

Guidelines for the Diagnosis and Treatment of Malaria in Somalia 2016



Developed and Endorsed by the Zonal NMCPs/MoH of The
Federal Government of Somalia, Puntland & Somaliland

Contents

Contents	3
Acknowledgements	9
Introduction	11
Malaria epidemiology	11
Malaria burden in Somalia	11
Malaria endemic zones.....	12
<i>Figure 1 Prevalence of Plasmodium falciparum in different regions of Somalia (from Food Security and Nutrition Analysis Unit Somalia surveys 2004–2007) PfPR,</i>	<i>13</i>
Malaria treatment	14
Anti-malarial drug efficacy	14
Recommended medicines for the treatment of malaria	14
Malaria diagnosis	15
Monitoring and evaluation	15
Implementation.....	16
Health care delivery system	16
Challenges and constraints.....	16
Uncomplicated malaria	18
Definition	18
Suspected uncomplicated malaria	18
Confirmed uncomplicated malaria	18
Signs and symptoms	18
Treatment of uncomplicated malaria.....	18
<i>Treatment failure</i>	18
Chemo-prevention of malaria in pregnancy	19
Management of malaria at different service delivery.....	20

Health post level.....	20
Diagnosis	20
Treatment.....	20
Box 1 Recommended treatments for uncomplicated malaria at health post level.....	20
First-line treatment	20
Box 2 DOTS involves the following:.....	21
Supportive treatment.....	21
Follow-up.....	21
Maternal and child health centre/outpatient department level	21
Diagnosis	21
Treatment.....	22
Box 3 Recommended treatments for uncomplicated malaria at maternal and child care/outpatient department level	23
First-line treatment	23
Gametocytocidal treatment*	23
Supportive treatment.....	23
Follow-up.....	23
Intermittent preventive treatment with sulfadoxine-pyrimethamine should be given monthly to all pregnant women from the second trimester until delivery.	24
District and regional hospital level	24
Diagnosis	24
Treatment.....	24
Treatment failure	25
Box 4 Recommended First-line treatments for uncomplicated malaria at hospital level	26
First-line treatment	26

Gametocytocidal treatment**	26
Second-line treatment	26
Severe malaria.....	27
Definition	27
Signs and symptoms	27
Clinical features	27
Laboratory features	28
Diagnosis	28
Management at different levels.....	28
Health post level.....	28
At the health post level, health workers can identify some important signs and symptoms of severe malaria. After judging the severity of the illness, severe malaria cases should be immediately referred to the hospital level after pre-referral treatment and advice are given. Diagnosis.....	28
Pre-referral treatment	29
Maternal and child health centre/outpatient department level	30
Diagnosis	30
District/regional hospital level	31
Diagnosis	31
General management.....	32
Ten essential steps for the treatment of severe malaria	32
Nursing care.....	33
Treatment.....	33
Clinical features and supportive treatment	35
Complications/severe conditions	37
Cerebral malaria	37
Clinical features in adults	37

Management of cerebral malaria in adults.....	37
Clinical features in children	38
Management in children	39
Treatment of convulsions.....	40
Anaemia.....	41
Management in adults	41
Management in children	42
Renal failure.....	42
Management in adults	42
Management in children	43
Hypoglycaemia	43
Clinical features in adults	43
Management in adults	44
Clinical features in children	44
Management in children	44
Fluid, electrolyte and acid–base disturbances	44
Clinical features in adults	44
Management in adults	45
Clinical features in children	46
Management in children	46
Pulmonary oedema	47
Management.....	47
Circulatory collapse (“algid malaria”).....	47
Management.....	48
Spontaneous bleeding and disseminated intravascular coagulation.....	48
Management.....	48

Hyperpyrexia.....	49
Management in adults	49
Management in children	49
Hyperparasitaemia	49
Management	49
Malarial haemoglobinuria	49
Management.....	49
Common errors in diagnosis.....	50
Common errors in management	50
Malaria in special groups.....	52
Pregnant women	52
Intermittent preventive treatment	52
Non-immune pregnant women	52
Semi-immune pregnant women	53
Prevention and treatment of anaemia in pregnancy	53
Management of uncomplicated malaria in pregnancy	53
Management of severe malaria in pregnancy.....	54
Anti-malarial drug treatment	54
Presentation and treatment of complications.....	54
Malnourished persons	55
Severe acute malnutrition	55
Diagnosis	55
Treatment.....	56
Moderate acute malnutrition.....	56
Patients co-infected with HIV	56
Currently there is insufficient information to modify the malaria treatment recommendations for patients with HIV/AIDS. Annex 1. Malaria Morbidity and Mortality Data	56

Annex 2 Epidemiological profile per zone in Somalia	58
Annex 3 Dosage charts, with side-effects	59
Artemether–lumefantrine (Coartem®).....	59
Quinine (300 mg salt tablets).....	60
Quinine dihydrochloride (600 mg salt/2 ml) intravenous (IV).....	60
Quinine dihydrochloride (600 mg salt/2 ml) intramuscular (IM)	60
Dosage	60
Side-effects	62
Artesunate injectable (60 mg/vial)	62
Artemether injectables.....	63
Artesunate rectal capsules	63
Dose chart by age (children) for artesunate 50 mg and 200 mg rectal capsules.....	63
Paracetamol.....	63
Dosage	63
Ferrous sulfate + folic acid (200 mg + 0.25 mg).....	64
Dosage (based on dosage for ferrous sulfate)	64
Side-effects (mainly because of ferrous sulfate).....	64
Annex 4 Flow charts for case management	66
Annex 5 Coma scales.....	67
Glasgow coma scale (adults).....	67
Blantyre coma scale (for children)	67
Annex 6 Treatment observation chart for inpatients	69
References.....	72
Bibliography	72
Glossary.....	73

Acknowledgements

This document was jointly developed with technical support from the United Nations Children's Fund and WHO and is a product of an elaborate consultative process involving several key stakeholders in malaria control at national and international level.

The commitment, technical support and overall stewardship from United Nations Children's Fund and WHO (Somali Country Office, WHO Global Malaria Programme, WHO Regional Office for the Eastern Mediterranean) have made possible the development and the subsequent revision of the *Malaria diagnosis and treatment guidelines for Somalia*.

Further, the contribution and participation of representatives from the Ministry of Health, academic institutions, the private sector and nongovernmental organizations are highly appreciated.

Sincere gratitude goes to the Global Fund to Fight Aids, Tuberculosis and Malaria for financial support.

Introduction

The main objective of the malaria prevention and control programme in Somalia is to prevent mortality and reduce morbidity due to malaria. The groups most vulnerable to the disease, children aged under 5 years and pregnant women, are especially targeted. Effective case management - early diagnosis and treatment - is a critical component of malaria prevention and control. To achieve the main objective of reducing malaria morbidity and prevention of malaria mortality, the availability of safe, effective, affordable and accessible anti-malarial drugs is a prerequisite.

The first national diagnosis and treatment guidelines were developed in May 2005 following a consensus meeting held in Nairobi¹ and updated in January 2011.² Therapeutic efficacy studies conducted in 2011, 2013 and 2015 revealed high level of artesunate+sulfadoxine/pyrimethamine treatment failures (12-22%).³ These failure rates were above the 10% threshold level recommended by WHO (4) for changing antimalarial treatment policy. In these studies high efficacy (above 97% cure rate) of artemether+lumefantrine, second-line drug was found.

In view of the these findings, the guidelines were again updated during a consensus workshop on 22 – 23 February 2016 in Hargeisa, Somaliland. The recommendations in these updated guidelines are consistent with the National Malaria Control Strategy 2016–2020. The updated guidelines provide adequate information to health workers on the specific details of malaria diagnosis and treatment at different levels of the health care system. The first part describes the management of uncomplicated malaria while the second part deals with management of severe malaria. The guidelines also provide recommendations for anti-malarial medicines and dose regimens for intermittent preventive treatment for pregnant women.

The objectives of treatment for uncomplicated malaria are to cure (radical) the infection rapidly, prevent progression to severe disease, reduce transmission of the infection to others and prevent the emergence of anti-malarial drug resistance.

The objectives of treatment for severe malaria are to prevent death, neurological deficit and recrudescence.

Malaria epidemiology

Malaria burden in Somalia

Although there are limited national data and statistics on the burden of malaria in Somalia, it is considered a major public health problem in the country. The dominant malaria species in the country has been *Plasmodium falciparum* accounting more than 95%. However,

increased proportion of *P. vivax* has been reported from North-west (Somaliland) and North-east (Puntland) zones. A screening of patients with fever of history of attending the Bosaso regional hospital during 4 January to 14 February 2016 revealed 37.0% (258/697) 12.8% (89/697) of *P. falciparum* and *P. vivax* respectively indicating that *P. vivax* accounted for 25.6% of the infections. Mixed infection accounted for 0.4% (3/697). In 2015, a total of 88 139 cases, of which only 17913 were laboratory confirmed, were reported (annex 1). However, the reported figure seems far below the real burden considering that:

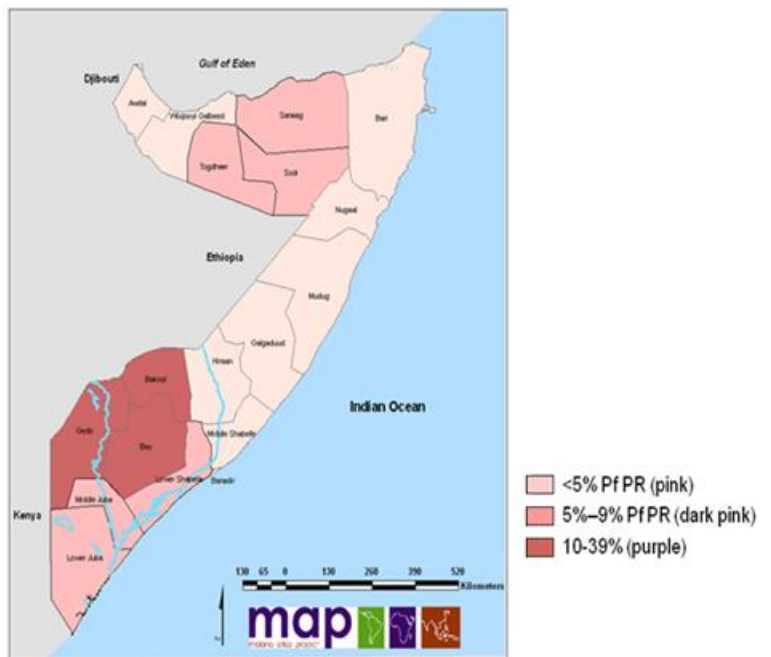
- 70% of people suffering from malaria symptoms seek help outside public health facilities;
- the performance of the health information system as a whole is far from satisfactory;
- recording of malaria cases at maternal and child health centres is poor;
- reporting by health facilities to WHO is irregular, inaccurate and incomplete.

On the other hand, owing to the inadequacy, inaccessibility and non-availability of public health care facilities with reliable laboratory diagnostic facilities for the confirmation of malaria, overdiagnosis of malaria remains a serious problem. In most cases, the diagnosis of malaria is clinical and based only on fever or a history of fever. This makes it difficult to arrive at a true estimation of the malaria burden. The *World malaria report 2015* estimated that there were 310 000-1 300 000 cases of uncomplicated malaria and 42-4800 malaria deaths in Somalia ⁴

Malaria endemic zones

Malaria transmission in Somalia varies from hypoendemic to mesoendemic with areas having areas of year-round transmission with two peaks of increased number of cases during the two wet seasons: April to June and October to November .⁵ *Plasmodium falciparum* is the predominant malaria parasite species, contributing to more than 90% of malaria infections with different levels of prevalence across the country (Figure 1). Different levels of endemicity, each with specific epidemiological features and epidemic prone potential, can be found (Annex 2). Past surveys showed lower prevalence in the north and centre of the country and higher prevalence in the riverine areas of the Juba and habelle rivers (Figure 1).

Figure 1 Prevalence of Plasmodium falciparum in different regions of Somalia (from Food Security and Nutrition Analysis Unit Somalia surveys 2004–2007) PfPR,



Malaria treatment

Anti-malarial drug efficacy

Drug efficacy studies were conducted by WHO in 2004–2006 for monotherapies of chloroquine, amodiaquine, and sulfadoxine–pyrimethamine; and artemisinin-based combination therapies of artesunate plus sulfadoxine–pyrimethamine and artesunate plus amodiaquine in three sentinel sites in Somalia.⁶ These studies revealed a high level (>76%) of treatment failure with chloroquine. The levels of treatment failure with amodiaquine monotherapy in the three sites were 2.8%, 8% and 23%, while treatment failure with sulfadoxine–pyrimethamine was between 8% and 12 %.

