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Glossary

Artemisinin-based combination therapy (ACT) – A combination of artemisinin or one of its derivatives with an antimalarial or antimalarials with a longer elimination half-life of a different class.

Asexual cycle – The life-cycle of the malaria parasite in host from merozoite invasion of red blood cells to schizont rupture (merozoite → ring stage → trophozoite → schizont → merozoites). Duration approximately 48 hours in Plasmodium falciparum, P. ovale and P. vivax; 72 hours in P. malariae.

Asexual parasitaemia – The presence in host red blood cells of asexual parasites. The level of asexual parasitaemia can be expressed in several different ways: the percentage of infected red blood cells, the number of infected cells per unit volume of blood, the number of parasites seen in one microscopic field in a high-power examination of a thick blood film, or the number of parasites seen per 200–1000 white blood cells in a high power examination of a thick blood film.

Cerebral malaria – Severe P. falciparum malaria with cerebral manifestations, usually including coma (Glasgow coma scale < 11, Blantyre coma scale < 3). Malaria with coma persisting for > 30 min after a seizure is considered to be cerebral malaria.

Combination treatment (CT) – A combination of two or more different classes of antimalarial medicines with unrelated mechanisms of action.

Cure – Elimination of the symptoms and asexual blood stages of the malaria parasite that caused the patient or caregiver to seek treatment.

Drug resistance – The World Health Organization (WHO) defines resistance to antimalarials as the ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a medicine given in doses equal to or higher than those usually recommended but within the tolerance of the subject, provided drug exposure at the site of action is adequate. Resistance to antimalarials arises because of the selection of parasites with genetic mutations or gene amplifications that confer reduced susceptibility.

Gametocytes – Sexual stages of malaria parasites present in the host red blood cells.

Hypnozoites – Persistent liver stages of P. vivax and P. ovale malaria that remain dormant in host hepatocytes for an interval (most often 3–45 weeks) before maturing to hepatic schizonts. These then burst and release merozoites, which infect red blood cells. Hypnozoites are the source of relapses.

Monotherapy – Antimalarial treatment with a single medicine (either a single active compound or a synergistic combination of two compounds with related mechanism of action).

Plasmodium – A genus of protozoan vertebrate blood parasites that includes the causal agents of malaria. Plasmodium falciparum, P. malariae, P. ovale and P. vivax cause malaria in humans. Human infections with the monkey malaria parasite, P. knowlesi have also been reported from forested regions of South-East Asia.
Radical cure – In *P. vivax* and *P. ovale* infections only, this comprises a cure as defined above plus prevention of relapses by killing hypnozoites.

Rapid diagnostic test (RDT) – An antigen-based stick, cassette or card test for malaria in which a colored line indicates that plasmodial antigens have been detected.

Recrudescence – The recurrence of asexual parasitaemia after treatment of the infection with the same infection that caused the original illness. This results from incomplete clearance of parasitaemia due to inadequate or ineffective treatment. It is, therefore, different to a relapse in *P. vivax* and *P. ovale* infections, and it differs from a new infection or re-infection (as identified by molecular genotyping in endemic areas).

Recurrence – The recurrence of asexual parasitaemia following treatment. This can be caused by a recrudescence, a relapse (in *P. vivax* and *P. ovale* infections only) or a new infection.

Relapse – The recurrence of asexual parasitaemia in *P. vivax* and *P. ovale* malaria deriving from persisting liver stages. Relapse occurs when the blood stage infection has been eliminated but hypnozoites persist in the liver and mature to form hepatic schizonts. After variable intervals of weeks to months, the hepatic schizonts burst and liberate merozoites into the bloodstream.

Severe anaemia – Haemoglobin concentration of < 5 g/100 ml (haematocrit < 15%). Severe *falciparum* malaria. Acute *falciparum* malaria with signs of severity and/or evidence of vital organ dysfunction.

Transmission intensity – The intensity of malaria transmission measured by the frequency with which people living in an area are bitten by anopheline mosquitoes carrying sporozoites. This is often expressed as the annual entomological inoculation rate (EIR), which is the number of inoculations of malaria parasites received by one person in one year.

Trophozoites – Stage of development of the malaria parasites within host red blood cells from the ring stage and before nuclear division. Mature trophozoites contain visible malaria pigment.

Uncomplicated malaria – Symptomatic infection with malaria parasitaemia without signs of severity and/or evidence of vital organ dysfunction.

Vectorial Capacity – Number of new infections the population of a given vector would distribute per case per day at a given place and time, assuming conditions of non-immunity.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ACT</td>
<td>Artemisinin-based combination therapy</td>
</tr>
<tr>
<td>ACPR</td>
<td>Adequate clinical and parasitological response</td>
</tr>
<tr>
<td>AL</td>
<td>Artemether plus Lumefantrine combination</td>
</tr>
<tr>
<td>AQ</td>
<td>Amodiaquine</td>
</tr>
<tr>
<td>AS</td>
<td>Artesunate</td>
</tr>
<tr>
<td>AS+AQ</td>
<td>Artesunate plus Amodiaquine combination</td>
</tr>
<tr>
<td>AS+MQ</td>
<td>Artesunate plus Mefloquine combination</td>
</tr>
<tr>
<td>AS+SP</td>
<td>Artesunate plus Sulfadoxine-Pyrimethamine combination</td>
</tr>
<tr>
<td>BW</td>
<td>Body weight</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CQ</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>DHA+PPQ</td>
<td>Dihydroartemisinin plus Piperaquine combination</td>
</tr>
<tr>
<td>DMR</td>
<td>Department of Medical Research</td>
</tr>
<tr>
<td>DRC-TEG</td>
<td>Technical Expert Group on Drug Resistance and Containment of WHO</td>
</tr>
<tr>
<td>EIR</td>
<td>Entomological Inoculation Rate</td>
</tr>
<tr>
<td>G6PD</td>
<td>Glucose-6-Phosphate Dehydrogenase</td>
</tr>
<tr>
<td>GMS</td>
<td>Greater Mekong Sub-region</td>
</tr>
<tr>
<td>GPARC</td>
<td>Global Plan for Artemisinin Resistance Containment</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>HRP2</td>
<td>Histidine-rich protein 2</td>
</tr>
<tr>
<td>IC50</td>
<td>Concentration providing 50% inhibition</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum inhibitory concentration</td>
</tr>
<tr>
<td>MQ</td>
<td>Mefloquine</td>
</tr>
<tr>
<td>MDR</td>
<td>Multi Drug Resistance</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PfHRP2</td>
<td><em>Plasmodium falciparum</em> histidine-rich protein-2</td>
</tr>
<tr>
<td>PQ</td>
<td>Primaquine</td>
</tr>
<tr>
<td>RAI</td>
<td>Regional Artemisinin Resistance Initiative</td>
</tr>
<tr>
<td>RDT</td>
<td>Rapid diagnostic test</td>
</tr>
<tr>
<td>SP</td>
<td>Sulfadoxine-Pyrimethamine</td>
</tr>
<tr>
<td>TES</td>
<td>Therapeutic Efficacy Study</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>
Working Group for revision of National Malaria Treatment Guidelines

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Executive Summary

National Malaria Programme (Myanmar) had developed National Malaria Treatment Policy and guideline since 2002 and it was updated in 2008 and minor modifications were made in 2011. Malaria case management remains a vital component of the malaria control strategies. This entails early diagnosis and prompt treatment with effective antimalarial medicines. Now-a-days the scope of malaria treatment expands not only to reduce malaria morbidity and mortality but also to prevent transmission. Although this guideline is aiming mainly for all medical personnel who treat the patients, it also intends for the public and private sectors concerning antimalarial drugs quality assurance and quality control. Without understanding the malaria treatment policy and updated regimes, availability of obsolete and substandard antimalarials in the market may hinder the adherence of treatment guideline by private sector and community. Banning of oral artemisinin monotherapy also should be smoothly encountered by collaborative effort of respective departments and companies after recognition of this national guideline. As National Malaria Programme (Myanmar) is preparing to move from malaria “Control” to “Elimination”, the treatment policy and guideline on malaria is also transforming especially at community level. However, this guideline tries to encompass all aspects of malaria treatment at all levels in every stage (i.e. uncomplicated or severe & complicated) of any species infection of *Plasmodiae*. 
1. Introduction

1.1. **Background**

Malaria remains a leading cause of morbidity and mortality in the Republic of the Union of Myanmar. Considerable progress has been made over the past 10-15 years in reducing the burden. However, the disease is still a priority public health problem in the country. It occurs mainly in or near forests, but also in some coastal areas and plantations. Because of these environmental determinants, the malaria burden is particularly high among national races in remote areas and migrants, who seek economic opportunities in rural economic frontier areas, and the economic development activities such as forestry, mining, plantations and road-building. The significant reduction of malaria morbidity and mortality so far made in Myanmar is threatened by evolving complexity of the problem, especially multiple resistance of the parasites to antimalarial medications and the uncertainty about the financial basis for continued malaria control. The epidemiology of malaria, biology of vectors, socio-behavioral characteristics of the communities and geographical areas also present a challenge to achieve further progress in the implementation of malaria control interventions, making it necessary to develop and validate new implementation strategies.

Compared to other countries in the South-East Asia and the Greater Mekong Sub-Region (GMS), malaria situation of Myanmar ranked third in the WHO South-East Asia Region, and first in the GMS countries.

1.2. **Objectives of the guidelines and target audience**

The purpose of these guidelines is to provide information regarding evidence-based recommendations on the diagnosis and treatment of malaria.

