving glucose-rich solution if the patient can take fluids orally and making sure that fluids are taken in adequate volumes to tackle the problem of dehydration. Appropriate food should be offered during transfer to the hospital if the patient can eat food by mouth/nasogastric tube feeding. Make the patient as comfortable as possible. Oxygen therapy should be provided during transport when necessary and feasible.

Prepare a referral card

After getting the agreement from the patient/attendant and rendering first aid, the staff in the health facility/hospital should prepare a referral card. Write the name, age, sex of the patient and his/her address with full details. Summarize the complaints, findings, classification of the disease and all treatment given. The reason(s) for referral should be written. Also, include the contact details of the referring facility. Write clearly the name of the referral hospital and its full address with telephone number and other details. If possible draw a notional map to guide the patient/attendant to reach the referral facility without any problems. The doctor should also indicate, if possible, whom to contact in the referral facility. A carefully filled referral card can help the patient get timely attention in the referral hospital.

Provide guidance to the patient/attendant

Explain to the patient/attendant clearly where to go, how to go and whom to contact. Tell how long it might take for them to reach the hospital. Provide guidance to the attendant what to do while the patient is being transferred and how to maintain the supportive and specific treatment during transport. A patient with severe malaria is critically ill. If it is possible then a trained attendant *i.e.* a staff member from the health facility/hospital should accompany the patient. This might save the patient's life.

Transfer the patient to a large hospital

When transferring a patient for referral to a large hospital or a higher level (tertiary hospital) make sure to do the following:

- Maintain ABC (airway-breathing-circulation), *i.e.* patient's airway and breathing (endotracheal intubation should be done in unconscious patient to prevent aspiration), and IV infusion to give medicines and correct dehydration (See details in Annex 3)
- Provide specific guidance to the person accompanying the patient

- Start appropriate antimalarial drugs and other essential medicines required so as to be sufficient until the patient is admitted
- Insert a urethral catheter to monitor urine output if necessary
- Provide a referral note (A format for referral card is included in Annex 4).

Dealing with a situation when referral is not possible

Sometimes despite the best efforts by the staff from the facility, referral is not possible. In such situations, the staff at the health facility should offer the best possible treatment. It should be clearly understood by the patient/attendant that what is being offered when referral is not possible is not the best. However, whatever treatment can be provided is being given. This comprises of the following:

- First aid measures
- IV fluids/nasogastric feeding if the patient is unable to drink fluids orally
- Monitor fluid intake and urinary output. Urine catheterization may be useful to measure accurate urine output particularly in oliguric/anuric or unconscious patients
- Specific antimalarial medicines
- Treatment of other complications that include convulsions (with anticonvulsants), dehydration, acidosis, renal failure, anaemia, pulmonary oedema, anuria/oliguria, circulatory failure, and abnormal bleeding. Optimal treatment for such complications depends very much on the facility available at each small hospital
- Supportive treatment to include treatment of high fever with paracetamol, nutritional support, warmth and positioning of the patient
- Monitor the progress of the patient

All efforts should be made to continue to convince the patient/attendant to use the referral facility as advised to reduce the risk of death/complications.

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Annex 1

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

This classification on the basis of the number of beds/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 the basic health unit in Bhutan (in these facilities there are no doctors but the basic health workers are expected to diagnose and treat illnesses); Upazila health complexes in Bangladesh; community health centres and subdistrict (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; 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 and include routine blood examination, microscopy, urine, stools, X-ray chest, cerebro-spinal fluid (CSF) examination, and ECG. However, biochemical tests and microbiology is not available. These facilities have trained staff but there are no specialists. IV treatment can be initiated but generally not maintained because of lack of biochemical support. Oxygen may be available but is not very reliable. Round-the-clock monitoring of patients is difficult. The range of medicines available for the treatment of complications of malaria is limited.

Large hospitals are medium-sized hospitals. These mostly include district hospitals in Member countries of the Region. This category includes private hospitals. In many countries, large hospitals are located 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. In these hospitals trained doctors and nurses are available and some of them are specialists. Round-the-clock monitoring of patients is possible. Laboratory facilities include routine blood, urine and stool

examination, biochemical tests, radiology and microbiology. Pathology services may be available but are not advanced. Treatment facilities include a wide range of medicines to treat a variety of problems caused by severe malaria. These include blood transfusion, oxygen, and IV fluids.

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

Tertiary hospitals generally have more than 200 beds, with doctors and nurses who are trained and there are many specialists. Round-the-clock services are available. These hospitals are able to do 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 undertake some research and have adequate library facilities.