The findings from these studies however demonstrated that the artemisinin-based combination therapies were highly efficacious, with cure rates of 98%–100%. With the efficacy of sulfadoxine–pyrimethamine as monotherapy above 80%, it was suitable for use as a combination partner with artesunate. Thus artesunate plus sulfadoxine–was recommended as first-line drug for the treatment of uncomplicated falciparum malaria in 2005.(5) The efficacy of artesunate plus sulfadoxine– was assessed in 2011 and 2015 and revealed 12-22% treatment failures, while in 2013 and 2015, efficacy studies on artemether+lumefantrine, the second-line drug, revealed a cure rate of more than 97%. .

Recommended medicines for the treatment of malaria

Artemether+lumefantrine has now been recommended as first-line drug for uncomplicated malaria (all species) based on the evidence of its high cure rate (>97%) and the low cure rate (<80%) with artesunate plus sulfadoxine–pyrimethamine (, Dihydroartemisinin+piperazine was chosen as the second-line treatment for uncomplicated falciparum malaria

For pregnant women, quinine should be used during the first trimester and artemether+lumefantrine during the second and third trimester. If quinine is not available not available, or adherence to a 7 day treatment regimen cannot be assured, artemether+lumefantrine can be given.

As antigameteocidal drug, a single dose primaquine should be added to the artemether+lumefantrine treatment for falciparum infected patients except **infants <6 months, pregnant women and women breastfeeding infants aged <6 months.**

For vivax anti-relapse, primaquine for 14 day treatment should be used except **infants <6 months, pregnant women and women breastfeeding infants aged <6 months and individuals with G6PD deficiency.**

For severe malaria, artesunate injectables (first option) or artemether injectables (second option) or quinine injectables are recommended. Where complete treatment of severe malaria is not possible but injections are available, a single dose of artesunate im should be given before referral to an appropriate facility for further care. If artesunate im is not available use artemether im, if that is not available use quinine im. Where these intramuscular injectables are not available, artesunate suppositories should be used as a pre-referral treatment in children <6 years.

Malaria diagnosis

In all patients suspected of malaria, anti-malarial treatment should be provided on the basis of parasitological confirmation, either by microscopy or rapid diagnostic test.. Where there are no laboratory facilities, malaria diagnosis should be based on clinical signs and symptoms using the Integrated Management of Childhood Illness algorithm.

Rapid diagnostic tests detect specific antigens (proteins) produced by malaria parasites. These antigens are present in the blood of infected, or recently infected, people. The rapid diagnostic test signifies their presence by a colour change on an absorbing nitrocellulose strip. The rapid diagnostic test recommended for Somalia is the one that detects only *Plasmodium falciparum* species by detecting histidine-rich protein-2.

For all malaria cases in all malaria transmission settings, and where diagnostic testing (by microscopy or rapid diagnostic) is feasible, it is recommended that artemether+lumefantrine treatment is only given to confirmed cases). Results of all rapid diagnostic tests and blood smears performed should be registered in the facility registers. In areas where there are presently no diagnostic services, treatment with artemether+lumefantrine in the interim should be based on clinical diagnosis.

Monitoring and evaluation

There is a continuous need to ensure availability and proper use of safe, effective and affordable anti-malarial drugs that contribute to achieving high cure rates and reducing transmission. Therefore, the efficacy, effectiveness, tolerance and safety (including mild side-effects) of recommended treatments should be monitored. Health workers at all levels should report all severe serious adverse events seen after the administration of artemether+lumefantrine.

Particular emphasis should be given to monitoring the emergence of resistance to anti-malarial drugs. WHO has developed and updated the methodology for monitoring the therapeutic efficacy of anti-malarial medicines. The efficacy of first-line and second-line medicines should be monitored regularly (at least once every 2 years).

These guidelines for malaria diagnosis and treatment should be reviewed periodically and updated as necessary based on evidence. **Regular, timely and well-organized in-service training sessions should be given to update and refresh health workers on malaria diagnosis and treatment. Information should also be given to the general public through appropriately designed behaviour change communication strategies to improve early diagnosis and treatment-seeking practices and compliance to prescribed drug dose regimens. Treatment guidelines and charts should be displayed inside health facility rooms.**

The health information system tools that are currently available at health facilities have spaces to monitor consumption and supply management to ensure a sustained service delivery at its optimum.

Implementation

Health care delivery system

Current public health care facilities in Somalia include health posts, maternal and child health centres, with or without an inpatient department, and district and regional hospitals. The most basic level, the health post, is staffed by a community health worker working on a voluntary basis without incentives and often with very limited or no supportive supervision. At the maternal and child health centre level, there are midwives, qualified nurses or auxiliary nurses. The hospital level is staffed with qualified nurses, doctors and pharmacists. Laboratory facilities are found in hospitals and at a few maternal and child health centres. Currently, there is a regular malaria quality-control system in place in Somaliland and Puntland but in CS this is under establishment with the support of the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Health workers at all levels should be reoriented and trained on the revised anti-malarial treatment policy. In addition, this should be included in the curricula of all medical and public schools or institutions (e.g. for nursing, midwifery, medical doctors, etc.).

Challenges and constraints

In Somalia, there are several challenges and constraints that may make the implementation of the guidelines and treatment protocol difficult. These include:

- inaccessibility and unavailability of public health facilities;
- uncontrolled importation and dispensation of drugs due to the absence of drug regulatory authorities;

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- non-availability of reliable diagnostic facilities for malaria;
 - unregulated private health care providers with access to multiple non-certified anti-malarial medicines, leading to self-prescription and drug misuse;
 - inadequate monitoring and quality assurance of malaria treatment at public health facilities in most areas;
 - limited community awareness of appropriate diagnosis and treatment of malaria;
 - Lack of security due to the longstanding civil war.

The support and help of all health care providers and decision-makers is, therefore, required to advocate and ensure adherence to the new guidelines at all levels of health care service.

Uncomplicated malaria

Definition

Suspected uncomplicated malaria

A person living in a malaria area, or with a history of travel to a malaria area within the past 6 weeks, who has an acute onset of fever with or without other signs and symptoms of malaria.

Confirmed uncomplicated malaria

A patient with symptoms and/or signs of malaria, with parasitological confirmation (microscopy and/or rapid diagnostic test) of the presence of malaria parasites.

Note: other causes of fever should also always be considered and investigated as co-infections occur regularly.

Signs and symptoms

Uncomplicated malaria is mainly characterized by clinical symptoms such as fever, chills, shivering, headache, joint pains and generalized aches in the presence of malaria parasites in the blood. None of the severe features or complications, described in the referral section on page 29, should be present. Patients with uncomplicated malaria may also have symptoms such as nausea, vomiting, abdominal pain, diarrhoea, thirst and poor appetite.

Treatment of uncomplicated malaria

The objectives of treating uncomplicated malaria are (i) eliminate malaria parasites as rapidly as possible, (ii) prevent progression to severe disease, (iii) prevent onward transmission of the infection to others and (iv) prevent the emergence and spread of resistance to antimalarial drugs. Patients with uncomplicated malaria infection should be treated with the first-line drug (artemether+lumefantrine) except pregnant women in their first trimester. These patients should be given oral quinine three time a day for 7 days.

Treatment failure

Consider treatment failure in a patient who has had a complete treatment of confirmed malaria but who returns to the hospital, or is referred from a health post or maternal and

child health centre/outpatient department, with signs and symptoms of malaria and with microscopically confirmed malaria parasites within 4 weeks of treatment.

Possible causes of treatment failure are:

- vomiting
- poor quality or counterfeit anti-malarial drugs
- previous prescription of an incomplete course
- poor adherence
- parasite resistance

In case of treatment failure, the patient should be given the second-line treatment (dihydroartemisinin+piperquine).

In case fever and parasitaemia recur after 4 weeks, these patients should be treated as new infection and be given artemether+lumefantrine.

Chemo-prevention of malaria in pregnancy

IMPORTANT NOTE: Malaria in pregnancy is always a serious disease and therefore needs to be treated promptly with safe anti-malarial drugs and other supportive therapy for anaemia. For prevention of malaria in pregnancy in Somalia, all pregnant women in moderate to high transmission areas should receive recommended anti-malarial drug sulfadoxine–pyrimethamine as intermittent preventive treatment during the scheduled ANC visit. The first dose should be administered as early as possible during the 2nd trimester of gestation (determined by the onset of “quickening” or by fundal height by ANC personnel). Each SP dose should be given at least 1 month apart and up to delivery.”.

Malaria in pregnant women is estimated to be a major cause of maternal anaemia and low birth weight in babies. Atypical manifestations of malaria are common in pregnancy, particularly in the second half of the pregnancy. Anaemia is more common and severe between 16 and 29 weeks. Anaemia increases the risk of perinatal mortality, maternal mortality and morbidity. Risk of malaria for pregnant women in moderate to high transmission zones is high and intermittent preventative treatment (sulfadoxine–pyrimethamine) is recommended. In Somalia, Intermittent preventive treatment with sulfadoxine–pyrimethamine is recommended only in the southern and central zones of Somalia where malaria is mesoedemic with hyperendemic pockets. The drug should be given during the second trimester and third trimester with a minimum interval of 1 month (for dosage, see Annex 3).

Management of malaria at different service delivery

Health post level

Diagnosis

At health post level, malaria diagnosis will be based on rapid diagnostic tests. However, if rapid diagnostic tests are not available, the patient should be treated on the basis of clinical diagnosis. A patient with a fever or a history of fever at least within the past 2 days is assumed to have clinical malaria. However, other common causes of acute febrile illness such as tonsillitis, common cold, typhoid, brucellosis, dengue fever, pneumonia and meningitis should also be looked for.

Treatment

At health post level, the recommended first-line treatment artemether+lumefantrine (Box 1) will be used to treat uncomplicated malaria cases (for dosage, see Annex 3). The first dose should be given immediately diagnosis is made in the presence of the health worker (Box 2).

In case of treatment failure the patient (all age groups) must be referred to a higher-level facility for further assessment and treatment. In case of severe malaria, refer patient aged 6 years and above directly to facility where parenteral treatment is available. For children <6 years give rectal artesunate as pre-referral treatment and refer to facility where parenteral treatment is available.

Box 1 Recommended treatments for uncomplicated malaria at health post level

First-line treatment

Artemether+lumefantrine (twice daily doses for three days), except first-trimester pregnant women.

Pregnant women in the first trimester should be referred to the nearest maternal and child health centre/outpatient department or to hospital.

For vivax anti-relapse treatment, refer the patient to the hospital where primaquine treatment is available.

Box 2 DOTS involves the following:

- the first dose of the first-line drug should be given under direct observation;
- the patient should be kept for about 30 minutes in case he or she vomits. Where a patient vomits within this time, another dose should be given to replace the first dose given (counted as first dose) and observed. If repeated vomiting, refer the patient to the nearest health facilities where parenteral treatment is available (for children less than 6 years of age, give rectal artesunate as pre-referral medication).

Supportive treatment

Patients with uncomplicated malaria may require additional treatment to manage conditions such as high fever, dehydration and anaemia:

- in the case of high fever (axillary temperature above 38°C), give paracetamol and advise tepid sponging of patient, removal of heavy clothes and fanning;
- for patients who are dehydrated or have diarrhoea, give oral rehydration salts and advise to take increased amounts of clean water or other fluids (in the case of infants, encourage mothers to provide extra breastfeeding).

Follow-up

If fever and other symptoms persist in a patient who has started malaria treatment, the patient should be advised to return to the health post within 72 hours (3 days). However, patients should also be advised to come at any time even before 72 hours if there is a need or a worsening in the clinical condition. For all patients who come back to the health post, a full assessment should be carried out and appropriate action taken:

- assess the overall condition of the patient (for danger signs and criteria for referral, see page 29);
- if the patient has not taken the treatment, administer first-line treatment (artemether+lumefantrine);
- if patient has taken artemether+lumefantrine correctly and still has clinical signs and symptoms of malaria, refer to the nearest maternal and child care centre/outpatient department or hospital.

Maternal and child health centre/outpatient department level

Diagnosis

Diagnosis should be based on parasitological confirmation (microscopic examination of blood films or rapid diagnostic test) in all malaria transmission levels. In settings where

laboratory facilities (microscope or rapid diagnostic tests) are not available or during confirmed epidemics, patients should be treated based on clinical diagnosis.

Treatment

Artemether+lumefantrine (Box 3) should be given to parasitologically confirmed (by microscopy or rapid diagnostic test) malaria patients, except first-trimester pregnant women, in all malaria transmission levels. However, presumptive treatment of patients should be undertaken only during confirmed epidemics and in settings where laboratory facilities (microscope or rapid diagnostic testing) are not available. First-trimester pregnant women with malaria should be treated with oral quinine (for dosage, see Annex 3). The first dose should be given by the health worker as under DOTS.