Recommendation and guidance is shown on the treatment of:

- uncomplicated malaria, including disease in special risk groups (young children, pregnant women, people living with HIV/AIDS, migrants and mobile populations and travelers from non-malaria endemic regions), and in epidemics and complex emergency situations; and
- severe malaria including symptoms and comprehensive treatment for each complicated case

**Target audience**

These guidelines are primarily targeted at:

- health professionals (doctors, nurses and paramedical officers)
- public health and policy makers, research institutions, medical schools, nongovernmental organizations and agencies working as partners in health or malaria control
- primary health-care services and the drug sellers
Malaria is caused by infection of red blood cells with protozoan parasites of the genus *Plasmodium*. The parasites are inoculated into the human host by a feeding female anopheline mosquito. The four *Plasmodium* species that infect humans are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Increasingly, human infections with the monkey malaria parasite, *P. knowlesi*, have also been reported from the forested regions of South-East Asia. The first symptoms of malaria are nonspecific and similar to the symptoms of a minor systemic viral illness. The clinical features of uncomplicated and severe & complicated malaria are described in respective section².

In Myanmar, the reported numbers of confirmed malaria cases at outpatient departments were 649522 in 2010, 533720 in 2011 and 333871 in 2013; whereas reported numbers of in patients were 43602 in 2010, 33732 in 2011 and 18362 in 2013. Reported malaria deaths were 788 in 2010, 581 in 2011, and 236 in 2013. Both morbidity and mortality trends of malaria showed decreasing trend, i.e. morbidity rates of 11.09 per 1000 in 1999 to 6.81 per 1000 in 2013 and mortality rate of 6.23 per 10000 to 0.48 per 100000 in 2013 respectively. *P. falciparum* species continued to be dominant (73%), *P. vivax* (24%) with negligible *malariae* and *ovale* malaria, as well as mixed species (3%); Pf:Pv ratio was 3:1. All age groups are affected but around two thirds of confirmed cases are 15 years old and above. Malaria problem encountered in Myanmar is forest related and migrant and mobile population groups³. In Myanmar, out of 37 species of *Anopheles* so far recorded throughout the country, 6 have been found to be infected with malaria parasite based on entomological and parasitological evidences; *An. minimus* and *An. dirus* as Primary vectors; *An. annularis* and *An. sundaicus* as Local vectors, and *An. culicifacies* and *An. philippinensis* as Secondary vectors. In addition to the above, it is suspected that *An. sinensis* may also play a secondary role in malaria transmission: *An. maculatus* is also suspected a secondary vector in the hilly and foothill areas of the country: *An. aconitus* could also play a secondary role depending on the man/cattle ratio of a particular area: *An. jeyporiensis* is to be regarded as possible vector wherever it occurs in abundance³.
3. Resistance to antimalarial medicines

3.1. **Situation of antimalarial drug resistance in GMS countries**

Resistance to antimalarial medicines has been documented in all classes of antimalarials, including the artemisinin derivatives, and it is a major threat to malaria control. The emergence of artemisinin resistance in the Greater Mekong Sub-region (GMS) is a matter of great concern. Resistance to other antimalarial medicine was also detected first in GMS, eventually appearing elsewhere. *P. falciparum* resistance to artemisinins has been detected in four countries in the GMS: Cambodia, Myanmar, Thailand and Viet Nam. Containment activities were started in 2008 on the Cambodia–Thailand border and are now being conducted in all four countries. The aim of the first response to artemisinin resistance along the Cambodia–Thailand border was to contain the problem to that geographical area. Evidence of resistance has now been detected at several other sites, indicating that the initial hopes of containment in one area was not fulfilled, either because of spread of resistance or its spontaneous emergence elsewhere.

Nevertheless, the strategies that are applied to eliminate resistant parasites in any areas where resistance is detected can reasonably be considered as efforts to ‘contain’ the problem. These efforts are not addressing only artemisinin resistance but also at resistance to ACT partner drugs. However, the GPARC and plans in four countries describe activities designated as artemisinin resistance containment. In 2013, Regional Coordination Mechanism was formed and called for concept note application for Regional Artemisinin Resistance Initiative (RAI) from the GMS countries except People’s Republic of China with support from the Global Fund.

3.2. **Assessing drug efficacy and drug resistance**

3.2.1. **Summary of drug resistance situation in Myanmar**

In 1969, it was first noticed that patients with malaria frequently had recrudescence soon after a standard dose of Chloroquine. A small clinical trial in Bago in 1969 indicated that Chloroquine resistant *P. falciparum* existed in Myanmar. In 1980, Franco Tin & Nyunt Hlaing reported resistance to standard dose of Amodiaquine in Thandaung. In 1971, SP resistance was first reported by F Tin & N Hlaing. In 1979, a hospital based study on 30 patients followed up for 28 days also reported 20% resistance (including R1, R2 and R3). Mefloquine S/R1 declined to 68% in Tarchileik in 1999 (WHO Bulletin 1999, 77/3). According to studies by Technical Support Network (2002-2003), the efficacy of Mefloquine (1000 mg) was reported as ACPR 94% in Myeik (Tanindaryi Division), 81% in Myitkyina (Kachin State) and 91% in Kalay (Sagaing Division). In 1993, Quinine sensitivity using the standard 7 day regimen was found to be 85.7% in Lashio (Northern Shan States) and another hospital based study reported 55% on 20 patients in 1998 -1999.

3.2.2. **Artemisinin resistance**

Artemisinin resistance was first documented in 2007 along the Cambodia-Thai border and more recently along the Thai–Myanmar border and in some sites in Southern Viet Nam. In 2009, Therapeutic Efficacy Studies (TES) were done at three sites in Myanmar examining the efficacy of
ACTs (Artemether-Lumefantrine and Dihydroartemisinin-Piperaquine). The institutions that carried out TES are DMR (Lower Myanmar), DMR (Upper Myanmar) and Research Unit (Ministry of Defense) in collaboration with Mahidol University, The Faculty of Tropical Medicine, Thailand; Oxford Tropical Research Ethics Committee (UK) and Pasteur Institute, Cambodia in line with WHO Standard TES protocol of 28 / 42 days follow-up has been used since 2009 under Mekong Network. The data from the study in Kawthaung was worrisome as 19% of patients treated with Dihydroartemisinin-Piperaquine and 4.5% of patients treated with Artemether-Lumefantrine were positive on Day 3.

In 2009-2010, Myanmar reported suspected artemisinin resistance that was likely to flow from the Thai-Cambodia multi-drug resistant foci. The country took immediate action by developing the Myanmar Artemisinin Resistance Containment (MARC) framework during 2010-2011. TES sites in Myanmar are shown in the map in Annex 1. The following table shows the TES results of AL, DHA+PPQ and AS+MQ in certain areas in 2009 and 2011. According to the % of Day 3 parasitaemia in those areas, Myanmar started its response, Artemisinin Resistance Containment in 2011.

<table>
<thead>
<tr>
<th>Type of Antimalarial Drug</th>
<th>Study Site</th>
<th>% of Day3 Parasitaemia of P.falciparum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2009</td>
</tr>
<tr>
<td>Artemether + Lumefantrine (Coartem®)</td>
<td>Shwekyin/Bago</td>
<td>10.20</td>
</tr>
<tr>
<td></td>
<td>Kawthaung/Tanintharyi</td>
<td>6.25</td>
</tr>
<tr>
<td>Dihydroartemisinin + Piperaquine (Duocotexin®)</td>
<td>Kawthaung/Tanintharyi</td>
<td>18.75</td>
</tr>
<tr>
<td></td>
<td>Mon &amp;Kayin</td>
<td>22.50</td>
</tr>
<tr>
<td>Artesunate + Mefloquine</td>
<td>Muse/Northern Shan State</td>
<td>2.20</td>
</tr>
</tbody>
</table>

More information on TES study results was shown in Annex 2.

In 2013, the molecular marker for Artemisinin drug resistance, Kelch 13 can be detected and K-13 mutation studies were carried out in Myanmar in 2014. Total 2378 samples were tested from 55 townships of 10 States/Regions. 371 out of 940 samples (39%) had a propeller domain mutation. 24 types of mutations were detected (13 types newly detected). In summary, K-13 mutations are widespread in Myanmar showing different genetic patterns. A number of individual mutations have appeared independently on more than one occasion (different genetic backgrounds in different locations). Although there is high prevalence of K-13 propeller mutations extend many sites of Upper Myanmar, TES results showed high level of ACPR to all ACTs. K-13 mutations are supposed to be in the earlier phase of evolution process for Artemisinin Resistance. A number of individual mutations might have appeared independently on more than one occasion (different genetic backgrounds in different locations). Extensive study is necessary for having detail information on association between K-13 isolates and AR in various sites of Myanmar6.
4. Antimalarial treatment policy

The main determinant of antimalarial treatment policy is the therapeutic efficacy of the antimalarial medicines in use. Therapeutic efficacy monitoring involves the assessment of clinical and parasitological outcomes of treatment over at least 28 days following the start of adequate treatment to monitor for the reappearance of parasites in the blood. Reappearance of the same genotype indicates reduced parasite sensitivity to the treatment drug. The current recommended duration of follow-up is a minimum of 28 days for all antimalarial medicines, while it is extended for longer periods of time depending on elimination half-life (42 days for combinations with Mefloquine and Piperaquine).

Other important determinants include: changing patterns of malaria-associated morbidity and mortality; consumer and provider dissatisfaction with the current policy; and the availability of alternative medicines, strategies and approaches.²

A change of an antimalarial medicine recommended in the national malaria treatment policy should be initiated if the total treatment failure proportion is ≥ 10%, as assessed through in vivo monitoring of therapeutic efficacy. The selection of a new and/or alternative antimalarial medicine for use at public health level within the context of national treatment guidelines, should be based on an average cure rate of > 95%, as assessed in clinical trials.² Current situation of TES results show that although Day 3 parasitaemia is ≥ 10% in some areas (results shown in Annex 2), there is no evidence of treatment failure which means that partner drugs are still effective. Therefore, it is no need to change existing ACT combinations. But Artesunate + Mefloquine combination must be “Fixed-dose combinations” rather than co-blistered or loose single agent formulations tablet because of banning oral monotherapy of Artemisinin in Myanmar.