Annex 2a

Modified Glasgow coma scale for adults

Eye opening	Spontaneously	4	
	To speech	3	
	To pain	2	
	No response	1	
Best Verbal Response <i>(Nonintubated)</i>	Oriented and talks	5	
	Disoriented and talks	4	
	Inappropriate words	3	
	Incomprehensible sounds	2	
	No response	1	
	<i>(Intubated)</i>	Seems able to talk	5
		Questionable ability to talk	3
Generally unresponsive		1	
Best Motor Response	Verbal commands	6	
	Localizes to pain	5	
	Withdraws to pain	4	
	Decorticate	3	
	Decerebrate	2	
	None	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)	1
	Not directed	0
Verbal Response	Appropriate cry	2
	Inappropriate cry or moan	1
	None	0
Best Motor Response	Localises painful stimuli	2
	Withdraws limb from pain	1
	Non-specific or absent response	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 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 two 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:

If tachypnoea, laboured respiration, acidotic breathing is present or develops in the course of the management, patient may need oxygen inhalation and ventilatory support. Hence, 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
<input type="checkbox"/> witnessed convulsions		<input type="checkbox"/> hypoglycaemia	
<input type="checkbox"/> presence of bleeding		<input type="checkbox"/> blood transfusion	
<input type="checkbox"/> oliguria		<input type="checkbox"/>	
<input type="checkbox"/> respiratory distress/ pulmonary oedema		<input type="checkbox"/>	
<input type="checkbox"/> shock		<input type="checkbox"/>	

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					

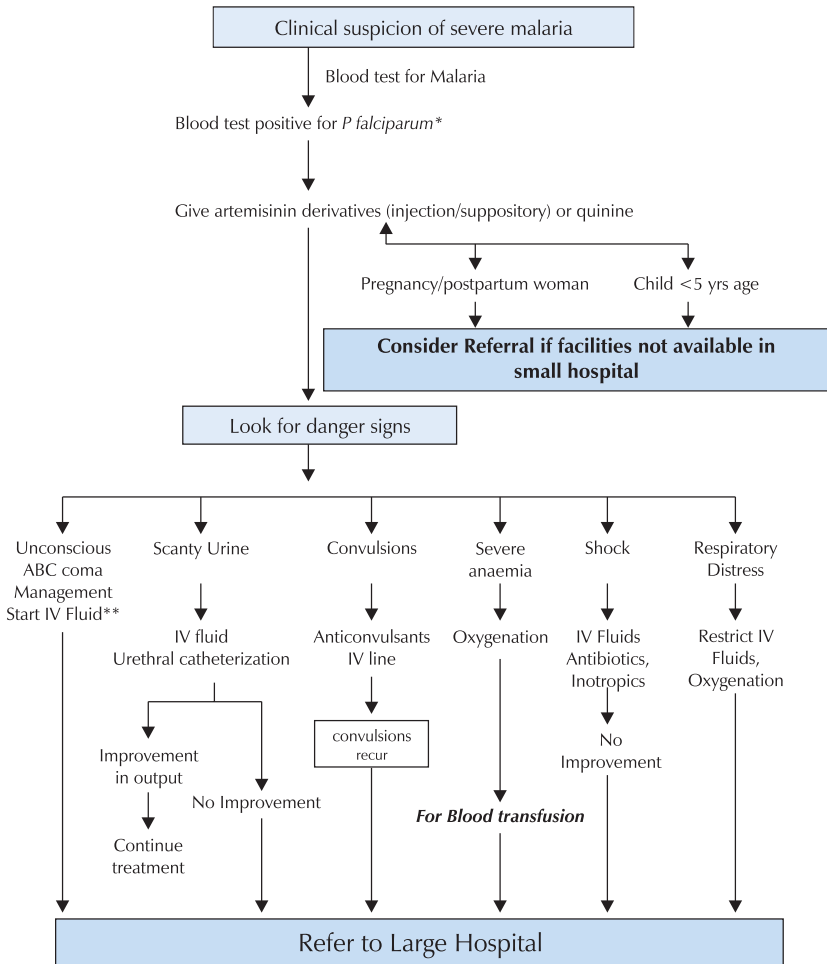
Other investigations:

	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

Management of severe malaria in small hospital/health facility



* If the patient has manifestation of severe malaria even if other species has been reported, treat them as severe *P. falciparum* malaria. Even if the slide is negative, with high index of clinical suspicion of malaria (and excluding other diseases) and if the patient is from an endemic area, treat patient as severe malaria

** 50% glucose 50 ml injection intravenously and continue with 5-10% dextrose IV fluid for maintenance.

Annex 6

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These guidelines for clinical management of severe malaria have been produced by the South-East Asia Regional Office of the World Health Organization. The guidelines will be an effective tool for use by medical personnel in small hospitals who treat patients with severe malaria referred from lower-level health facilities, and include diagnosis of malaria, clinical manifestations and treatment of severe malaria cases at small hospitals. The guidelines also include relevant information on referral of severe malaria cases which require more specialized diagnostic and treatment facilities and care.



**World Health
Organization**

Regional Office for South-East Asia
New Delhi

Price: Ind. Rs.80