Microscopy/rapid diagnostic test results and treatment outcomes should be noted in the registers for future analysis. In case of treatment failure (failure within 28 days) or severe malaria, the patient must be referred to a hospital for further assessment and treatment. In case of new infection (failure after 28 days), give artemether+lumefantrine. Pre-referral treatment should be given for severe malaria cases (see Treatment of severe malaria, page 27).

For anti-relapse treatment for vivax infection, refer the patient to the hospital where primaquine treatment is available.

Box 3 Recommended treatments for uncomplicated malaria at maternal and child care/outpatient department level

First-line treatment

1. Artemether+lumefantrine (twice daily doses for three days)except first-trimester pregnant women.
2. Quinine tablets for first-trimester pregnant women (for dosage, see Annex 3).

Gametocytocidal treatment*

Primaquine*: A single dose of 0.25 mg/kg body weight should be added to the first-line treatment of falciparum malaria (for dosage, see Annex 3) in all transmission settings.

P. Vivax anti-relapse treatment

Refer the patient to the hospital where primaquine treatment is available.

***Primaquine is contraindicated in infants <6 months, pregnant women, women breastfeeding infants aged <6 months. G6PD testing is needed prior to treatment for this indication.**

Supportive treatment

A patient with uncomplicated malaria may require additional treatment to correct conditions such as dehydration, high fever and anaemia:

- in the case of high fever (axillary temperature above 38°C), give paracetamol and advise tepid sponging of patient, removal of heavy clothes and fanning;
- for patients with dehydration or diarrhoea, give oral rehydration salts and advise to take increased amounts of clean water or other fluids (in the case of infants, encourage mothers to provide extra breastfeeding);
- ferrous sulfate and folic acid for 30 days (for dosage, see Annex 3) in case of anaemia but refer severe anaemia to a higher-level health facility where appropriate treatment can be given.

Follow-up

If fever and other signs of illness persist in a patient who has started malaria treatment, the patient should be advised to return to the maternal and child health centre/outpatient department within 72 hours (3 days). However, patients should also be advised to return any time before 72 hours if there is a need. For all patients who return to the maternal and child health/outpatient department, a full assessment should be done and appropriate action taken:

- assess the overall condition of the patient (for danger signs and criteria for referral, see page 29);
- if the patient has not taken the full course of treatment, administer the remaining dose of treatment;
- if the patient has taken a full course of artemether+lumefantrine and still has clinical signs and symptoms of malaria, refer to the nearest hospital.

In maternal and child health centres/outpatient departments where functioning laboratory (microscopy) facilities are available, a blood examination for malaria parasites, *not* a rapid diagnostic test, should be done on all previous *P. falciparum* positive patients returning to the health facility with fever or a history of fever within 28 days after treatment with artemether+lumefantrine. In addition, ask the patient if he or she has vomited the drug or had diarrhoea after treatment. Also, if the patient has taken anti-malarial drugs from private or lower-level health facilities, check whether the drug is a reliable brand and has not expired. If the blood film is positive for asexual malaria parasites and other conditions are excluded, this is a case of treatment failure. These patients should be referred to the nearest hospital for further treatment. When it is *not* possible to refer the patient, dihydroartemisinin+piperazine can be administered (for dosage, see Annex 3).

In maternal and child health centres/outpatient departments where functioning laboratory (microscopy) facilities are available, the patient should be referred to the nearest hospital. A rapid diagnostic test should *not* be performed in this situation as most tests will give a positive result for up to 28 days, even if the patient received an effective treatment. If referral to a hospital is not possible, dihydroartemisinin+piperazine tabs should be given immediately. Special attention should be given to completing a referral form and proper registration and reporting of such cases in health facility registers.

Intermittent preventive treatment Intermittent preventive treatment with sulfadoxine-pyrimethamine should be given monthly to all pregnant women from the second trimester until delivery.

District and regional hospital level

Diagnosis

At hospital level microscopic diagnosis or rapid diagnostic testing should be done for all suspected malaria cases.

Treatment

At hospital level, the first-line (artemether+lumefantrine) and second-line (dihydroartemisinin+piperazine) treatments for uncomplicated malaria should be made

available. Artemether+lumefantrine (Box 4; for dosage, see Annex 3) should be given to parasitologically confirmed malaria patients, except first-trimester pregnant women, in all malaria transmission levels. However, presumptive treatment of patients should be undertaken only during confirmed epidemics. Women in their first trimester of pregnancy with malaria should be treated with oral quinine (for dosage, see Annex 3). The first dose should be given straight away, under DOTS.

Second-line treatment should only be given following microscopy confirmation of malaria treatment failure. If the hospital facility does not have the capacity for confirming malaria, the patient with suspected treatment failure should be referred to such facilities with parasitological confirmatory capacity using microscopy.

Microscopy/rapid diagnostic test results and treatment outcomes should be noted in the registers for outpatient and inpatient units for future analysis.

Treatment failure

Consider treatment failure in a patient who has had a complete treatment of confirmed malaria but who returns to the hospital, or is referred from a health post or maternal and child health centre/outpatient department, with signs and symptoms of malaria and with microscopically confirmed malaria parasites within 4 weeks of treatment.

Possible causes of treatment failure are:

- vomiting
- poor quality or counterfeit anti-malarial drugs
- previous prescription of an incomplete course
- poor adherence
- parasite resistance

In case of treatment failure, the patient should be given the second-line treatment (dihydroartemisinin+piperquine).

In case fever and parasitaemia recur after 4 weeks, these patients should be treated as new infection and be given artemether+lumefantrine.

Box 4 Recommended First-line treatments for uncomplicated malaria at hospital level

First-line treatment

1. Artemether+lumefantrine (twice daily doses for three days) except first-trimester pregnant women.
2. Quinine tablets (three times daily doses for 7 days) for first-trimester pregnant women.

Vivax anti-relapse treatment

Primaquine: 0.25 mg/kg body weight daily for 14 days.*

Gametocytocidal treatment**

Primaquine*: 0.25 mg/kg body weight single dose should be added to the first-line treatment in all transmission settings.

Second-line treatment

Dihydroartemisinin+piperquine

*Primaquine is contraindicated in infants <6 months, pregnant women, women breastfeeding infants aged <6 months and individuals with G6PD deficiency. 14 day regimen of Primaquine should be given under supervision.

Severe malaria

Definition

Severe malaria is a medical emergency. It is defined as *P. falciparum* malaria that is sufficiently serious to be an immediate threat to life and that requires hospitalization. Usually it is a result of delayed, inappropriate or inadequate treatment of uncomplicated malaria.

Pregnant women, young children and severely malnourished patients are specifically at risk of developing severe malaria in Somalia. In high-transmission areas, the risk of severe falciparum malaria developing is greatest among young children, and visitors (of any age) from non-endemic areas. In non-transmission and low-transmission areas the risk is greatest among:

- Non immune travellers returning with undiagnosed malaria infection from any area where *P. falciparum* transmission occurs;
- people of all ages with little or no immunity, particularly during epidemics.

Signs and symptoms

A patient with severe falciparum malaria may present with one or more of the following clinical or laboratory features.

Clinical features

Clinical features include:

- impaired consciousness or unarousable coma not attributable to any other cause in a patient with falciparum malaria;
- prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance (affected children are unable to feed);
- repeated convulsions – more than two episodes in 24 hours;
- deep breathing, respiratory distress (acidotic breathing);
- pulmonary oedema and adult respiratory distress syndrome;
- circulatory collapse or shock, systolic blood pressure <70 mmHg in adults and <50 mmHg in children;

- abnormal spontaneous bleeding;
- jaundice with evidence of other vital organ dysfunction.

Laboratory features

Laboratory features include:

- hypoglycaemia (blood glucose <2.2 mmol/l or <40 mg/dl);
- metabolic acidosis (plasma bicarbonate <15 mmol/l);
- severe normocytic anaemia (haemoglobin <5 g/dl, packed cell volume <15%);
- hyperparasitaemia (>10%)
- haemoglobinuria;
- hyperlactataemia (lactate >5 mmol/l);
- acute kidney injury (serum creatinine >265 µmol/l).

Important: these severe manifestations can occur singly or, more commonly, in combination in the same patient.

Diagnosis

A patient presenting with fever and any of the above-mentioned signs and symptoms is a suspected severe malaria case until laboratory tests results are available for confirmation. They should be treated without delay. Laboratory tests (microscopy or rapid diagnostic tests) will determine if the patient is a confirmed severe malaria case or not.

Management at different levels

Health post level

At the health post level, health workers can identify some important signs and symptoms of severe malaria. After judging the severity of the illness, severe malaria cases should be immediately referred to the hospital level after pre-referral treatment and advice are given. Diagnosis

At this level, generally, a patient should be considered as having severe malaria if one or more of the danger signs or criteria for referral are present and the patient is living in, or has travelled from, a malaria-endemic area.

A patient with one or more of the following conditions should be referred immediately to the nearest health centre or hospital:

- unable to drink (especially important in children)
- convulsions (fits)
- repeated vomiting (vomiting everything)
- passing no urine, very little urine or dark urine
- abnormally sleepy, difficult to wake or confused
- unconscious and unresponsive to pain (coma)
- weak and rapid pulse
- severe anaemia
- yellow eyes (jaundice)
- severe dehydration
- bleeding with no known cause (including vaginal bleeding in pregnancy)
- difficulty breathing
- inability to stand or sit.

These criteria can be found on the poster “Severe malaria: danger signs and criteria for referral”, which should be on the wall in each health post.

Pre-referral treatment

For patients seen at community health posts or by community health workers with one or more of the above signs and symptoms following action should be taken:

- children 6 years and above with severe malaria should be immediately referred to health facility where parenteral treatment is available.
- For children <6 years severe malaria, single dose of rectal artesunate should be given and referred as above. If rectal artesunate is not available, they should also be referred health facility where parenteral treatment is available.

However, as a routine measure, the following should be done before referral of the patient:

- if the patient can swallow, give sugar water, oral rehydration salts (or for babies give expressed breast milk) as they will have low blood sugar;
- encourage the caretaker to undertake sponging during the journey to keep the temperature down;

- record all findings and drugs given on a referral slip and refer the patient to the nearest hospital.

Maternal and child health centre/outpatient department level

At the maternal and child health centre/outpatient department level, health workers can identify some important signs and symptoms of severe malaria. After judging the severity of the illness, severe malaria cases should be immediately referred to the hospital level.

Diagnosis

At this level, generally, a patient should be considered as having severe malaria if one or more of the danger signs or criteria for referral are present and the patient is living in, or has travelled from, a malaria-endemic area.

Patients with the following conditions should be referred immediately to hospital:

- unable to drink (especially important in children)
- convulsions (fits)
- repeated vomiting
- passing no urine, very little urine or dark urine
- abnormally sleepy, difficult to wake or confused
- unconscious and unresponsive to pain (coma)
- weak and rapid pulse
- severe anaemia
- yellow eyes (jaundice)
- severe dehydration
- bleeding with no known cause (including vaginal bleeding in pregnancy)
- difficulty breathing
- unable to stand or sit (>1 year).

Severe malaria should be treated as a life-threatening medical emergency requiring dedicated attention from the most qualified health staff presents in the maternal and child health centre/outpatient department.

Patients seen at the maternal and child health centre/outpatient department level with severe malaria (one or more of the signs and symptoms above) should be given a single pre-

referral dose of artesunate im or artemether im or quinine im and immediately referred to the nearby hospital. However, as a routine measure, the following should be done before referral of the patient:

- if the patient can swallow, give sugar water, oral rehydration salts (or for babies expressed breast milk) as the patient will have low blood sugar;
- encourage the caretaker to undertake sponging during the journey to keep the temperature down;
- record all findings and drugs given on a referral slip and the maternal and child health centre/outpatient department level register and refer the patient to the nearest hospital.

District/regional hospital level

Diagnosis

At this level, a correct diagnosis should be based upon a complete case history, a physical examination and laboratory investigations. Severe falciparum malaria should be diagnosed if there are asexual forms of *P. falciparum* in a blood film from a patient showing any of the following conditions:

- unable to drink (especially important in children)
- convulsions (fits)
- repeated vomiting
- passing no urine, very little urine or dark urine
- abnormally sleepy, difficult to wake or confused
- unconscious and unresponsive to pain (coma)
- weak and rapid pulse
- severe anaemia
- yellow eyes (jaundice)
- severe dehydration
- bleeding with no known cause (including vaginal bleeding in pregnancy)
- difficulty breathing

- unable to stand or sit (>1 year).