4.1. Monitoring of resistance to antimalarials

Monitoring of resistance should be redefined in each country based on revised WHO guidelines for GMS. First-line treatment efficacy should be monitored through TES, where blood samples can also be collected for K-13 and mdr1 copy number. For continued studies on artemisinin resistance, K-13 mapping will be the essential tool. When the number of patients becomes low, it is no longer possible to perform TES studies; it should then be attempted to follow up all patients, especially Pf patients with clinical and blood slide checks on the same days as recommended in TES protocols. Complete adherence cannot be expected, but in an elimination perspective, the advantage of this practice is that any treatment failure case will be given a second-line treatment. For this, patient mobility makes it necessary for treatment providers to give each patient an identifier number and a malaria treatment card. This is practiced on the Cambodia-Thailand border with a bilingual card.
5. Diagnosis of malaria

Prompt and accurate diagnosis of malaria is part of effective disease management. The diagnosis of malaria is based on clinical suspicion and on the detection of parasites in the blood (parasitological or confirmatory diagnosis). High sensitivity of diagnosis in malaria endemic areas is particularly important for the most vulnerable population groups, such as young children and the non-immune population, in whom the disease can be rapidly fatal, while high specificity will reduce unnecessary treatment with antimalarials and improve diagnosis of other febrile illnesses in all settings.

5.1. Clinical diagnosis

Diagnosis based on clinical features alone has very low specificity and results in over-treatment. Other possible causes of fever and the need for alternative or additional treatment must always be carefully considered. In Myanmar, it was recommended that all clinically suspected cases of malaria should be confirmed with a parasitological diagnosis before treating patient.

5.2. Parasitological diagnosis at different levels

5.2.1. Peripheral

At the village level, where there are trained Village Health Volunteers, the majority of patients who have uncomplicated malaria will be diagnosed based on the patients’ symptoms, a simple history taking and a few basic clinical observations which should include temperature measurement, and blood examination by using RDT. Patients who are tested positive for malaria parasites are treated in accordance with the national treatment guidelines.

A small number of patients who present with signs and symptoms of severe or complicated malaria including non-per-os patients will be referred immediately to the nearest hospital which is capable of managing such cases. Pre-referral treatment should be given as recommended in section 8.3.

Patients who failed to respond to initial antimalarial treatment will also be referred to a facility that has alternative antimalarial drugs and microscopic facility.

5.2.2. Intermediate without a laboratory

By definition such health institutions are staffed with health assistant (HA) and other trained health workers (LHV/PHS-I/MW/PHS-II) who are permitted to administer antimalarial drugs intramuscularly in addition to the oral route. They do not have the microscopic facilities for making a microscopic diagnosis of malaria, but they have RDT.

At this level, diagnosis has to be based on clinical signs and symptoms and blood examination with RDT; additionally, there should be more detailed history taken and clinical and physical observations made. Simple examination using a thermometer, stethoscope, etc. should be done and thus there is a better possibility of diagnosing other diseases which are not malaria.
Three types of patients are expected at this level, those coming for the first attendance, those attending for follow up, and those having been referred from the periphery.

5.2.3. Intermediate with a laboratory

These institutions are staffed with health assistant and other trained health workers who are permitted to administer antimalarial drugs intramuscularly in addition to the oral route. In addition to what is done at the intermediate level without laboratory, the parasitological examination of blood by microscopy will enable confirmation of malaria. Every effort should be made to develop laboratory facilities as near as possible to the peripheral level, particularly in areas where there is *Plasmodium falciparum* resistance to more than two different groups of antimalarial drugs (i.e. multi-drug resistant *P. falciparum*) and areas where elimination of malaria is targeted.

5.2.4. Hospital

In addition to what is done at the intermediate level with a laboratory, the township hospital which is staffed with a medical officer, laboratory technician of Grade I or Grade II, and has facilities for more sophisticated diagnosis for the management of severe and complicated malaria cases.

At this level, a trained physician should be available and have facilities for full clinical assessment. There should be sufficient clinical expertise for the diagnosis of severe malaria and its complications and for other medical conditions resembling malaria, as well as facilities and medicines are available for satisfactory treatment of these conditions.

At this level, the laboratory should have a capability for greater efficiency and accuracy in the microscopic diagnosis of malaria including species identification, sexual and asexual forms and for performance of quantitative parasite counts. The laboratory technician should also be refreshed for the malaria microscopy though they are trained during their training course. Laboratory tests such as blood for haemoglobin, blood test for total & differential count, urine analysis and basic biochemical tests such as blood sugar, liver function tests, blood urea, etc. are also available.

All hospitalized and severely ill patients should be assessed by microscopic blood examination before antimalarial treatment and 3rd day of treatment, for the early detection of Artemisinin tolerance by monitoring parasite count. Referred patients should be assessed by microscopic diagnosis and treated accordingly.

5.3. Use of Rapid Diagnostic Test (COMBO Test)\(^6\)

Since 2002, RDT test kits for the diagnosis of *P. falciparum* has been used at the community level, sub-rural health centers and RHCs that have no microscopy services and widely used from 2005 onwards. Identification and effective treatment of *P. falciparum* is important not only for the reduction of severity and mortality, but also for delaying the development of resistant and reducing the spread of multi-drug resistant *P. falciparum*. Starting from 2011, RDT test kits for identification of both *Pf* and *Pv* were used.

Use of RDT should not replace the microscopy test. It should be used only where microscopy is not available or when the patient condition is severe and no time to wait for microscopy result.
In 2015, the national programme is aiming to move from control to pre-elimination/elimination of malaria in line with Global Malaria Action Plan and Regional strategy of GMS. The role of microscopy is crucially important for the surveillance of Day 3 parasitaemia and follow up activities. Quality Control and Quality Assurance of laboratory services from both public and private sector play an important role in pre-elimination/elimination of malaria.
Treatment of uncomplicated malaria

6. Treatment of uncomplicated *P. falciparum* malaria

After confirming the clinical diagnosis by RDT or microscopy, prompt treatment (i.e. treatment of malaria patient within 24 hours after appearance of fever) is desirable with effective and quality antimalarial drugs. Treatment should be supervised i.e. Directly Observed Treatment for 3 days (DOT strategy) which is recommended for the patient up to the volunteer level. Basic Health Staffs should also try to achieve DOT activity with the help of trained volunteers. If there is no one for supervision, patients and their families should understand the importance of the prescribed treatment and the need to ensure the compliance of treatment course with AL plus Primaquine (stat dose) for *Pf* cases. Severe and complicated malaria cases should be referred immediately to the nearest hospital.

Health workers should be alerted to the possibility that patients may have sought and received care from some other sources before coming to them. A brief history should be taken including whether certain drugs have already been taken for this illness episode and if so what drugs and in what quantities.

Malaria can be a very serious illness, leading to severe complications and death if not properly managed and so all staffs handling malaria must be properly trained.

6.1. **Objectives of treatment of uncomplicated malaria**

The objective of treating uncomplicated malaria is to cure the infection as rapidly as possible or to shorten the course of illness. Cure is defined as the elimination from the body of the parasites that caused the illness. This prevents progression to severe disease, and additional morbidity associated with treatment failure and death. The public health goal of treatment is to reduce transmission of the infection to others, i.e. to reduce the infectious reservoir and to prevent the emergence and spread of resistance to antimalarial medicines.

6.2. **Definition of uncomplicated malaria**

Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction. The first symptoms of malaria are nonspecific and similar to the symptoms of a minor systemic viral illness. They comprise: headache, lassitude, fatigue, abdominal discomfort, muscle and joint aches, usually followed by fever, chills followed by rigor, perspiration, anorexia, vomiting and worsening malaise. Malaria is, therefore, suspected clinically mostly based on symptoms mentioned and/or a history of fever with history of traveling to malarious areas within 1-3 months.

6.3. **ACT options in Myanmar**

Although WHO has recommended the following 5 ACT combinations:

1. Artemether plus Lumefantrine (AL)
2. Artesunate plus Mefloquine (AS+MQ)
3. Dihydroartemisinin plus Piperaquine (DHA+PPQ)
4. Artesunate plus Amodiaquine (AS+AQ) and
5. Artesunate plus Sulfadoxine-Pyrimethamine (AS+SP)

Only the first 3 combinations are accepted and recommended in Myanmar because the partner drugs of the last 2 combinations showed highly resistance status.

These are combinations in which one of the components is artemisinin and its derivatives (Artesunate, Artemether, and Dihydroartemisinin). The artemisinins produce rapid clearance of parasitaemia and rapid resolution of symptoms, by reducing parasite numbers 100- to 1000-fold per asexual cycle of the parasite (a factor of approximately 10 000 in each 48-h asexual cycle), which is more than the other currently available antimalarials achieved. Because artemisinin and its derivatives are eliminated rapidly, when given alone or in combination with rapidly eliminated compounds (Tetracyclines, Clindamycin), a 7-day course of treatment with an artemisinin compound is required. This long duration of treatment with the artemisinins can be reduced to 3 days when given in combination with slowly eliminated antimalarials. With this shorter 3-day course, the complete clearance of all parasites is dependent on the partner medicine being effective and persisting at parasiticidal concentrations until all the infecting parasites have been killed.

Thus, the partner compounds need to be relatively slowly eliminated. This also results in the artemisinin component being protected from resistance by the partner medicine, while the partner medicine is also partly protected by the artemisinin derivative.

An additional advantage from a public health perspective is the ability of the artemisinins to reduce gametocyte carriage and, thus, the transmissibility of malaria. This contributes to malaria control. To eliminate at least 90% of the parasitaemia, a 3-day course of the artemisinin is required to cover up to three post-treatment asexual cycles of the parasite. This ensures that only about 10% of the parasitaemia is present for clearance by the partner medicine, thus reducing the potential for development of resistance.

Shorter courses of 1–2 days of the artemisinin component of the ACTs would lead to a larger proportion of parasitaemia for clearance by the partner medicine; this is not recommended for the following additional reasons:

- they are less efficacious (except when the partner drug is highly effective),
- they have less of an effect on gametocyte carriage,
- they provide less protection of the slowly eliminated partner antimalarial.