Both thick and thin blood films should be examined, or malaria antigen detection by rapid diagnostic testing should be done, to demonstrate the presence of *P. falciparum* asexual parasites. However, it is important to note that waiting for a parasite confirmation must not be allowed to delay the start of treatment unduly; if clinical features strongly suggest severe falciparum malaria, treatment may be started before the reports are available.

General management

All patients with signs of severe malaria must receive immediate treatment. Prompt resuscitation of patients with severe malaria saves lives.

Ten essential steps for the treatment of severe malaria

The ten essential steps for the treatment of severe malaria are:

1. clear the airway and check that the patient is breathing;
2. establish intravenous (IV) access;
3. treat convulsions (see Treatment of convulsions, page 40).
4. take blood for malaria parasites, blood glucose and haemoglobin (urea and electrolytes, blood gas and blood culture are also extremely useful, but are unlikely to be feasible in most hospitals);
5. treat hypoglycaemia (blood glucose <2.2 mmol/l) (see Management of hypoglycaemia, page 43);
6. rapidly assess circulation, hydration and nutritional status, and resuscitate as necessary with normal (0.9%) saline (see page 21);
7. if haemoglobin is <5 g/dl and patient has respiratory distress, transfuse blood;
8. for unconscious patients, insert a nasogastric tube and aspirate stomach contents to prevent aspiration pneumonia (place the patient in the recovery position and perform a lumbar puncture to exclude meningitis).
9. start anti-malarial drug treatment;
10. start antibiotic therapy if needed (see page 35).

More sophisticated monitoring may be useful if complications develop, and will depend on the local availability of equipment, experience and skills.

Nursing care

The management of the patient with severe malaria is as important as chemotherapy and here the nurse has a crucial role to play. The following measures should be undertaken:

- meticulous nursing care should be given to unconscious patients:
 - maintain a clear airway;
 - turn the patient every 2 hours;
 - do not allow the patient to lie in a wet bed;
 - pay particular attention to pressure points and nurse the patient on his or her side to avoid aspiration of fluid;
- aspiration pneumonia is a potentially fatal complication and must be dealt with immediately;
- a careful record of fluid intake and output must be kept, the appearance of black urine noted and specific gravity measured;
- the speed of infusion of fluids should be checked frequently and insertion sites for IV lines should be cleaned at least twice daily with iodine and alcohol;
- temperature, pulse, respiration and blood pressure must be monitored regularly every 4–6 hours for at least the first 48 hours;
- changes in the level of consciousness, occurrence of convulsions or changes in behaviour of the patient must be reported immediately;
- if axillary temperature rises above 38°C, vigorous tepid sponging and fanning must be applied and paracetamol given.

Treatment

The recommended treatments for confirmed severe malaria are described below:

1. Artesunate parenteral (first choice)

- Artesunate 2.4 mg/kg body weight (3.0mg/kg in children less than 20kg) given by IV or intramuscular (IM) injection on admission (time = 0), repeated at 12 hours and 24 hours, then once a day.
 - after at least 24 hours of parenteral treatment and the patient can tolerate oral medication, complete treatment with a full course of artemether+lumefantrine. At least 24 hours of parenteral artesunate (3 doses) should be given irrespective

of the ability to tolerate oral medication or not before switching to oral medication (artemether+lumefantrine).

2. Artemether injectables (second choice)

3. Quinine dihydrochloride (third option)

(a) Intravenous (IV) administration of quinine dihydrochloride should be given as follows:

- Loading dose: 20 mg quinine salt/kg:
 - omit the loading dose if the patient has had an adequate dose of quinine (>40 mg salt/kg) in the previous 2 days;
 - the loading dose should be given as an IV infusion over 4 hours (see annex 3).
- Maintenance dose: 10 mg quinine salt/kg:
 - the maintenance dose must be given every 8 hours from the start of the previous dose;
 - the maintenance dose should be given as an infusion over 4 hours (see below);
 - if IV therapy is still required after 48 hours, the maintenance dose should be reduced to 7 mg salt/kg to avoid the risk of accumulation. This is done programmatically by increasing the timing between each dose from 8hrly to 12hourly;
 - a minimum of three doses of IV quinine should be given before changing to oral treatment (see below).

Quinine can cause hypoglycaemia; therefore blood glucose should therefore be monitored every 4 hours.

After at least 24 hours of parenteral treatment and the patient can tolerate oral medication, complete treatment with a full course of artemether+lumefantrine. At least 24 hours of parenteral artesunate (3 doses) should be given irrespective of the ability to tolerate oral medication or not before switching to oral medication (artemether+lumefantrine).

(b) Intramuscular (IM) administration of quinine dihydrochloride should be given as follows:

- quinine IM should only be given if and when IV administration is not feasible
- quinine IM is administered at the same dose of IV as described above (for dosage and how to reconstitute quinine, see Annex 3);

- a minimum of 24 hours of parenteral treatment (three doses of quinine) should be given before changing to oral treatment (see below);
- once the patient can tolerate oral medication, or after at least 24 hours of parenteral treatment irrespective of the ability to tolerate oral medication or not, complete treatment with a full course of artemether+lumefantrine.

Clinical features and supportive treatment

Table 1 gives an overview of the assessment and treatment of danger signs in severe malaria. In all cases of severe malaria, IV anti-malarial therapy should be started immediately. Any complications can then be dealt with as described on page 37.

Table 1 Overview of the assessment and treatment of danger signs in severe malaria

Signs	Check	If	Treatment
Convulsions	Duration	>5 minutes	Diazepam IV or per rectum
	Blood glucose	<2.2 mmol/l or test not possible	Give 50% dextrose IV
	Malaria slide or RDT	Positive or test not possible	Start artesunate IV
	Lumbar puncture	Evidence of meningitis or lumbar puncture not possible	Start antibiotics for meningitis
Prostration	Circulation:	Any sign positive (shock) <i>and</i> no evidence of severe malnutrition	Start rapid IV fluids and give oxygen if possible
	<ul style="list-style-type: none"> • Capillary refill >3 s • Weak fast pulse • Cold hands 		
	Hydration:		
	<ul style="list-style-type: none"> • Sunken eyes • Lax skin turgor 	Any sign positive (dehydration) <i>and</i> no evidence of severe malnutrition	Start rapid IV fluids or insert nasogastric tube and start oral rehydration solution
	Nutrition:	Any sign positive (severe malnutrition)	Transfer to therapeutic feeding centre if possible
	<ul style="list-style-type: none"> • Visible severe 		

	wasting <i>and/or</i> flaking skin and oedema of both feet		
	Blood glucose	<2.2 mmol/l or test not possible	Give 50% dextrose IV
	Lumbar puncture (if none of the above signs is present)	Evidence of meningitis or lumbar puncture not possible	Start antibiotics for meningitis
	Malaria slide or RDT	Positive or test not possible	Start artesunate IV
Coma	Blood glucose	<2.2 mmol/l or test not possible	Give 50% dextrose IV
	Lumbar puncture (if none of the above signs is present)	Evidence of meningitis or lumbar puncture not possible	Start antibiotics for meningitis
	Malaria slide or RDT	Positive or test not possible	Start artesunate IV
	All comatose patients	–	Insert nasogastric tube and aspirate stomach contents
Respiratory distress	Palmar pallor: • Check Hb	Hb <5 g/dl	Give immediate blood transfusion
	Circulation: • Capillary refill >3 s • Weak fast pulse • Cold hands	Any sign positive (shock) <i>and</i> no evidence of severe malnutrition.	Start rapid IV fluids
	Hydration:	Any sign positive (dehydration) <i>and</i> no	Start rapid IV fluids

• Sunken eyes	evidence of severe malnutrition	
• Lax skin turgor		
Listen to chest	Chest crackles	Verify pulmonary oedema, start antibiotics for pneumonia

Hb, haemoglobin; IV, intravenous; RDT, rapid diagnostic test.

Complications/severe conditions

Cerebral malaria

Clinical features in adults

The patient with cerebral malaria is comatose, the depth of consciousness being variable (for assessment of coma, see Annex 5). Convulsions are common in both adults and children. Retinal bleeding is associated with a poor prognosis in adults; papilloedema is rare. Varieties of transient abnormalities of eye movement have been noted. Fixed jaw closure and tooth grinding (bruxism) are common. Pouting may occur or a pout reflex may be elicited by stroking the sides of the mouth. Mild neck stiffness occurs but neck rigidity and photophobia are absent. The commonest neurological picture in adults is one of a symmetrical upper motor neuron lesion. The duration of coma varies from about 6 to 96 hours in adults.

Motor abnormalities such as decerebrate rigidity, decorticate rigidity (arms flexed and legs stretched), and opisthotonos occur. The opening pressure at lumbar puncture is usually normal in adults but may be elevated; the cerebrospinal fluid is clear, with fewer than 10 white cells per microlitre (μl); the protein is raised, as is the cerebrospinal fluid lactic acid concentration. Abdominal reflexes are invariably absent. This is a useful sign for distinguishing hysterical adult patients with fevers of other causes, in whom these reflexes are usually brisk.

Management of cerebral malaria in adults

The patient with cerebral malaria should be managed as follows:

- the comatose patient should be given meticulous nursing care;
- insert a urethral catheter using a sterile technique, unless the patient is anuric;
- keep an accurate record of fluid intake and output.;
- monitor and record the level of consciousness using the Glasgow coma scale (Annex 5), temperature, respiratory rate, blood pressure and vital signs;
- treat convulsions (see page 35).

Clinical features in children

Many of the clinical features of severe malaria described above also occur in children. Only certain additional points are highlighted here. The commonest and most important complications of *P. falciparum* infection in children are cerebral malaria and severe anaemia.

- The earliest symptom of cerebral malaria in children is usually fever (37.5°C–41°C), followed by failure to eat or drink. Vomiting and coughing are common; diarrhoea is unusual.
- The history of symptoms preceding coma may be very brief; commonly 1–2 days.
- A child who loses consciousness after a febrile convulsion should not be considered to have cerebral malaria unless coma persists for more than 0.5 hours after the convulsion.
- The depth of coma may be assessed according to the Blantyre coma scale (Annex 5), by observing the response to standard vocal or painful stimuli (rub knuckles on child's sternum. If no response, apply firm pressure on thumbnail bed with horizontal pencil).
- Always exclude or treat hypoglycaemia (see page 43).
- Convulsions are common before or after the onset of coma. They are significantly associated with morbidity and sequelae.
- In some children the breathing is laboured and noisy; in others, deep breathing with a clear chest suggests acidosis.
- A few children have cold, clammy skin, with a core-to-skin temperature difference of 10°C. Some of these patients are in a state of shock with systolic blood pressure <50 mmHg.
- In patients in profound coma, corneal reflexes or "doll's eye" movements may be absent.
- In some children, extreme opisthotonos is present which may lead to a mistaken diagnosis of tetanus or meningitis.
- Cerebral spinal fluid opening pressure is variable; it is raised more frequently than in adults and is sometimes very high.
- Leukocytosis (increased white blood cells) is not unusual in severe disease and does not necessarily imply an associated bacterial infection (this is also true in adults).

- A proportion of children (about 10%) who survive cerebral malaria have neurological sequelae that persist into the convalescent period. Sequelae may take the form of hemiparesis (mild paralysis of half of the body), cerebellar ataxia (loss of balance while walking), cortical blindness, severe hypotonia (less muscle tone), mental retardation, generalized spasticity, or aphasia.

Management in children

Management is similar to that in adults. Specific aspects are re-emphasized here.

- Parents/relatives should be questioned about:
 - history of residence or travel
 - previous treatment with antimalarials or other drugs
 - recent fluid intake and urine output
 - recent or past history of convulsions.
- A rapid initial examination should be carried out to assess:
 - hydration
 - anaemia
 - pulmonary oedema
 - level of consciousness
 - hyperpyrexia (Annex 5).
- Immediate tests must include:
 - thick and thin blood films
 - haematocrit
 - finger-prick blood glucose
 - lumbar puncture.
- If parasitological confirmation is likely to take more than 1 hour, treatment should be started before the diagnosis is confirmed.
- If the child has a convulsion, this should be treated with diazepam 0.15 mg/kg of body weight. It can be used intravenously but with very slow administration and under very close monitoring. Diazepam (0.5–1 mg/kg) could be also safely administered intrarectally.

- Any child with convulsions should be examined for hyperpyrexia and hypoglycaemia and given appropriate treatment.
- Simple practical manoeuvres, such as tepid sponging and fanning, should be employed to try to keep the rectal temperature below 39°C. Relatives can be instructed to do this.
- Paracetamol, 15 mg/kg of body weight, may also be given as an antipyretic.