**Recommendation – First line treatment for Uncomplicated Pf malaria**

1. Avoid using **ORAL** Artemisinin Monotherapy
2. AL for 3 days + PQ at Day 0 with first dose
6.4. Management of treatment failures \(^{(17)}\)

6.4.1. Diagnosis of treatment failure

Recurrence of *P. falciparum* malaria can be the result of a re-infection, or a recrudescence (i.e. failure). In an individual patient, it may not be possible to distinguish recrudescence from re-infection, although if fever and parasitaemia fail to resolve or recur within 28 days of treatment then this is considered a failure of treatment.

Treatment failures may result from drug resistance, poor adherence or inadequate drug exposure (from under-dosing, vomiting or unusual pharmacokinetic properties in that individual) or substandard medicines. It is important to determine from the patient’s history whether he or she vomited the previous treatment or did not complete a full course.

Wherever possible, treatment failure must be confirmed parasitologically – preferably by blood slide examination (as *P. falciparum* histidine-rich protein-2 (PfHRP2)-based RDT tests may remain positive for weeks after the initial infection, even without recrudescence). This may require referring the patient to a facility with microscopy. In many cases, failures are missed because patients who present with malaria are not asked whether they have received antimalarial treatment within the preceding 1-2 months. This should be a routine question in patients who present with malaria. However, volunteers and BHS staffs should not manage the treatment failure and must refer the patient to the nearest hospital where microscopic facility is available for species identification of malaria parasite.

6.4.2. Failure after 28 days \(^{(18)}\)

Recurrence of fever and parasitaemia more than two weeks after treatment could result either from recrudescence or new infection and this distinction can only be made through parasite genotyping by PCR. Since PCR is not routinely used in patient management, to simplify drug deployment, all presumed treatment failures after two weeks of initial treatment should, from an operational standpoint, be considered as new infections, especially in areas of high transmission, and be treated with the AL+PQ. This simplifies operational management and drug deployment. If the failure is a recrudescence, then the first-line treatment should still be effective in most cases.

Antimalarial treatments for failure within 28 days \(^{(18)}\)
- An alternative ACT such as AS+MQ (or) DHA+PPQ for 3 days (+PQ at Day 0)

Antimalarial treatments for failure after 28 days
- Considered as new infection and it can be treated with AL (+PQ at Day 0)

6.4.3. Treatment of Day 3 positive *P. falciparum* malaria

Day 3 Parasitaemia is monitored during TES studies done by research units and some small scale studies done by CAP-Malaria (Myanmar). The rate is 2-3 percent to more than 15% at different sites. Results of Day 3 parasitaemia are shown in Annex 3. The rate of Day 3 parasitaemia in general
Population is ≤ 3% in the study sites of TES study. Presence of Pf on Day 3 does not mean that it is “Treatment failure”. Some evidences during TES studies showed the clearance of parasite within 28 days of treatment with currently using ACT because partner drug is still effective. Therefore, no additional or alternative treatment was given to Day 3 parasitaemia at present.

6.5. Treatment of uncomplicated Pf malaria in specific populations and situations \(^{2(26)}\)

6.5.1. Pregnant women

Pregnant women with symptomatic acute malaria are a high-risk group, and they must promptly receive effective antimalarial treatment. Malaria in pregnancy is associated with low birth weight, increased anemia, and in low-transmission areas, an increased risk of severe malaria and death. In high-transmission settings, despite the adverse effects on fetal growth, malaria is usually asymptomatic in pregnancy or associated with only mild, non-specific symptoms. There is insufficient information on the safety and efficacy of most antimalarials in pregnancy, particularly for exposure in the first trimester.

1. Antimalarial drugs considered safe in the first trimester of pregnancy are:
   a. Quinine
   b. Chloroquine
   c. Clindamycin

2. Antimalarials **contraindicaded** throughout the pregnancy are:
   - Primaquine and Tetracyclines

6.5.1.1. First trimester \(^{2(26)}\)

Organogenesis occurs mainly in the first trimester; this is, therefore, the time of greatest concern for potential teratogenicity, although development of the nervous system continues throughout pregnancy.

**Recommendation on the treatment of uncomplicated Pf malaria in first trimester of pregnancy\(^2\):**

- Quinine plus Clindamycin is to be given for 7 days
- AL for 3 days is indicated only if this is the only treatment immediately available, or if treatment with 7-day Quinine plus Clindamycin fails or if there is uncertainty of compliance with a 7-day treatment

In reality, women often do not declare their pregnancies in the first trimester or are not yet aware that they are pregnant; so all women of child bearing age should be asked about the possibility of their being pregnant before being given antimalarials. Nevertheless, early pregnancies will often be exposed inadvertently to the available first-line treatment in the population, mostly ACTs.
6.5.1.2. Second and third trimesters \(^2\)\(^{28}\)

There is increasing experience with artemisinin derivatives in the second and third trimesters (over 1500 documented pregnancies). There have been no adverse effects on the mother or fetus.

**Recommendation on the treatment of uncomplicated \(_PF\) malaria in second and third trimester of pregnancy:**

- AL to be given for 3 days

6.5.2. Lactating women \(^2\)\(^{28}\)

The amounts of antimalarials that enter breast milk and are consumed by the breastfeeding infant are relatively small. Tetracycline is contraindicated in breastfeeding mothers because of its potential effect on the infant’s bones and teeth. Primaquine should not be used in nursing women, unless the breastfed infant has been determined not to be G6PD-deficient.

**Recommendation on treatment for lactating women with uncomplicated \(_falciparum\) malaria:**

- AL to be given for 3 days
- Primaquine should not be given to breast feeding mothers of infants \(<6\) months of age

6.5.3. Infants and young children \(^2\)\(^{28}\)

6.5.3.1. Choice of antimalarial drug

There are important differences in the pharmacokinetic parameters of many medicines in young children. Accurate dosing is particularly important in infants. Despite this, only a few clinical studies have focused specifically on this age range; this is partly because of ethical considerations relating to the recruitment of very young children to clinical trials, and it is also because of the difficulty of repeated blood sampling. As a result, the available evidence in young infants (\(<5\) kg) is insufficient for confident recommendations for any of the ACTs, to the extent that many of the drugs carry label restrictions that they should not be used.

The artemisinin derivatives are safe and well tolerated by young children, and so the choice of ACT will be determined largely by the safety and tolerability of the partner drug. With these exceptions there is no evidence for specific serious toxicity for any of the other currently recommended antimalarial treatments in infancy.
6.5.4. Travellers

Travellers who acquire malaria are often non-immune persons either who reside in cities with little or no transmission within endemic countries, or visitors from non-endemic countries who travel to areas of malaria transmission. Both are likely to be at a higher risk for severe malaria. When living in Myanmar, they should be treated according to national treatment guidelines.

Travellers who return to a non-endemic country and then develop malaria present particular problems, and they have a relatively high case fatality rate. Doctors in non-malarious areas may be unfamiliar with malaria, so the diagnosis may be delayed. Effective antimalarials may not be registered or may be unavailable. On the other hand, prevention of transmission or the emergence of resistance is irrelevant outside malaria endemic areas. Thus, monotherapy may be given if it is effective. Furthermore, the cost of treatment is usually not a limiting factor. The principles underlying the recommendations given below are that effective medicines should be used to treat travellers; if the patient has taken chemoprophylaxis, then the same medicine should not be used for treatment.

The treatment for *P. vivax*, *P. ovale* and *P. malariae* in travellers should be the same as for these infections in patients from endemic areas.

In the management of severe malaria outside endemic areas, there may be delays in obtaining Artesunate, Artemether or Quinine. If parenteral Quinidine is available but other parenteral drugs are not, then this should be given with careful clinical and electrocardiographic monitoring.

**Recommendation on treatment for infants and young children with uncomplicated *P. falciparum* malaria**:  
1. AL should be used as first line treatment  
2. Treat infants weighing <5kg with uncomplicated *P falciparum* malaria with AL dosed at the same mg/kg target as for children weighing 5kg  
3. Careful attention should be paid to accurate dosing and ensuring the administered dose is retained  
4. Referral to a health center or hospital is indicated for young children who cannot swallow antimalarial medicines reliably  
5. Pre-referral treatment with rectal Artesunate is indicated  
6. Primaquine should also be avoided in the first 6 month of age  
7. Tetracyclines must be avoided throughout infancy and in children < 8 years of age

**Recommendations on the treatment for travellers returning to non-endemic countries with uncomplicated *P. falciparum* malaria:**  
- Artemether plus Lumefantrine,  
- Dihydroartemisinin plus Piperaquine,  
- Quinine plus Doxycycline or Clindamycin; all drugs to be given for 7 days.
Chemoprophylaxis should be provided to international travellers going to high risk areas in and outside GMS; it is particularly important in the elimination phase. Because of the multi-drug resistance problem in malaria, chemoprophylaxis is not encouraged in Myanmar. Instead personal protective measures are prescribed for travellers with holding RDT and AL+PQ as standby treatment.

6.5.5. Mobile and migrant populations

Mobile populations are difficult to reach for a number of reasons including illegal status for some of them. Improving their access to needed health services can be a complex multi-sector task. While some migrants employed in informal or even illegal labor may prefer to avoid any contact with public services, others may be in regular employment and easy to work with, if they and their employers are approached in a sensitive manner. Different modalities for service provision have been carried out in GMS countries. In Myanmar, different approaches for providing malaria case management and other preventive services such as; mapping of migrants for accessibility to the health services provision, establishment of screening points both internal and border crossing points, scheduled visits of mobile teams to the worksites/remote villages, recruitment of worksite volunteers and training for malaria case management, and social marketing of quality assured ACT by private sector have been carried out by NMCP and implementing partners.