Avoid the following in the treatment of cerebral malaria, in both adults and children:

- corticosteroids
- other anti-inflammatory agents
- other agents given for cerebral oedema (urea, invert sugar)
- low-molecular-weight dextran
- adrenaline (epinephrine)
- heparin
- epoprostenol (prostacyclin)
- pentoxifylline (oxpentifylline)
- hyperbaric oxygen
- Cuckisoirub (cyclosporin A).

Treatment of convulsions

Convulsions should be treated as follows:

- maintain the airway;
- turn the patient on his or her side to reduce risk of aspiration;
- do not attempt to force anything into the patient's mouth;
- check blood glucose and treat if <2.2 mmol/l (see page 43);
- treat with:
 - diazepam, 0.3 mg/kg (up to a maximum 10 mg), as a slow IV injection over 2 minutes; or

- diazepam, 0.5 mg/kg per rectum, administered by inserting a 1-ml syringe (without a needle) into the rectum; or
- paraldehyde, 0.2 ml/kg (up to a maximum of 10 ml) by deep IM injection into the anterior thigh; or
- paraldehyde, 0.4 ml/kg per rectum.
- if the patient continues to convulse, give further doses of diazepam or paraldehyde every 10 minutes (up to a maximum of three doses of either drug);
- treat patients who have multiple (three or more) or prolonged (lasting 30 minutes or more) convulsions with a loading dose of IM phenobarbital, 10–15 mg/kg, but extreme vigilance is necessary because these two drugs (phenobarbitone and diazepam) in combination may cause respiratory arrest - monitor breathing continuously and be ready to give assisted ventilation, by bag-and-mask if a manual ventilator is not available.

Anaemia

Anaemia is common in severe malaria. The rate of development and degree of anaemia depend on the severity and duration of parasitaemia. In some children, repeated untreated episodes of otherwise uncomplicated malaria may lead to anaemia. In other children, severe anaemia may develop rapidly in association with hyperparasitaemia. In these cases, acute destruction of parasitized red cells is responsible.

Children with severe anaemia may present with tachycardia and dyspnoea. Anaemia may contribute to:

- cerebral signs (confusion, restlessness, coma and retinal haemorrhages);
- cardiopulmonary signs (gallop rhythm, cardiac failure, pulmonary oedema);
- hepatomegaly (enlargement of liver).

Anaemia is often associated with secondary bacterial infection, retinal haemorrhage and pregnancy in adults.

Management in adults

- If the haematocrit packed cell volume falls below 20% or the haemoglobin concentration falls below 7 g/dl, give a transfusion of pathogen-free compatible fresh blood or packed cells (stored bank blood may be used if fresh blood is not available). In areas where HIV is prevalent and facilities for screening are inadequate, the general condition of the patient (e.g. shock, cardiac failure) and the response to oxygen and colloid infusion should be the guiding principles rather than the haematocrit alone.

- Provided that the patient's renal function is adequate, give small IV doses of furosemide 20 mg during the blood transfusion as necessary to avoid circulatory overload.
- 500 ml of blood should be transfused over 3–4 hours.
- Remember to include the volume of transfused cells or blood in calculations of fluid balance.

Management in children

- The need for blood transfusion must be addressed with great care in each individual child. Not only the level of the haematocrit or haemoglobin concentration but also the density of parasitaemia and the clinical condition of the patient must be taken into account.
- In general and with the proviso mentioned above, a haematocrit of less than 15% or haemoglobin <5 g/dl in a normally hydrated child is an indication for blood transfusion (20 ml/kg over 3–4 hours). In children with respiratory distress (mostly due to acidosis), an initial transfusion is required with the utmost urgency (10 ml of packed cells or 20 ml of whole blood per kg of body weight, the first 10 ml/kg over 30 minutes, the second 10 ml/kg over 2 hours).
- A diuretic is usually not indicated, as many of these children are hypovolaemic. If there is volume overload, furosemide, 1–2 mg/kg of body weight up to a maximum of 20 mg, may be given intravenously.

Renal failure

Renal failure as a complication of malaria is virtually confined to adults. There is a rise in serum creatinine and urea, oliguria (scanty urination, <4 ml/kg per hour in adults and <5 ml/kg per hour in children) and eventually anuria (no urination) due to acute tubular necrosis. Acute renal failure is usually reversible. In children, renal failure is rare and poor urine output is often secondary to dehydration.

Management in adults

- Patients must be catheterized so that urine output can be measured accurately.
- Exclude dehydration or shock (hypovolaemia) by clinical examination, including measurement of jugular or central venous pressure, and blood pressure drop between the patient lying supine and when propped up to 45°. Give a test infusion of 1000 ml of normal saline (0.9%).

- Once dehydration is corrected, give a single dose of furosemide, 40 mg IV. If oliguria persists, increase furosemide dose in a stepwise fashion at 60-minute intervals to 100 mg, 200 mg (1-hour infusion), and finally 400 mg (2-hour infusion).
- If urine output remains <0.4 ml/kg per hour, assume renal failure is established and restrict fluids to approximately 1000 ml/day plus urine output.
- Peritoneal dialysis should not be undertaken lightly. If possible, refer the patient to a dialysis unit or centre.

Management in children

- Patients must be catheterized so that urine output can be measured accurately.
- Exclude dehydration or shock (hypovolaemia) by clinical examination, including measurement of jugular or central venous pressure, and blood pressure drop between the patient lying supine and when propped up to 45°. Give a test infusion of 20 ml/kg of normal saline (0.9%).
- Once dehydration is corrected, give a single dose of furosemide, 3 mg/kg IV.
- If urine output remains <0.5 ml/kg per hour, assume renal failure is established and restrict fluids to approximately 30 ml/kg per day plus urine output.
- Peritoneal dialysis should not be undertaken lightly. If possible, refer the patient to a dialysis unit or centre.

Hypoglycaemia

Clinical features in adults

Hypoglycaemia (blood glucose <2.2 mmol/l) is an important manifestation of falciparum malaria. It occurs in three different groups of patients, which may overlap:

- patients with severe disease, especially young children;
- patients treated with quinine, as a result of a quinine-induced hyperinsulinaemia;
- pregnant women, either on admission or following quinine treatment.

In conscious patients, hypoglycaemia may present with classic symptoms of anxiety, sweating, dilatation of the pupils, breathlessness, laboured and noisy breathing, oliguria, a feeling of coldness, tachycardia and light-headedness. This clinical picture may develop into deteriorating consciousness, generalized convulsions, extensor posturing, shock and coma.

The diagnosis is easily overlooked because all these clinical features also occur in severe malaria itself. Deterioration in the level of consciousness may be the only sign. If

hypoglycaemia is suspected clinically in an unconscious person and it is not possible to check the blood glucose, give a presumptive infusion of glucose 50% as described below.

Management in adults

- If hypoglycaemia is detected by blood testing or is suspected on clinical grounds, insert an IV line and give 50% glucose, 50 ml by IV bolus injection.
- Follow with an IV infusion of 5% or 10% glucose.
- Continue to monitor blood glucose levels every 15 minutes (using a “stix” method if available, or clinically and biochemically if not) in order to regulate the glucose infusion.
- If blood glucose is still <2.2 mmol/l, repeat glucose infusion as above.
- If it is not possible to insert an IV line and the patient is unconscious, give 1 ml/kg 50% dextrose via nasogastric tube.
- Give oral sugar solution and food once the patient regains consciousness.

Clinical features in children

Hypoglycaemia is particularly common in young children (under 3 years), in those with convulsions or hyperparasitaemia, and in patients with profound coma. It is easily overlooked clinically because the manifestations may be similar to those of cerebral malaria.

Management in children

- Unconscious children should be given glucose regularly to prevent starvation hypoglycaemia. It is most conveniently provided as 5% dextrose in water infusion but if this is likely to lead to fluid overload, smaller volumes of more concentrated glucose may be given at regular intervals.
- If hypoglycaemia occurs, it should be treated with 50% glucose, up to 1.0 ml/kg, in an equal volume of any infusion fluid, followed by a slow IV infusion of 10% glucose to prevent recurrence of hypoglycaemia.
- Monitoring of blood glucose level should continue (see above) even after apparent recovery, since hypoglycaemia may recur.
- Give breast milk or sugar solution once the patient regains consciousness.

Fluid, electrolyte and acid–base disturbances

Clinical features in adults

Patients with severe falciparum malaria often show the following on admission:

- clinical evidence of hypovolaemia (low jugular venous pressure, postural hypotension, and oliguria with high urine specific gravity);
- clinical signs of dehydration (reduced ocular tension and decreased skin turgor).

Acidotic breathing (hyperventilation) may develop in severely ill patients who are shocked, hypoglycaemic, hyperparasitaemic or in renal failure. Lactic acidosis is a common complication and both blood and cerebrospinal fluid lactic acid concentrations are raised. Perfusion is improved by correcting hypovolaemia.

Management in adults

- Look for evidence of dehydration and hypovolaemia:
 - reduced ocular tension;
 - reduced skin turgor;
 - cool extremities;
 - postural drop in blood pressure (as the patient is propped up from the lying-down position to 45°);
 - reduced peripheral venous filling;
 - low jugular venous pressure;
 - reduced urine output;
 - high urine specific gravity;
 - urine sodium concentration less than 20 mmol/l.
- If there is evidence of dehydration, give modest volumes of isotonic fluids (0.9% saline or 5% dextrose) by IV infusion, but avoid fluid overload:
 - check if the patient does not have severe malnutrition (patients with severe malnutrition should not be given large volumes of IV fluids);
 - infuse 1000 ml of normal saline over 15 minutes;
 - reassess and give a second 1000 ml infusion if no improvement;
 - if after the third infusion there is no improvement, give 20 ml/kg of blood over 60 minutes;
 - give presumptive treatment with antibiotics to all patients who are in shock.
- Monitor blood pressure, urine volume (every hour).

- Improve oxygenation:
 - clear airway;
 - increase concentration of inspired oxygen;
 - support ventilation artificially, if necessary.

Clinical features in children

The best clinical indications of mild to moderate dehydration in children are:

- decreased peripheral perfusion
- deep (acidotic) breathing
- decreased skin elasticity
- raised blood urea (>6.5 mmol/l)
- increased thirst
- loss of about 3%–4% of total body weight
- evidence of metabolic acidosis.

In children presenting with oliguria and dehydration, examination of urine usually reveals a high specific gravity, low urinary sodium and normal urinary sediment, indicating simple dehydration rather than renal failure, which is rare in children.

Management in children

- Careful rehydration with isotonic saline is mandatory, with frequent examination of the jugular venous pressure, blood pressure and chest:
 - check if the patient does not have severe malnutrition – patients with severe malnutrition should not be given large volumes of IV fluids;
 - infuse 20 ml/kg of normal saline over 15 minutes;
 - reassess and give a second 20 ml/kg infusion if no improvement;
 - if after the third infusion there is no improvement, give 20 ml/kg of blood over 60 minutes;
 - give presumptive treatment with antibiotics to all patients who are in shock.
- Where facilities for monitoring and maintenance of adequate sterility exist, fluid balance may be adjusted in accordance with direct measurement of the central venous pressure through a central venous catheter.

- If, after careful rehydration, urine output over 24 hours is less than 4 ml/kg of body weight, furosemide can be given intravenously, initially at 2 mg/kg of body weight, then doubled at hourly intervals to a maximum of 8 mg/kg of body weight (given over 15 minutes).

Pulmonary oedema

Pulmonary oedema is a grave complication of severe malaria, with a high mortality (over 80%). Pulmonary may appear several days after treatment has been started and at a time when the patient's general condition is improving and the peripheral parasitaemia is diminishing. It must be differentiated from iatrogenically produced pulmonary oedema resulting from fluid overload. Hyperparasitaemia, renal failure and pregnancy are often associated, as well as hypoglycaemia and metabolic acidosis. The first indication of impending pulmonary oedema is an increase in the respiratory rate, which precedes the development of other chest signs. Check for crackles on auscultation, and hepatomegaly.

Hypoxia may cause convulsions and deterioration in the level of consciousness and the patient may die within a few hours.

Management

- Keep patient upright; raise the head of the bed or lower the foot of the bed.
- Give a high concentration of oxygen by any convenient method available, including mechanical ventilation.
- Give the patient a diuretic, such as furosemide 40 mg (1 mg/kg) by IV injection. If there is no response, increase the dose progressively to a maximum of 200 mg.
- In well-equipped intensive care units, mechanical ventilation with positive end expiratory pressure, a wide range of vasoactive drugs and haemodynamic monitoring will be available.
- If there is overhydration/fluid overload:
 - stop all IV fluids;
 - use haemofiltration immediately, if available;
 - if there is no improvement, withdraw 250 ml of blood initially by venesection into a blood transfusion donor bag so that it can be given back to the patient later.