Standby treatment – is the treatment decided without a diagnostic test by the patient or somebody close and is a common practice, which has often been incriminated in relation to resistance to antimalarials in the GMS. With greatly improved service coverage (up to work site level) and especially the availability of RDTs, this should now be much less needed. However, there may be some mobile groups, who are so small and so isolated that standby treatment is the best that can be done. It is then better for public services to work with such groups and provide quality treatment and information than to neglect the problem. In Myanmar, social marketing of RDT along with quality ACT is encouraged to private sector to avoid enhancement of drug resistance problem by using ACT unnecessarily.

6.6. Co-existing morbidities

Sometimes people living with HIV/AIDS may get malaria infection should receive prompt, effective antimalarial treatment regimens as recommended in the relevant sections of these guidelines. Since National Treatment Policy for Malaria does not include Sulfadoxine-Pyrimethamine and Amodiaquine, no special consideration is needed for those HIV/AIDS patients who are taking Cotrimoxazole and Efavirenz, because AS+SP and AS+AQ combination have to be avoided for those HIV/AIDS who are on Cotrimoxazole and Efavirenz.

6.7. Mixed malaria infections

Mixed malaria infections are common. ACTs are effective against all malaria species, and they are the treatment of choice. Radical treatment with Primaquine should be given to patients with confirmed *P. vivax* and *P. ovale* infections.
**Recommendation on treatment of mixed malaria infections:**

Give AL+PQ as follows:

- By BHS/Hospital staff: AL+PQ (0.25mg/kg) daily (starting from Day 0) up to 14 days
- By Volunteers: AL+PQ (0.75mg/kg on Day 0), followed by PQ (0.75mg/kg) weekly for 7 weeks
7. Treatment of uncomplicated malaria caused by *P. vivax*, *P. ovale* and *P. malariae* \(^2\(^{(47)}\)

*P. vivax*, the second most important species causing human malaria, accounts for about 40% of malaria cases worldwide; it is the dominant malaria species outside Africa. In Myanmar, it accounts for 30% of total malaria cases. In most areas where *P. vivax* is prevalent, malaria transmission rates are low, and the affected populations, therefore, achieve little immunity to this parasite. Consequently, people of all ages are at risk. The other two human malaria parasite species *P. malariae* and *P. ovale* are generally less prevalent in Myanmar, but they are distributed worldwide. Among the four species of *Plasmodium* that affect humans, only *P. vivax* and *P. ovale* form hypnozoites, parasite stages in the liver, which can result in multiple relapses of infection weeks to months after the primary infection.

Thus, a single infection causes repeated bouts of illness. The objective of treating malaria caused by *P. vivax* and *P. ovale* is to cure (radical cure) both the blood stage and the liver stage infections, and thereby, prevent both recrudescence and relapse respectively\(^2\).

7.1. **Diagnosis** \(^2\(^{(48)}\)

The clinical features of uncomplicated malaria are too non-specific for a clinical diagnosis of the species of malaria infection to be made. Diagnosis of *P. vivax* can be done by both microscopy and RDT (Combo Test). Molecular markers for genotyping *P. vivax* parasites have been developed to assist epidemiological and treatment studies, but these are still under evaluation.

7.2. **Treatment of uncomplicated malaria caused by *P. vivax*, *P. ovale* and *P. malariae* \(^2\(^{(48)}\)

*P. vivax* is generally still sensitive to Chloroquine, although resistance is prevalent and increasing in some areas (notably Indonesia, Peru and Oceania). Resistance to Pyrimethamine has increased rapidly in some areas, and Sulfadoxine-Pyrimethamine is, consequently, ineffective in Myanmar.

### Recommendations on the treatment for uncomplicated *P. vivax*, *P. ovale* & *P. malariae* malaria\(^2\):

1. Chloroquine (total dose of 25mg base/kg) is still the treatment of choice for these malarials
2. *Plasmodium vivax* and *Plasmodium ovale* infections also require radical curative treatment with Primaquine on the last day of Chloroquine
   - Health staffs are asked to give Primaquine 0.25mg base/kg/day for 14 days for radical treatment
   - Volunteers must give Primaquine 0.75mg/kg once weekly for 8 weeks
3. For *Plasmodium malariae* infection, give Chloroquine which is still sensitive, but no need to give Primaquine as it has no hypnozoites
When Primaquine is given, patient must be informed to stop the drug as soon as urine colour becomes red.

The only drugs with significant activity against the hypnozoites are the 8-aminoquinolines (Buloquine, Primaquine, Tafenoquine).

### 7.3. Facts about Plasmodium knowlesi

*Plasmodium knowlesi* was first identified in India in 1931 from a long-tailed macaque (*Macaca fascicularis*) imported from Singapore (Knowles and Das Gupta, 1932). Its ability to infect humans was first described in 1932, when Knowles and Das Gupta successfully transmitted the parasite to two human volunteers by blood passages from infected macaques. However, the first natural human infection of *P. knowlesi* was only reported in 1965 in an American army surveyor who had acquired the disease while working in the jungle in the state of Pahang, Malaysia (about 300km north of Singapore). This was followed by a presumptive case reported from the state of Johor, Malaysia, which is adjacent to the island of Singapore (Yap et al., 1971). Human infections were thought to be rare until a large focus of humans infected with *P. knowlesi* were identified by nested polymerase chain reaction (PCR) detection assays in Sarawak, Malaysian Borneo, in 2004. Since then, cases of *P. knowlesi* infections in humans have been reported in other parts of Malaysia, China, Thailand, Singapore and the Philippines, resulting in *knowlesi* being recognized as the first *Plasmodium* species implicated in zoonotic disease. *P. knowlesi* infections have also been reported from European travelers returning from endemic countries.

The vectors of *P. knowlesi* in Singapore have yet to be identified. Currently, only mosquitoes belonging to the *Anopheles leucosphyrus* group have been incriminated for transmitting *P. knowlesi* in nature. These include *Anopheles hackeri* and *Anopheles cracens* in Peninsular Malaysia and *Anopheles latens* in Sarawak, Malaysian Borneo. Several anopheline species of the *Anopheles leucosphyrus* group have also been found to transmit other simian malaria parasites under natural or experimental conditions. The geographic distribution of this group of mosquitoes ranges from Southwestern India, eastward to Southern China, Taiwan, mainland Southeast Asia, Indonesia, and Philippines. However, to date, there have not been any reports of mosquitoes belonging to the *An. leucosphyrus* group in Singapore. During routine entomological surveillance of adult mosquitoes by the Singapore military in 2007 and 2008 at the affected areas under investigation, at least six species of anopheline mosquitoes were caught biting humans. These include *Anopheles barbirostris* species group, *Anopheles sinensis*, *Anopheles tesselatus*, *Anopheles sundaicus*, *Anopheles lesteri*, and *Anopheles kochi*.

In Myanmar, *P. knowlesi* cases have not been yet reported but the *Anopheles leucosphyrus* group (i.e. *Anopheles barbirostris* sp. group, *Anopheles sinensis*, *Anopheles tesselatus*, *Anopheles sundaicus*, *Anopheles lesteri*, and *Anopheles kochi*) are existing as secondary vectors in Myanmar.

**Treatment of *P. knowlesi***:

- Give AL for 3 days
- No need to give Primaquine since it has no hypnozoites
Treatment of severe and complicated malaria

8. Treatment of severe *P. falciparum* malaria

8.1. **Definition**\(^2\)(35)

In a patient with *P. falciparum* asexual parasitaemia and no other obvious cause of symptoms, the presence of one or more of the following clinical or laboratory features classifies the patient as suffering from severe malaria.

**Clinical features**\(^2\)(35)

- altered or decreased consciousness (e.g. confusion, delirium, coma)
- convulsions more than two episodes in 24 hours
- persistent vomiting (this may also be a neurological manifestation)
- prostration, i.e. generalized weakness so that the patient is unable to walk or sit up without assistance
- hyperpyrexia (39°C & higher, with dry skin)
- severe anaemia
- Renal failure – failure to make urine or making a very small quantity of urine
- pulmonary oedema (difficulty in lying flat due to breathing problems usually with cough)
- circulatory collapse (shock) – shown by a feeble, very rapid pulse and cold and clammy limbs
- spontaneous bleeding
- haemoglobinuria (black urine)
- jaundice, yellow coloration of the eyes, failure to respond to treatment within 3 to 7 days

(First four categories are included in Non-per-os patients)

**Laboratory findings:**

- hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
- haemoglobinuria
- hyperparasitaemia (> 2%/100,000/μl in low intensity transmission areas or > 5% or 250,000/μl in areas of high stable malaria transmission intensity)
- hyperlactataemia (lactate > 5 mmol/l)
- renal impairment (serum creatinine > 265 μmol/l)

8.2. **Treatment objectives**\(^2\)(36)

The primary objective of antimalarial treatment in severe malaria is to prevent death. In treating cerebral malaria, prevention of neurological deficit is also an important objective. In the treatment
of severe malaria in pregnancy, saving the life of the mother is the primary objective. In all cases of severe malaria, prevention of recrudescence and avoidance of minor adverse effects are secondary.

8.3. **Pre-referral treatment options**

One or more of the clinical features mentioned above is an indication for referral of severe and complicated malaria patients to a hospital. In general, those patients who are too ill to ingest oral medicines should be referred to a hospital. The risk of death from severe malaria is greatest in the first 24 hours, yet, in most malaria endemic countries, the transit time between referral and arrival at health facilities able to administer intravenous treatment is usually prolonged; this delays the commencement of appropriate antimalarial treatment. As during this time the patient may deteriorate or die, it is recommended that patients be treated with the first dose of one of the recommended treatments before referral (unless the referral time is less than 6 hours).

Severe and complicated malaria cases should be referred to hospital level after a pre-referral dose of IM injection Artesunate or Artemether, intramuscular Quinine (600 mg for adult), or Artesunate suppository, along with blood film/RDT result and referral letter that includes history of treatment given. If injection is impractical, using a single dose of rectal Artesunate as pre-referral treatment reduces the risk of death or permanent disability in young children less than 6 years of age. If referral is not feasible within 24 hours, treatment should be continued with the same pre-referral drug at appropriate time interval until referral is feasible.

### Recommendation for Referral

**Volunteer & BHS (SubRHC/RHC) level**

1. One or more of the clinical features mentioned above is an indication for referral
2. Patients with severe malaria should be referred to nearest hospital after a pre-referral dose of IM injection Artesunate or Artemether, IM Quinine or Artesunate suppository (10mg/kg) in young children <6 years of age.
Figure 1: Algorithm for management of severe *falciparum* malaria in small hospitals

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

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

When the patient is admitted to the hospital, it is crucially important to perform thorough history taking and clinical assessment.

- Severe malaria is a medical emergency.
- An open airway should be secured in unconscious patients and breathing and circulation (ABC of Coma) assessed (Annex 5).
- An intravenous cannula should be inserted and immediate measurements of blood glucose (stick test), haematocrit/haemoglobin, and parasitaemia.
- The assessment of fluid balance is critical in severe malaria. Renal function should be monitored by intake/output and fluid and electrolyte analysis.
- A detailed clinical examination should be conducted, including a record of the coma score by using modified Glasgow Coma Scale (Annex 6a) which is suitable for adults, and the simple Blantyre modification or children’s Glasgow Coma Scale which is suitable for children (Annex 6b).
Unconscious patients should have a lumbar puncture for cerebrospinal fluid analysis to exclude bacterial meningitis.

Monitor acidosis by respiratory rate/rhythm, plasma bicarbonate or venous lactate level.

Blood should be taken for cross-match, full blood count, platelet count, clotting studies, blood culture and full biochemistry (wherever possible).

Respiratory distress, in particular with acidic breathing in severely anaemic children, often indicates hypovolaemia and requires prompt rehydration and, where indicated, blood transfusion.

### 8.5. Specific antimalarial treatment

In all cases of severe malaria, parenteral antimalarial chemotherapy should be started immediately. Principles of treatment in severe malaria are as follows:

- Treat children and adults with severe malaria (including infants, pregnant women in all trimester, and lactating women) with intravenous or intramuscular Artesunate for at least 24 hours and until able to tolerate oral medication.
- Once the patient has received at least 24 hours of parenteral therapy, AND is able to tolerate oral therapy, complete treatment with three-days of an ACT.
- Children weighing less than 20 kg should receive a higher dose of Artesunate (3 mg/kg/dose) than larger children and adults (2.4 mg/kg/dose) to ensure an equivalent drug exposure.
- If parenteral Artesunate is not available, use Artemether in preference to Quinine for treating children and adults with severe malaria.

Clinical features and management of each type of severe and complicated malaria are mentioned in the next section.

Table 1: Dosage of antimalarial drugs in severe malaria

<table>
<thead>
<tr>
<th>S/N</th>
<th>Antimalarial Drug</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Artemisinin derivatives</td>
<td><strong>Artesunate:</strong> 2.4 mg/kg (BW) IV or IM on admission (time=0hr); followed by (F/by) 2.4 mg/kg at 12 &amp; 24 hrs; F/by once daily for 7 days. Once the patient can tolerate oral therapy, treatment should be switched to a complete dosage of ACT for 3 days + Primaquine single dose with the first dose of the ACT as recommended in the national treatment guidelines for Uncomplicated malaria. <strong>Artemether:</strong> 3.2 mg/kg BW IM on the first day F/by 1.6 mg/kg BW daily for 7 days. Once the patient can tolerate oral therapy, treatment should be switched to a complete dosage of ACT + Primaquine as recommended in the national treatment guidelines for Uncomplicated malaria.</td>
</tr>
<tr>
<td>2</td>
<td>Quinine</td>
<td><strong>Loading dose:</strong> Quinine dihydrochloride 20 mg/kg BW diluted in 10 ml/kg BW of 5% D/W or D/S administered by IV infusion over a period of 4 hrs. <strong>Maintenance dose:</strong> Quinine dihydrochloride 10 mg/kg BW diluted in 10 ml/kg BW of 5% D/W or D/S administered by IV infusion over a period of 4 hrs and repeated every 8 hrs. Once the patient can tolerate oral therapy, give a full treatment with an ACT + Primaquine according to national policy.</td>
</tr>
</tbody>
</table>
Remark:

- Artemisinin derivatives are safe, effective, have a wider therapeutic window, can be administered intramuscularly and should be considered a safer alternative to Quinine.
- A loading dose of quinine should not be given if
  i. the patient has received or suspected to have received Quinine, Quinidine or Mefloquine within the preceding 12 hours, and
  ii. facilities for controlled rate of flow of Quinine infusion are not available.
- If there is no clinical improvement after 48 hours of parenteral therapy, the maintenance dose of parenteral Quinine should be reduced by one third to a half (i.e. 5-7 mg/kg BW of Quinine dihydrochloride). The total daily dose of Quinine in patients requiring parenteral therapy beyond 48 hours is as follows:
  - Adults:
    o Day 0: (first day of treatment) 30-40 mg salt/kg of BW
    o Day 1: 30 mg salt/kg of BW
    o Day 2 and subsequent days: 15-21 mg salt/kg of BW
  - Children:
    o Day 0: (first day of treatment) 30-40 mg salt/kg of BW
    o Day 1: 20 mg salt/kg of BW
    o Day 2 and subsequent days: 10-14 mg salt/kg of BW
- Intravenous Quinine should be administered at recommended dosage for the first 48 hours even if acute renal failure (ARF) or severe jaundice is present.
- Quinine is not contraindicated in pregnancy.
- Pulse and blood pressure should be monitored ideally every hour and at least once in six hours while the patient is on Quinine, particularly for those with underlying heart disease or taking anti-arrhythmic drugs.
- Patient should be kept in bed while on parenteral Quinine to avoid severe postural hypotension.
- Volume of infusion fluid for administration of Quinine can be reduced to half (Quinine dihydrochloride 10 mg salt/kg BW diluted into 5 ml, or 1 mg of Quinine salt/0.5 ml of fluid) if volume overload is suspected. However, the duration of infusion should be the same.
- Quinine can be given by IM injections in the same dosages if IV infusion is not possible. It should be diluted in normal saline to a concentration of 60-100 mg salt/ml, the dose divided equally and administered in the two anterior thighs (not in the buttocks). An uncomplicated P. falciparum malaria patient may progress to a severe and complicated state if not treated early and appropriately.

8.6. Follow-on treatment

Following initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial using a full course of an effective ACT. Regimens containing Mefloquine should be avoided, if the patient presented initially with impaired consciousness. This is because of an increased incidence of neuropsychiatric complications associated with Mefloquine following cerebral malaria.
8.7. **Practical aspects of treatment**

The dosage schemes for uncomplicated Pf malaria is described in Annex 7, and that of uncomplicated Pv, Po and Pm malaria are described in Annex 8. Pharmacology of antimalarials recommended and used in Myanmar are described in Annex 10. The dosage of artemisinin derivatives does not need adjustment in vital organ dysfunction. Adjustment of dosing will be needed in renal failure or hepatic dysfunction for Quinine (and Quinidine) which may accumulate in severe vital organ dysfunction. If the patient remains in acute renal failure or has hepatic dysfunction, then the dose should be reduced by one third after 48 hours. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration.

8.8. **Adjunctive treatment**

In an attempt to reduce the unacceptably high mortality of severe malaria, various adjunctive treatments for the complications of malaria have been evaluated in clinical trials. These are summarized below (Table 2).

**Table 2: Immediate clinical management of severe manifestations and complications of Pf malaria**

<table>
<thead>
<tr>
<th>Manifestation/complication</th>
<th>Immediate Management a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma (cerebral malaria)</td>
<td>Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatment, such as corticosteroids, heparin and adrenaline; intubate if necessary.</td>
</tr>
<tr>
<td>Hyperpyrexia</td>
<td>Administer tepid sponging, fanning, a cooling blanket and antipyretic drugs Paracetamol is preferred over more nephrotoxic drugs (e.g. NSAIDs b).</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde. Check blood glucose.</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Check blood glucose, correct hypoglycaemia and maintain with glucose containing infusion.</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>Transfuse with screened fresh whole blood.</td>
</tr>
<tr>
<td>Acute pulmonary oedema c</td>
<td>Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxaemia.</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure add haemofiltration or haemodialysis, or if unavailable, peritoneal dialysis.</td>
</tr>
<tr>
<td>Spontaneous bleeding and coagulopathy</td>
<td>Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection.</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis.</td>
</tr>
<tr>
<td>Shock</td>
<td>Suspect septicaemia, take blood for cultures; give parenteral broad-spectrum antimicrobials, correct haemodynamic disturbances.</td>
</tr>
</tbody>
</table>

a - It is assumed that appropriate antimalarial treatment will have been started in all cases  
b - Non-steroidal anti-inflammatory drugs  
c - Prevent by avoiding excess hydration
8.9. **Continuing supportive care**

- Patients with severe malaria require intensive nursing care, preferably in an intensive care unit where possible. Clinical observations should be made as frequently as possible. These should include monitoring of vital signs, coma score, and urine output. Fluid requirements should be assessed individually. Adults with severe malaria are very vulnerable to fluid overload. Children, on the other hand, are more likely to be dehydrated. The fluid regimen must also be tailored around infusion of the antimalarial drugs.
- Central venous pressure should be maintained at 0-5 cm. If available, haemofiltration should be started early for acute renal failure or severe metabolic acidosis, which are unresponsive to rehydration.
- Blood glucose should also be monitored every four hours, if possible, particularly in unconscious patients. If blood glucose is < 2.2 mmol/l, then hypoglycaemia should be treated immediately (0.3-0.5 g/kg body weight of glucose). Hypoglycaemia should be suspected in any patient who deteriorates suddenly.
- Patients with clinically significant disseminated intravascular coagulation should be given fresh whole blood transfusions and vitamin K.
- Patients with secondary pneumonia or with clear evidence of aspiration should be given empirical treatment with a third-generation cephalosporin, or the appropriate antibiotic of known sensitivity in that locality.
- In children with persistent fever despite parasite clearance other possible causes of fever should be excluded. This includes a systemic Salmonella infection and urinary tract infections, especially in catheterized patients.
- However, in the majority of cases of persistent fever, no other pathogen is identified after parasite clearance. Antibiotic treatments should be based on culture and sensitivity results, or if not available, take into account likely local antibiotic sensitivity patterns.