Circulatory collapse ("algid malaria")

Some patients are admitted in a state of collapse with:

- systolic blood pressure less than 80 mmHg in the supine position (less than 50 mmHg in children);
- a cold, clammy, cyanotic skin;
- constricted peripheral veins;
- rapid feeble pulse.

Circulatory collapse is also seen in patients with pulmonary oedema or metabolic acidosis, and following massive gastrointestinal haemorrhage. Dehydration with hypovolaemia may also contribute to hypotension.

Possible sites of associated infection should be sought, for example lung, urinary tract (especially if there is an indwelling catheter), meningitis, IV injection sites and IV lines.

Management

- Correct hypovolaemia with an appropriate plasma expander (fresh blood, plasma, polygeline or dextran 70). If these are not available give isotonic saline.
- Take a blood culture (where possible) and start patient on broad-spectrum antibiotics immediately (e.g. combined treatment with benzylpenicillin and gentamicin).
- Once the results of blood culture and sensitivity testing are available, give the appropriate antibiotic.
- Maintain central venous pressure between 0 cm H₂O and 5 cm H₂O (if hypotension persists dopamine may be given through a central line).

Spontaneous bleeding and disseminated intravascular coagulation

Bleeding gums, epistaxis, petechiae and subconjunctival haemorrhages may occur. Disseminated intravascular coagulation, complicated by clinically significant bleeding (e.g. haematemesis or melaena), occurs in fewer than 10% of patients; it seems to occur more often in non-immune patients. Thrombocytopenia is common, and is not related to other measures of coagulation or to plasma fibrinogen concentrations; in most cases it is unaccompanied by bleeding. The platelet count usually returns to normal after successful treatment of the malaria.

Management

- Transfuse fresh blood, clotting factors or platelets as required.
- Give vitamin K, 10 mg, by slow IV injection.

Hyperpyrexia

Hyperpyrexia is more common in children and is associated with convulsions, delirium and coma. In visitors not acclimatized to living in hot countries, it must be differentiated from heat stroke. Sustained very high body temperatures (42°C and above), rarely seen in malaria, may cause permanent, severe neurological sequelae. There is evidence that high body temperature in pregnant women contributes to fetal distress.

Management in adults

- Monitor temperature frequently.
- If the axillary temperature is above 39°C, give 1 g paracetamol orally in addition to fanning and tepid sponging.

Management in children

- Monitor temperature frequently.
- If axillary temperature is above 39°C, apply vigorous tepid sponging and fanning, and give paracetamol, 15 mg/kg of body weight by mouth, suppository or nasogastric tube.

Hyperparasitaemia

In general, and especially in non-immune subjects, high parasite densities (above 10% infected RBCs in thin blood film or $>250\,000/\mu\text{l}$ and peripheral schizontaemia) are associated with severe disease. However, in hyperendemic areas, partially immune children can tolerate surprisingly high densities (20%–30%), often without clinical symptoms.

Management

- An initial dose of parenteral anti-malarial therapy should be given immediately, even if the patient can take medication by mouth.

Malarial haemoglobinuria

Patients with glucose-6-phosphate dehydrogenase deficiency and some other erythrocyte enzyme deficiencies may develop vascular haemolysis and haemoglobinuria when treated with oxidant drugs such as primaquine, even in the absence of malaria.

Malarial haemoglobinuria (“black water fever”) is uncommon and usually presents in adults as severe disease with anaemia and renal failure.

Management

- Continue appropriate anti-malarial treatment if parasitaemia is present.
- Transfuse fresh blood to maintain haematocrit is $> 15\%$ or Hb $> 5\text{g/dl}$.

- Monitor jugular or central venous pressure to avoid fluid overload and hypovolaemia.
- If oliguria develops and blood urea and serum creatinine levels rise, peritoneal dialysis or haemodialysis may be required.

Common errors in diagnosis

Common errors in diagnosis of severe malaria include:

- failure to do a malarial blood film;
- failure to take a travel history;
- misjudgement of severity;
- faulty parasitological diagnosis and laboratory management;
- failure to identify *P. falciparum* in a mixed infection with other species;
- missed hypoglycaemia;
- failure to carry out an ophthalmoscopic examination for the presence of retinal haemorrhages (bleeding inside the retina – a vital part in the eyeball);
- Failure to recognize respiratory distress;
- misdiagnosis (e.g. influenza, viral encephalitis, hepatitis, scrub typhus, etc.).

Common errors in management

Common errors in management of severe malaria include:

- inadequate nursing care;
- errors of fluid and electrolyte replacement;
- delay in starting anti-malarial therapy;
- use of an inappropriate drug
 - ineffective anti-malarial medicine
 - unjustified withholding of an anti-malarial treatment
 - dosage of anti-malarial medicine not correctly calculated
 - inappropriate route of administration
 - unjustified cessation of anti-malarial treatment

- failure to adjust the dose to prevent cumulative effects of anti-malarial medicines
 - failure to switch patients from parenteral to oral therapy as soon as they can take oral medication
 - unnecessary continuation of chemotherapy beyond the recommended length of treatment
 - failure to review anti-malarial treatment in a patient whose condition is deteriorating
- failure to elicit a history of recent of medicines;
 - failure to identify or treat metabolic acidosis;
 - unnecessary endotracheal intubation;delayed endotracheal intubation (when it is indicated and possible)
 - failure to prevent or control convulsions;
 - failure to recognize minor (“subtle”) convulsions;
 - failure to recognize and treat severe anaemia;
 - use of potentially dangerous ancillary therapies;
 - delay in considering obstetrical (related to child birth) interventions in late pregnancy;
 - failure to recognize and manage pulmonary oedema, aspiration pneumonia (pneumonia caused by inhaling fluid into lungs) and metabolic acidosis;
 - delay in starting peritoneal dialysis or haemodialysis (method of blood purification to remove accumulated toxic materials from the blood);
 - failure to review anti-malarial treatment in a patient whose condition is deteriorating.

Malaria in special groups

Pregnant women

Plasmodium falciparum is an important cause of maternal and perinatal morbidity and mortality. The clinical effects of falciparum malaria depend to a large extent on the immune status of the woman, which is determined by her previous exposure to malaria and on her parity.

In pregnant women from areas of low malaria transmission, who have little pre-existing immunity, malaria usually presents as an acute illness with detectable peripheral parasitaemia. Compared with non-pregnant women, non-immune pregnant women with *P. falciparum* malaria are two to three times more likely to develop severe disease and approximately three times more likely to die. Women in this group are also at increased risk of miscarriage, stillbirth and neonatal death. Pregnant women often present with life-threatening symptomatic disease and the clinical course may be complicated by hyperpyrexia (very high fever), hypoglycaemia, severe haemolytic anaemia, pulmonary oedema and cerebral malaria.

Pregnant women living in areas of moderate to high transmission, who have a degree of pre-existing immunity, often develop malaria with few, if any, symptoms and few, if any, parasites in the peripheral blood on microscopy, although the placenta may be heavily infected. A rapid diagnostic test may give a positive result and the woman should be treated. The main maternal effect of malaria infection in these circumstances is anaemia, which is often severe and may be life threatening when not recognized and treated effectively. Pregnancy reduces the degree of partial immunity to *P. falciparum* that most women from settings with moderate to high transmission will have acquired during childhood and subsequently. This effect is particularly acute in women in their first and second pregnancies and HIV-positive women during all pregnancies, who are thus at increased risk of malaria infection.

The main effect on the baby is low birth weight, a major risk factor for infant death.

Intermittent preventive treatment

Non-immune pregnant women

At present, there are no data on the efficacy of intermittent preventive treatment for preventing the adverse consequences of malaria in pregnant women with no pre-existing immunity to the disease. There is thus no evidence to support the use of intermittent preventive treatment in low-transmission areas and during epidemics. In these situations, the focus should be on case management and use of insecticide-treated nets.

Semi-immune pregnant women

Intermittent preventive treatment with sulfadoxine–pyrimethamine, provided through the maternal and child health centre, can reduce the incidence of severe anaemia and low birth weight in semi-immune women in areas of moderate to high *P. falciparum* transmission. Intermittent preventive treatment is an effective, safe and operationally feasible strategy for reducing the burden of malaria among semi-immune pregnant women, even in situations where the health infrastructure is weak. Intermittent preventive treatment involves the administration of a full treatment dose of sulfadoxine–pyrimethamine, at every scheduled antinatal visit, from the second trimester one month apart until delivery. At least 3 doses of IPT SP should be given during pregnancy. Intermittent preventive treatment is given whether or not malaria parasites are detected in the peripheral blood film.

Prevention and treatment of anaemia in pregnancy

Anaemia is a common and potentially dangerous complication of pregnancy. Therefore, prevention of anaemia should be a priority in all health facilities in Somalia dealing with pregnant women:

- ferrous sulfate, 200 mg (equivalent to 60 mg elemental iron), plus folic acid, 0.25 mg, should be given daily throughout pregnancy;
- in areas of moderate and high malaria transmission, where there is a high risk of asymptomatic malaria infection in pregnancy, pregnant women should be given intermittent preventive treatment with sulfadoxine–pyrimethamine , once in the second and once in the third trimester (see above);
- pregnant women who are anaemic (haemoglobin 10 g/dl or below) should be given ferrous sulfate, 200 mg (equivalent to 60 mg elemental iron) three times daily, and folic acid, 0.25 mg three times daily, for 2 months.
- presumptive treatment for intestinal worms (using a single 500-mg dose of mebendazole or 400-mg dose of albendazole) can be given once in the second or third trimester of pregnancy (note: these drugs should not be given in the first trimester).

Management of uncomplicated malaria in pregnancy

All pregnant women with symptomatic malaria should receive urgent treatment. Quinine should be used safely for treatment in the first trimester, and artemether+lumefantrine during the second and third trimesters:

- first trimester: oral quinine (for dosage, see Annex 3); if quinine is not available artemether+lumefantrine can be given.

- second and third trimester: artemether+lumefantrine (for dosage, see Annex 3).

Note: artemisinin derivatives should not be withheld in any trimester if they are considered life saving for the mother.

Management of severe malaria in pregnancy

Pregnant women with severe malaria should receive the highest level of inpatient medical care possible because of the high risk of maternal and perinatal mortality. Hypoglycaemia, acute pulmonary oedema, hyperpyrexia, postpartum haemorrhage, premature delivery and perinatal death are particular risks.

Anti-malarial drug treatment

Severe malaria in pregnant women should be treated with IV or IM artesunate (for dosage, see Annex 3) in all three trimesters of pregnancy..

Presentation and treatment of complications

Hypoglycaemia

Hypoglycaemia is a significant risk for all pregnant women with malaria. It may occur during the clinical course of uncomplicated malaria and may be asymptomatic, or may present with sweating, confusion, agitated behaviour, drowsiness, convulsions or loss of consciousness. Women in the second and third trimesters of pregnancy who are undergoing treatment with IV quinine are at particularly high risk, and this risk persists for several days postpartum. In patients with cerebral malaria, hypoglycaemia may be asymptomatic or may cause deterioration in the level of consciousness, extensor posturing or convulsions. Differential diagnoses include sepsis, meningitis and eclampsia. Hypoglycaemia may also recur after correction with IV glucose.

For these reasons, regular monitoring (at least 4-hourly) of the blood glucose of all pregnant women with severe malaria is extremely important, particularly if they are receiving treatment with quinine. Blood glucose must be checked if there is any change in the level of consciousness and immediate treatment must be given if it is <2.2 mmol/l (for treatment of hypoglycaemia, see page 43).

Acute pulmonary oedema

Acute pulmonary oedema commonly develops immediately after delivery, but may occur at any time during the first week postpartum. Severe anaemia and the increase in blood volume and peripheral resistance that follows placental separation may precipitate acute pulmonary oedema and heart failure. This is a medical emergency that requires immediate treatment:

- pregnant women are particularly prone to pulmonary oedema, especially during labour and immediately after delivery;

- check for increased respiratory rate, chest signs (crackles on auscultation) and hepatomegaly;
- if pulmonary oedema is suspected, position the patient upright, give oxygen, stop IV fluids and give IV furosemide, 1 mg/kg;
- if pulmonary oedema is associated with blood transfusion, give furosemide, 1 mg/kg IV, and restart transfusion at a slower rate.

Severe anaemia

Blood transfusion is indicated in the following situations:

- women of ≥ 36 weeks' gestation with haemoglobin < 7 g/dl, packed cell volume $< 21\%$ (even if asymptomatic, as women who are severely anaemic during labour are at increased risk of dying);
- women of < 36 weeks' gestation with haemoglobin < 7 g/dl plus symptoms (severe lethargy, prostration, breathlessness);
- women of < 36 weeks' gestation with haemoglobin < 5 g/dl (packed cell volume $< 15\%$).