8.10. **Additional aspects of management**

8.10.1. **Treatments not recommended**

Very few interventions are supported by evidence of benefit and many have proved harmful. Heparin, Prostacyclin, Desferoxamine, Pentoxifylline, low molecular weight dextran, urea, high-dose corticosteroids, Acetylsalicylic acid, Deferoxamine, anti-tumour necrosis factor antibody, Cyclosporine, Dichloroacetate, Adrenaline and hyper-immune serum are not recommended. In addition, the use of corticosteroids increases the risk of gastrointestinal bleeding and seizures, and has been associated with prolonged coma resolution times when compared with placebos.

8.10.2. **Fluid therapy**

The degree of fluid depletion varies considerably in patients with severe malaria. As a result, it is not possible to give general recommendations on fluid replacement. Each patient must be individually assessed and fluid resuscitation based on estimated deficit. In high-transmission settings, children commonly present with severe anaemia and hyperventilation (sometimes termed "respiratory
distress") resulting from severe metabolic acidosis and anaemia; they should be treated by blood transfusion. In general, children tolerate rapid fluid resuscitation better than adults; they are less likely to develop pulmonary oedema. In adults, there is a very thin dividing line between over-hydration, which may produce pulmonary oedema, and under-hydration contributing to shock, worsening acidosis and renal impairment. Careful and frequent evaluations of the jugular venous pressure, peripheral perfusion, venous filling, skin turgor and urine output should be made. Where the nursing facilities permit, a central venous catheter should be inserted and the central venous pressure measured directly (target 0-5 cmH₂O).

8.10.3. Blood transfusion

Severe malaria is associated with rapid development of anaemia as infected and uninfected erythrocytes are haemolysed and/or removed from the circulation by the spleen. Ideally fresh cross-matched blood should be transfused.

8.10.4. Exchange blood transfusion

There have been many anecdotal reports and several series claiming benefit for exchange blood transfusion (EBT) in severe malaria but no comparative trials, and there is no consensus on whether it reduces mortality or how it might work. It is, therefore, not possible to make any recommendation regarding the use of EBT.

8.10.5. Use of anticonvulsants

The treatment of convulsions in cerebral malaria with intravenous (or if this is not possible, rectal) benzodiazepines or intramuscular paraldehyde is similar to that for repeated seizures from any cause. A 20 mg/kg dose of phenobarbital should not be given without respiratory support, but whether a lower dose would be effective and safer, or whether if ventilation is given, mortality would not be increased is not known. In the absence of further information, prophylactic anticonvulsants are not recommended.

8.10.6. Concomitant use of antibiotics

The threshold for administering antibiotic treatment should be low in severe malaria. Septicaemia and severe malaria are associated and there is a diagnostic overlap, particularly in children. Unexplained deterioration may result from a supervening bacterial infection. Although enteric bacteria (notably Salmonella) have predominated in most trial series, so broad-spectrum antibiotic treatment should be given initially until a bacterial infection is excluded.
8.11. Management of severe complications

8.11.1. Cerebral malaria

Clinical features

Cerebral malaria is defined as unrousable coma (non-purposeful response or no response to a painful stimulus) in *falciparum* malaria. However, every patient of malaria with altered sensorium should be treated for cerebral malaria until proved otherwise. The altered sensorium may manifest as abnormal behaviour in a conscious patient in its mildest form to deep coma in its most severe form.

The patient with cerebral malaria may be manifested as:

- altered or decreased consciousness (e.g. confusion, delirium, coma)
- convulsions
- persistent vomiting (this may also be a neurological manifestation)

If in doubt as to the cause, test for other locally prevalent encephalopathies, e.g. bacterial and fungal meningo-encephalitis and viral encephalitis. Asexual malaria parasites are usually demonstrable on a peripheral blood smear. The opening pressure at lumber puncture is usually normal in adults, but may be elevated; the cerebrospinal fluid (CSF) is clear, with fewer than 10 white cells per microlitre; the protein is raised as is the CSF lactic acid concentration. Hepatosplenomegaly may be present. Microscopic examination of stained blood smears (both thick and thin films) should be done for confirmation of species, stages and density of malaria parasites. If clinical findings are suggestive of malaria, treatment of malaria should be given immediately even though malaria parasites are not detected by microscopic examination. Newly developed rapid diagnostic tests for detection of malaria antigens (Combo test, Card test, Optimal Test) and other available antigen test should be done for diagnosis can be obtained.

Management

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

(1) Care of the unconscious patient: Airway, breathing and circulation (ABC) (Annex 5) care of unconscious patients should be practiced in all patients of cerebral malaria in addition to meticulous nursing care.

(2) Symptomatic treatment: Convulsions and body temperature should be controlled:

- **Control of body temperature:** Body temperature may be controlled by tepid sponging and fanning. If the fever is not controlled then appropriate antipyretics (Paracetamol) may be used.
- **Control of convulsions:** Convulsions can be controlled with intravenous Diazepam of (0.15 mg/kg of body weight, maximum 10 mg for adults) should be used. Diazepam can also be given intrarectally (0.5-1.0mg/kg of body weight) if injection is not possible. The dose can be repeated every 15 minutes if the convulsion persists but the total should not exceed 20 mg
in an hour. This regimen can be repeated once every 2-4 hours up to a maximum dose of 100 mg in 24 hrs. Intramuscular injection of paraldehyde (0.2 ml/kg BW) or 0.4 ml/kg intrarectally is safe and an effective anti-epileptic drug. It carries a minimal risk of respiratory depression and may be given in repeated doses, even to children who have already received diazepam. For repeated and uncontrolled seizures, phenytoin 15-20 mg/kg BW (administered by slow intravenous injection, the rate not exceeding 0.5 mg/kg BW/min) can be used. The drug should not be diluted with dextrose-containing fluids as it precipitates easily. Maintenance, if necessary, is to be executed with 5 mg/kg BW every 12 hours.

- The comatose patient should be given meticulous nursing care and insert a urethral catheter using a sterile technique, unless the patient is anuric.
- Keep a precise record of fluid intake and output.
- Monitor & record the level of consciousness, temperature, respiratory rate, blood pressure, and vital signs.

The followings are generally not recommended:

- corticosteroids,
- other anti-inflammatory agents,
- other agents given for cerebral oedema (urea, invert sugar, mannitol),
- low molecular weight dextran,
- epinephrine (adrenaline),
- heparin, pentoxifylline (oxipentifylline),

N.B. If patient remains comatose after having malaria treatment for 24 hours, other possible complications should be looked for.

8.11.2. Anaemia¹₀

Clinical features

Anaemia of varying degree is a common accompaniment in severe malaria. Severe anaemia is defined as haemoglobin lower than 5g/dl or haematocrit lower than 15%. Parasitaemia is often low. The signs and symptoms of anaemia in malaria depend on the degree of anaemia and rate of decrease of blood haemoglobin concentration. Sudden fall in the haemoglobin concentration may lead to cerebral anoxia and may even manifest as cerebral malaria. Malaria patients having pre-existent severe iron deficiency anaemia may present with manifestations of heart failure. Anaemia decreases oxygen carrying capacity of the blood and severe anaemia may lead to tissue hypoxia and lactic acidosis. Haemoglobin level in finger-prick samples may be lower than venous blood due to serum oozing during squeezing the finger by finger prick.

Management

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

- Indications of blood transfusion:
(a) Based on blood haemoglobin:

1. when fall of haemoglobin is by 20% or more per day
2. haemoglobin concentration of <7.0 g/dl with symptoms of severe malaria (signs of hypoxia, severe metabolic acidosis with no other apparent cause) or features of heart failure, or
3. haemoglobin concentration of <5.0 g/dl with or without symptoms.

(b) Based on clinical criteria: anaemic patients with

1. hyperparasitaemia, in whom a large drop in haemoglobin is anticipated;
2. impaired consciousness, which might be exacerbated by reduced oxygen supply secondary to anaemia;
3. ARF where haemodialysis is required;
4. disseminated intravascular coagulation (DIC), and
5. high output cardiac failure.

- Transfusion of pathogen-free compatible fresh blood, preferably packed cells or settled cells should be given.
- Small intravenous doses of furosemide (adult: 20-40 mg; children: 1 mg/kg) may be given during the blood transfusion to avoid circulatory overload, provided that the patient’s renal function is adequate. In patients with ARF, only packed or settled cells should be transfused. The volume of transfused blood should be included in calculation of fluid balance.
- Haemoglobin or haematocrit should be monitored daily during treatment.
- Remember to include the volume of transfused cells or blood in calculations of fluid balance.
- Supplementary folic acid should be given.
- Iron or iron containing tonics should be prescribed only if the cause of anaemia is iron deficiency after recovery from acute malaria.

8.11.3. Acute renal failure

Clinical features

- ARF may present as oliguric or non-oliguric renal failure and even anuria in severe cases.
- The diagnosis of ARF is suspected when urine output decreases to 400 ml or less in 24 hours or 20 ml/hour (<0.5ml/kg BW per hour for children), which fails to improve after rehydration.
- The diagnosis is confirmed when the serum creatinine exceeds 3 mg/dl (265 μmol/l) in adults and 1.5 mg/dl (130 μmol/l) in children. Oliguric phase usually lasts about a week but may vary from a few days to a few weeks.
- Pre-renal azotemia usually presents with clinical signs of severe dehydration. However, prolonged anuria or oliguria may lead to inevitable volume overload because of diminished salt and water excretion. The distinction between pre-renal and established ARF is important for the correct clinical management, which can be differentiated by the simple measurement of urine specific gravity. In pre-renal azotemia it may be more than 1.020 while in established ARF it may be less than 1.010 due to loss of urine concentration ability of the kidneys. Renal failure as a complication of malaria is virtually confined to adults. There is a rise in serum creatinine and
urea, oliguria and eventually anuria due to acute tubular necrosis. Renal failure is usually oliguric but may occasionally be polyuric. Acute renal failure is usually reversible.