Management of blood transfusion is as follows:

- transfuse 500 ml blood (packed red cells ideally) slowly over 4–6 hours;
- furosemide, 40 mg IV, should be given halfway through the transfusion.

Transfusion should be avoided in the third stage of labour because of the risk of fluid overload (pulmonary oedema) associated with placental separation. It is essential to ensure that the blood supply is "safe". Local laboratory facilities must therefore be able to perform compatibility testing (cross-matching) and screening for HIV, malaria and, if possible, hepatitis B. If suitable donors without malaria infection cannot be found, the blood should be administered with an anti-malarial treatment.

Malnourished persons

Severe acute malnutrition

Diagnosis

All patients with severe malnutrition ($< 70\%$ of median weight-for-height, or z-score less than -3 standard deviations (< -3 SD)) may have asymptomatic malaria infection and should therefore be screened for malaria using microscopy or rapid diagnostic tests on admission to a therapeutic feeding centre and weekly thereafter until discharge. Once a patient has tested positive for malaria, further weekly screening can be done only with microscopy.

Treatment

Uncomplicated malaria

- *First-line treatment:* artemether+lumefantrine (for dosage, see Annex 3). The absorption and bioavailability of several anti-malarial drugs can be significantly impaired in patients with severe malnutrition. Increasing anti-malarial drug bioavailability may reduce the risk of treatment failure due to poor drug absorption. All oral anti-malarial drugs should be administered together with food, as this helps to increase absorption.
- *Second-line treatment:* dihydroartemisinin+piperazine. This should only be given following parasitological confirmation of malaria treatment failure. If the facility does not have the capacity for confirming malaria, the patients with suspected treatment failure should be referred to such facilities with parasitological confirmatory capacity.

Severe malaria

Parenteral artesunate is indicated for the treatment of severe malaria. In therapeutic feeding centres (especially during emergencies), IV or IM artesunate should be given. In places where parenteral administration is not feasible, a single dose of artesunate suppository (for dosage, see Annex 3) should be given and the patient immediately referred to the nearest hospital. Rectal artesunate can also be used for the treatment of malaria in severely malnourished children, especially when the child is vomiting (but is without severe diarrhoea).

Moderate acute malnutrition

For moderately malnourished children (<80% of median weight-for-height, or z-score less than -2SD) recommendations are the same as for non-malnourished children as detailed under uncomplicated and severe malaria sections (page 55).

Patients co-infected with HIV

Currently there is insufficient information to modify the malaria treatment recommendations for patients with HIV/AIDS.

Annex 1. Malaria Morbidity and Mortality Data

Year	Total tested	Total Positive	Positivity Rate	Malaria Incidence / 1000 Population	Total Malaria Mortality	Mortality Rate / 100,000 Population
2011	23213	10755	46%	0.97	Not Collected	N/A
2012	46943	6817	15%	0.60	10	0.09
2013	70163	7407	11%	0.62	23	0.19
2014	76974	11001	14%	0.89	14	0.11
2015	88139	17913	20%	1.41	2	0.02
5yr Range Average	61086	10779	21%	0.90	12.25	0.10

Annex 2 Epidemiological profile per zone in Somalia

	Somaliland	Puntland	Central zone	Southern zone
Epidemic potential	High	High	Moderate	Moderate–low
Populations at risk	All age groups	All age groups	All age groups, but particularly pregnant women and children under 5 years	Pregnant women and children under 5 years
Mosquito vectors (<i>Anopheles</i>)	<i>An arabiensis</i>	<i>An arabiensis</i>	<i>An. arabiensis</i> <i>An. funestus</i>	<i>An. arabiensis</i> <i>An. funestus</i>
<i>Plasmodium</i> species (in order of assumed prevalence)	<i>P. falciparum</i> <i>P. vivax</i> <i>P. malariae</i>	<i>P. falciparum</i> <i>P. vivax</i> <i>P. malariae</i>	<i>P. falciparum</i> <i>P. vivax</i> <i>P. malariae</i>	<i>P. falciparum</i> <i>P. vivax</i> <i>P. malariae</i>

Annex 3 Dosage charts, with side-effects

Artemether–lumefantrine (Coartem®)

A six-dose regimen of artemether–lumefantrine is administered twice a day for 3 days.

- Each tablet contains a combination of 20 mg artemether and 120 mg lumefantrine.

Body weight (kg)	Number of tablets of artemether–lumefantrine					
	Day 0		Day 1		Day 2	
	1st dose	2nd dose	3rd dose	4th dose	5th dose	6th dose
5–<15	1	1	1	1	1	1
15–<25	2	2	2	2	2	2
25–<35	3	3	3	3	3	3
≥35	4	4	4	4	4	4

- Each tablet contains a combination of 40 mg artemether and 240 mg lumefantrine

Body weight (kg)	Number of tablets of artemether–lumefantrine					
	Day 0		Day 1		Day 2	
	1st dose	2nd dose	3rd dose	4th dose	5th dose	6th dose
5–<15	½	½	½	½	½	½
15–<25	1	1	1	1	1	1
25–<35	1 ½	1 ½	1 ½	1 ½	1 ½	1 ½
≥35	2	2	2	2	2	2

Dihydroartemisinin+piperazine (40/320)

Body weight (kg)	Dihydroartemisinin+ Piperazine dose (mg)	Day 0 Tablets	Day 1 Tablets	Day 2 Tablets
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5 to <8	20+160	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$
8 to < 11	30+240	$\frac{3}{4}$	$\frac{3}{4}$	$\frac{3}{4}$
11 to <17	40+320	1	1	1
17 to <25	60+480	1 $\frac{1}{2}$	1 $\frac{1}{2}$	1 $\frac{1}{2}$
25 to <36	80+640	2	2	2
36 - <60	120+960	3	3	3
60 to <80	160+1280	4	4	4

Quinine (300 mg salt tablets)

Body weight(kg)	Number of tablets (300 mg tablet) 3 times/day (every 8 hours)						
	1st dose	2nd dose	3rd dose	4th dose	5th dose	6th dose	7th dose
7–11	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$
12–23	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$
24–37	1	1	1	1	1	1	1
38–52	1 $\frac{1}{2}$	1 $\frac{1}{2}$	1 $\frac{1}{2}$	1 $\frac{1}{2}$	1 $\frac{1}{2}$	1 $\frac{1}{2}$	1 $\frac{1}{2}$
≥53	2	2	2	2	2	2	2

Quinine dihydrochloride (600 mg salt/2 ml) intravenous (IV)

See page 34.

Quinine dihydrochloride (600 mg salt/2 ml) intramuscular (IM)

Dosage

The dosage is 10 mg salt/kg every 8 hours (start with loading dose of 20 mg/kg for severe malaria). The dose should be divided into halves and injected into the upper anterior thigh.

Total injection volume (ml)	Normal saline or distilled water dilution (ml)	Quinine for injection (ml)	Body weight (kg)	Age
1	0.8	0.2	5–6	<4 month
1.5	1.2	0.3	7–10	4–11 years
2	1.6	0.4	11–14	1–2 years
3	2.4	0.6	15–18	3–4 years
4	3.2	0.8	19–24	5–7 years
6	4.9	1.1	25–35	8–10 years
7	5.7	1.3	36–50	11–13 years
	Add distilled water 1/5th quinine + 4/5th H ₂ O	Calculate dose	Take weight	>13 years

- IM quinine may cause sterile abscesses and should be given only when IV therapy is not possible (for dosage, see Annex 3);
- dilute quinine 1 part in 5 with normal (0.9%) saline;
- divide the dose into two separate injections and administer by deep IM injection into both anterior thighs (IM quinine should not be injected into the buttock);

Volume of infusion:

- quinine can be diluted in 5% dextrose, 10% dextrose, 4% dextrose, 0.18% saline or normal (0.9%) saline;
- dilute quinine to a total volume of 10 ml/kg (the same volume is used for both loading and maintenance doses) and infuse over 4 hours;
- to avoid overloading the patient with IV fluids, the volume of the quinine infusion must be taken into account when calculating the total 24-hour fluid requirement.

Example: the 24-hour fluid requirement for an adult weighing 50 kg is 50 ml/kg, i.e. $50 \times 50 = 2500$ ml. The patient will receive 3 × 500-ml infusions of quinine each day =

1500 ml. Therefore, the patient needs an additional 1000 ml of maintenance fluid to bring the 24-hour total to 2500 ml.

Side-effects

- Dizziness.
- Ringing in the ears.
- Blurred vision and tremors, known collectively as cinchonism.
- Hypoglycaemia.

At the above dosages, these symptoms are not severe enough to stop treatment and will subside spontaneously when administration of the drugs ends.

Artesunate injectable (60 mg/vial)

Artesunate 2.4 mg/kg body weight IV or IM given on admission (time = 0), repeated at 12 hours and 24 hours, then once a day.

Shake the vial of artesunate powder with 1 ml of 5% sodium bicarbonate solution (provided) for 2–3 minutes for better dissolution. The solution should be prepared freshly for each administration and should not be stored. Then:

- *IV administration:* add 5 ml of 5% glucose or normal saline to make the concentration of artesunate as 10 mg/ml and administer by slow infusion.

Example, if a patient weighs 30 kg, the required dose can be calculated as:

$$2.4 \text{ mg/kg} \times 30 \text{ kg body weight} = 72 \text{ mg}$$

Since the solution prepared for IV administration contains artesunate 10 mg/ml, this patient will then need **7.2 ml**.

- *IM administration:* add 2 ml of 5% glucose or normal saline to make the concentration of artesunate 20 mg/ml.

Example, if a patient weighs 20 kg, the required dose can be calculated as:

$$2.4 \text{ mg/kg} \times 20 \text{ kg body weight} = 48 \text{ mg}$$

Since the solution prepared for IM administration contains artesunate 20 mg/ml, this patient will then need **2.4 ml**.

Artemether injectables

- Artemether im should be as a single dose for pre-referral treatment at child health centres/outpatient level when artesunate im is not available. It should also be used for severe malaria when artesunate injectables are not available.
- Give 3.2mg/kg im to the anterior thigh. The maintenance dose is 1.6mg/kg im daily until the patient can take oral medication

Artesunate rectal capsules

- Artesunate rectal capsules should be reserved for situations in which it is not possible to give IV or IM therapy.
- Give 10 mg/kg of artesunate rectal capsules, and repeat the dose if the capsule is expelled within 1 hour.
- Repeat the dose after 24 hours if it is not possible to refer the patient.

Dose chart by age (children) for artesunate 50 mg and 200 mg rectal capsules

Note: artesunate rectal capsules remain stable in temperatures of up to 40°C and therefore require cool – but not cold – transport and storage. They have to be inserted at least 2 cm into the rectum.

Body weight (kg)	No. of artesunate capsules	No. of artesunate capsules
	(50 mg) given as single dose	(200 mg) given as single dose
5–10	1	–
15–20	2	–
20–30	3	–
30–50	–	2
50–60	–	3

Paracetamol

Note: do not administer in cases of liver disease (hepatitis).

Dosage

- Child: 20–30 mg/kg/day divided into three doses.

- Adult: 2–3 g/day divided in three doses.

Age	Body weight (kg)	100 mg tablets	500 mg tablets
0–2 months	0–4	½ tablet x 3	–
2 months–1 year	4–8	¾–1½ tablets x 3	–
1–5 years	8–15	1½–3 tablets x 3	¼–½ tablet x 3
5–15 years	15–35	–	½–1½ tablets x 3
>15 years	>35	–	2 tablets x 3

Ferrous sulfate + folic acid (200 mg + 0.25 mg)

Dosage (based on dosage for ferrous sulfate)

- Prevention:
 - child: 1 tablet/day for 30 days
 - adult: 1–2 tablets/day for 30 days.
- Treatment:
 - child: 3–6 mg/kg/day divided in three doses
 - adults: 120–180 mg/day divided in two to three doses.

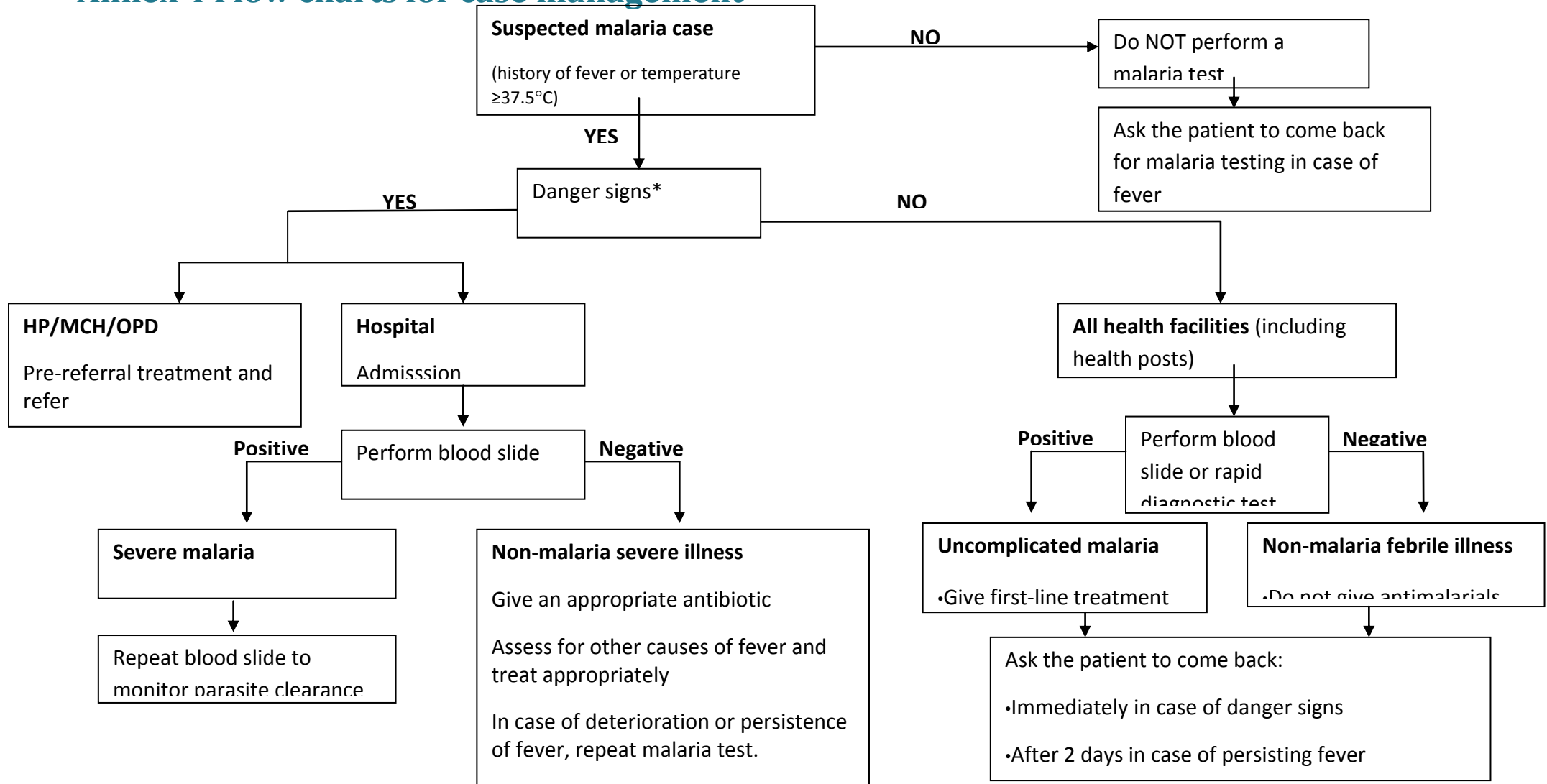
Age	Body weight	Prevention	Treatment
0–2 months	0–4 kg	–	–
2 months–1 year	4–8 kg	–	¼ tablet x 3
1–5 years	8–15 kg	¼ tablet	½ tablet x 3
5–15 years	15–35 kg	½ tablet	1 tablet x 3
>15 years	>35 kg	1–2 tablets	1 tablet x 2 or 3

Side-effects (mainly because of ferrous sulfate)

- Gastrointestinal problems.
- Black colouring of stools.

Note: do not combine with tetracycline and do not administer in cases of sickle-cell anaemia.

Annex 4 Flow charts for case management



HP, health posts; MCH, maternal and child health centres; OPD, outpatient departments.

*Danger signs/severe symptoms:

- *in children*: unable to drink or breastfeed, vomiting everything, having convulsions, are lethargic or unconscious and present with neck stiffness, chest in-drawing or stridor;
- *in adults*: very weak or unable to stand, lethargic or unconscious or have neck stiffness, convulsions, respiratory distress or severe abdominal pain.

Annex 5 Coma scales

Glasgow coma scale (adults)

A state of unarousable coma is reached at a score of <11. This scale can be used repeatedly to assess improvement or deterioration.

Parameter	Response	Score
Eyes open	Spontaneously	4
	To speech	3
	To pain	2
	Never	1
Best verbal response	Orientated	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Best motor response	Obeys commands	6
	Localizes pain	5
	Withdrawal from pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1
	Total score	3–15

Blantyre coma scale (for children)

A state of unarousable coma is reached at a score of <3. This scale can be used repeatedly to assess improvement or deterioration.

Parameter	Response	Score
Best motor response	Localizes painful stimulus ^a	2

	Withdraws limb from pain ^b	1
	Non-specific or absent response	0
Best verbal response	Appropriate cry	2
	Moan or inappropriate cry	1
	None	0
Eye movements	Directed (e.g. follows mother's face)	1
	Not directed	0
	Total score	0–5

^a Rub knuckles on patient's sternum.

^b Firm pressure on thumb nail bed with horizontal pencil.

Annex 6 Treatment observation chart for inpatients

Card No. _____ _____	Bed No.	Time																		
Name: _____		Time since admission																		
Age: _____ Sex: _____		Drugs (including intravenous fluids, glucose, blood transfusion) Drug dose route																		
Weight _____ kg		Temp. (°C) 41 40 39 38 37																		
Drugs prior to admission		Infusion fluid Specify, duration and volume, e.g. 5% D/S																		
Date/Time of admission:		Urine volume: _____ ml Input minus output: _____ [+/-]																		
Summary condition	of on	Frequency of	Weight: _____ kg																	

admission		observation																
Glasgow _____	Scale	(2-4 hourly)	Pulse (beats/min) _____															
Blantyre _____	Scale																	
Convulsions ? _____	Y	(1-4 hourly)	Blood pressure: ____/____mmHg															
N _____																		
Jaundice? _____	Y	*	Respiratory rate: _____/min															
_____	N																	
Shortness of breath? _____	Y	(12 hourly)	Level of consciousness scale:															
_____	N																	
Shock ? _____	Y	(1-8 hourly)	Haemoglobin (Hg) or haematocrit _____															
_____	N																	
Oliguria? _____	Y	(1-8 hourly)	Parasitaemia in “+”															
_____	N																	
Haemoglobinuria? Y _____		(1-8 hourly)	Able to drink?															

N ____																		
Parasitaemia in "+"? _____	(4 hourly)	Able to sit?																
Haemoglobin (Hg) or haematocrit _____	(8–12 hourly)	Convulsion?																
	(8–12 hourly)	Other observations																

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Glossary

Acidosis	A metabolic condition causing the pH of the blood to drop
Anuric	The complete suppression of urinary secretion by the kidneys
Aphasia	A defect or loss of the ability to speak or write, loss of ability to understand spoken or written language, due to injury or disease of the brain centres
Arthralgia	Joint pain
Bradycardia	A slowness of the heart beat, as evidenced by slowing of the pulse rate to less than 60 beats per minute
Cerebellar ataxia	Loss of muscle coordination caused by disorders of the cerebellum
Colloid	Microscopic particles suspended in some sort of liquid medium
Convalescent	Getting well, a person who is getting well
Corneal reflexes	A contraction of the eyelids when the cornea is lightly touched with a camel-hair pencil
Cortical blindness	Loss of sight due to an organic lesion in the visual cortex
Corticosteroids	A group of synthetic hormones
Cortical ischaemia	Less oxygen supply to the cortex of the brain
Cyanotic	A bluish discoloration, applied especially to such discoloration of skin and mucous membranes due to excessive concentration of reduced haemoglobin in the blood
Decerebrate rigidity	Spontaneous extension of elbows, wrists and legs, suggesting damage to the midbrain
Disconjugate gaze	Rotation of the two eyes in opposite directions
Dyserythropoietic	Disturbance in formation of red blood cells
Dyspnoea	Shortness of breath, difficult or laboured breathing
Electroencephalogram (EEG) abnormalities	Abnormalities in the EEG, a diagnostic test that measures the electrical activity of the brain (brain waves) using highly sensitive recording equipment attached to the scalp by fine

	electrodes
Encephalitis	Inflammation of the brain, most commonly from infection, usually by viruses
Encephalopathy	Any degenerative or non-inflammatory disorder affecting the brain in a widespread manner
Endotracheal intubation	The placement of a flexible plastic tube into the trachea for the purpose of ventilating the lungs
Erythrocyte enzyme	Enzyme of the red blood cell
Haematocrit	Relative volume of blood occupied by red blood cells
Haemodialysis	The removal of certain elements from the blood by virtue of the difference in the rates of their diffusion through a semipermeable membrane, for example by means of a haemodialysis machine or filter
Haematemesis	The vomiting of blood
Haemofiltration	Extracorporeal ultrafiltration technique without haemodialysis for treatment of fluid overload and electrolyte disturbances affecting renal, cardiac or pulmonary function
Haemoglobinuria	Haemoglobin in the urine
Haemolysis	Disruption of the integrity of the red cell membrane causing release of haemoglobin
Hemiparesis	Paralysis affecting only one side of the body
Hepatosplenomegaly	Abnormal enlargement of both the liver and the spleen
Hyperbaric oxygen	High pressure oxygen
Hyperinsulinaemia	Excessively high blood insulin levels
Hyperpyrexia	Exceptionally high fever
Hypoglycaemia	An abnormally low concentration of glucose in the blood
Hypotonia	A condition of diminished tone of the skeletal muscles, diminished resistance of muscles to passive stretching
Hypoxia	Reduction of oxygen supply to tissue below physiological levels, despite adequate perfusion of the tissue by blood

Lactic acidosis	Acidosis caused by accumulation of lactic acid more rapidly than it can be metabolized
Leukocytosis	Abnormal elevation of the white blood cell count
Meningoencephalitis	Inflammation of the brain and surrounding membranes
Medullary congestion	Congestion of the inner portion of an organ
Melaena	The passage of dark, pitchy and grumous stools stained with blood pigments or with altered blood
Monocytes	One of three types of white blood cells. Monocytes are precursors to macrophages
Myalgia	Pain in a muscle or muscles
Normochromic	Being normal in colour; referring especially to red blood cells that possess the normal quantity of haemoglobin
Oliguria	Secretion of a diminished amount of urine in relation to the fluid intake
Ophthalmoscopic	Relating to examination of the interior of the eye
Opisthotonos	A form of spasm in which the head and heels are bent backwards and the body is bowed forward
Papilloedema	Swelling and protrusion of the optic disc at the back of the inside of the eye
Pentoxifylline (oxpentifylline)	A drug that reduces levels of tumour necrosis factor
Perinatal	Pertaining to or occurring in the period shortly before and after birth
Peritoneal dialysis	In this type of dialysis, a special solution is run through a tube into the peritoneum, a thin tissue that lines the cavity of the abdomen
Petechiae	Small red spots on the skin that usually indicate a low platelet count
Phagocytes	A cell that is capable of phagocytosis
Photophobia	Undue tolerance to light

Plasma fibrinogen concentrations	Soluble plasma protein
Polyuric	The passage of a large volume of urine in a given period, a characteristic of diabetes
Postpartum haemorrhage	Haemorrhage occurring soon after labour or childbirth
Postural hypotension	The manifestation of low blood pressure when rising from a chair or bed
Primigravida	A woman in her first pregnancy
Pulmonary oedema	A severe state of increased interstitial fluid within the lung that leads to flooding of the alveoli with fluid
Sequelae	A condition following as a consequence of a disease
Serum creatinine	A waste product of protein metabolism that is found in the urine
Spasticity	A state of hypertonicity or increase over the normal tone of a muscle, with heightened deep tendon reflexes
Splenomegaly	Enlargement of the spleen
Subconjunctival haemorrhages	Bleeding beneath the clear membrane that coats the inner aspect of the eyelids and the outer surface of the eye
Supine	Lying on the back
Tachycardia	The excessive rapidity in the action of the heart, the term is usually applied to a heart rate above 100 per minute
Thrombocytopenia	A decrease in the number of platelets in the blood, resulting in the potential for increased bleeding and decreased ability for clotting
Tubular necrosis	The sum of the morphological changes indicative of cell death, occurring in tubules
Upper motor neurone lesion	Injury to cerebral descending fibres above the brainstem
Venesection	The act or operation of opening a vein for letting blood