Management of Acute Renal Failure

**Fluid replacement**

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

**Supportive therapy**

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

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

- Nephrotoxic drugs should be avoided when ARF is suspected or anticipated.
- Exclude dehydration (hypovolaemia) by clinical examination, including measurement of jugular or central venous pressure where available.
- Carefully infuse isotonic saline until venous pressure reaches between 0 and 5 cmH2O.
- Peritoneal dialysis or haemodialysis is indicated if the patient remains oliguric after adequate rehydration and the blood urea and creatinine rise progressively.
- Peritoneal dialysis should not be undertaken lightly. If possible, refer the patient to a dialysis unit or center.
The following drugs should be avoided in malaria patients because of their adverse reactions on renal function:

- Angiotensin-converting enzyme inhibitors (ACEI)
- Cloxygenase inhibitors
- Non-steroidal anti-inflammatory drug (NSAID) should not be given as they may precipitate pre-renal azotemia to ischaemic ARF.
- Assessment of renal function using measurement of urine volume should not be done in patients receiving diuretics.

8.11.4. Fluid, electrolytes and acid-base disturbances \(^{10(35)}\)

(i) Hypovolaemia

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

Clinical features of Hypovolaemia

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

- Clinical evidence of hypovolaemia
- Acidotic breathing
- Hyperventilation
- May develop in severely ill patients who are shocked, hypoglycemic, hyperparasitaemic, or in renal failure. Lactic acidosis is a common complication and both blood and CSF lactic acid concentration are raised. Perfusion is improved by correcting hypovolaemia.

Management

- Look for evidence of dehydration and hypovolaemia:
  - reduced ocular tension, reduced skin turgor,
  - relatively cool extremities, postural drop in blood pressure >10mmHg (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 < 20mmol/L.
- If there is evidence of dehydration, give modest volumes of isotonic fluids (0.9% saline or dextrose saline) by intravenous infusion, but avoid fluid overload. Dehydration should be corrected with 0.9% saline or 5% dextrose saline by IV infusion. Excessive administration of
isotonic dextrose solutions can induce hypoosmolality and hyponatremia. If severe, it may lead to cerebral oedema and neurological abnormalities, including seizures.

- For correction of metabolic acidosis sodium bicarbonate infusion (1.26% to 8.4%) is used in cases of extreme acidosis (e.g. blood potassium less than 7.1 (or) blood bicarbonate less than 10 mmol/litre) and shock since the acid-base disturbance is normally corrected by treating underlying cause. Avoid administration of sodium bicarbonate unless associated with severe life threatening acidosis.
- Monitor blood pressure, urine volume (every hour), and jugular or central venous pressure.
- Improve oxygenation by: clearing airway and oxygen therapy
  - increasing concentration of inspired oxygen, and
  - supporting ventilation artificially, if necessary.

(ii) Hyponatremia ¹⁰[36]

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

8.11.5. Circulatory collapse/shock/algid malaria ⁶, ¹⁰[36]

Clinical features

Some patients are admitted in a state of collapse, with a 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. In some countries clinical picture is often associated with a complicating Gram-negative septicaemia. Circulatory collapse is also seen in patients with pulmonary oedema or metabolic acidosis, and following massive gastrointestinal haemorrhage and ruptured spleen. Dehydration with hypovolaemia may also contribute to hypotension. Possible sites of associated infection should be sought, e.g. lung, urinary tract (especially if there is an indwelling catheter), meningitis, intravenous injection sites, intravenous lines.

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

(1) Having systolic blood pressure in supine position:

  - Lower than 80 mmHg in adults, adolescent and children aged over 10 years,
  - Lower than 70 mmHg in children aged 1 month-10 years,
  - Lower than 60 mmHg in neonates, and

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

- Correct hypovolaemia with an appropriate plasma expander (normal saline or 5% dextrose slaine/fresh blood/plasma/polygeline or dextran 70).
- Look for the possible sites of infection (lung, urinary tract, IV injection sites)
- Take blood culture and start patient on broad spectrum antibiotics immediately, e.g. third-generation cephalosporins
- Once the results of blood culture and sensitivity test are available, give the appropriate antibiotic.
- Dopamine infusion: If patient does not respond to adequate fluid therapy, Dopamine 5-20 gm/kg/min in 5% D/W or 500 ml of 0.9% sodium chloride IV infusion is given and in low dose for renal effect (2.5 mg/kg/min or 8-30 drops/min according to BP response.)

8.11.6. Metabolic acidosis

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

Clinical features

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

Management of metabolic acidosis

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

8.11.7. Jaundice

Although jaundice per se is not considered as severe malaria, it indicates a severe degree of the disease when combined with other vital-organ dysfunction. Jaundice in severe malaria is more commonly found in adults than in children. A tender enlargement of the liver and spleen are common in malaria. Mild jaundice may be due to haemolysis but a considerable rise in bilirubin levels is usually associated with hepatic dysfunction. The dose of liver enzymes Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) may be increased, but rarely more than 10 times the normal. Other causes of jaundice should be excluded if the enzyme levels are found to be very high. Jaundice in malaria patients may not be fatal on its own but mortality is increased significantly when high bilirubin values are associated with renal failure and cerebral malaria. Clinical signs of liver failure with hepatic encephalopathy are rare. Hepatic dysfunction may lead to altered handling of antimalarial drugs.
No specific treatment is required for jaundice.

8.11.8. Hypoglycaemia

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

Clinical features

In conscious patients, hypoglycaemia may present with classical symptoms of anxiety, sweating, palilpitation, dilatation of the pupils, breathlessness, alteration of consciousness, 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 possible, confirm in the high-risk groups mentioned above.

Management

- If hypoglycaemia is detected by blood testing or suspected on clinical grounds, give 25% or 50% glucose 50 ml (1.0 ml/kg for children) by intravenous bolus injection. Follow with an intravenous infusion of 10% glucose as maintenance and adequate feeding.
- Continue to monitor blood glucose levels (using a rapid test method if available, or clinically and biochemically if not) in order to regulate the glucose infusion.
- Take into account that hypoglycemia may recur even after an intravenous bolus of 50% glucose.

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

8.11.9. Pulmonary oedema/Acute Respiratory Distress Syndrome

Clinical features

Pulmonary oedema is a grave complication of severe malaria, with a high mortality (over 50%). It may appear several days after chemotherapy 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 fluid overload, but in some patients pulmonary oedema may develop even with normal or negative fluid balance. Malaria patients with ARF, severe anaemia and pregnant women – particularly after delivery – are vulnerable for pulmonary oedema/ARDS. The indication of impending pulmonary oedema is:

- An increase in the respiratory rate in the absence of metabolic acidosis and anaemia
- Shortness of breath (dyspnoea)
- Difficulty in lying down (orthopnoea)
- Basal crepitations
- Hypoxia may cause convulsions and deterioration in level of consciousness
  (Differentiation of pulmonary oedema, metabolic acidosis and pneumonia – See Annex 9)

**Management** 6, 10

- Keep patient semi-upright; raise the head end of the bed or lower the foot end of the bed, nurse the patient at 45°.
- Give a high concentration of oxygen by any convenient method available, including mechanical ventilation.
- Give the patient a diuretic, such as furosemide 40 mg, by intravenous injection.
- If there is no response (by monitoring of respiratory symptoms, urinary output and basal crepitations) increase the dose progressively to a maximum of 200 mg.
- In well-equipped intensive care units, mechanical ventilation with Positive End Expiratory Pressure (PEEP), a wide range of vasoactive drugs and haemodynamic monitoring will be available.
- If the pulmonary oedema is due to overhydration:
  - Stop all intravenous fluids.
  - Use haemofiltration immediately, if available.
  - Give furosemide 40 mg intravenously. If there is no response, increase the dose after ½ to 1 hour interval, progressively to a maximum of 200 mg.
- If there is no improvement, (by monitoring of respiratory symptoms, urine output and basal crepitations) withdraw 250ml of blood initially by venesection into a blood transfusion donor bag so that it can be given back to the patient later.

**8.11.10. Spontaneous bleeding/Disseminated Intravascular Coagulation** 10(41)

**Clinical features**

- 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.
- It is relatively common in non-immune patients with imported malaria in the temperate zone.
- Thrombocytopenia is common (with mild symptoms of ecchymosis of skin, and subconjunctival haemorrhage) 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, blood clotting factors or fresh plasma as required.
- If the prothrombin or partial thromboplastin times are prolonged, give vitamin K 10 mg by slow intravenous injection.
8.11.11.  Macroscopic haemoglobinuria (Black water fever)  

Clinical features

Malaria haemoglobinuria may be due to:

1. Patients with glucose-6-phosphate dehydrogenase (G6PD) 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.
2. Quinine hypersensitivity
3. Malaria itself

The mortality rate from black water fever is highest when it is associated with severe malaria and other evidence of vital organ dysfunction.

Management

- Continue appropriate antimalarial treatment
- Transfuse fresh blood to maintain haematocrit above 20% (or) haemoglobin level above 6g/dl.
- Monitor jugular or central venous pressure to avoid fluid overload and hypovolaemia.
- Steroid should be given if haemoglobinuria is due to quinine hypersensitivity
- Black water fever is often not associated with significant renal impairment. Manitol may be given after proper re-hydration to ensure adequate urine output.
- If oliguria develops and blood urea and serum creatinine levels rise, peritoneal dialysis or haemodialysis may be required.
- It is usually transient and resolves without complications though renal failure may develop in severe cases. In case of renal failure, the patient must be referred to a dialysis centre.

8.11.12.  Hyperpyrexia

Clinical features

Hyperpyrexia is more common in children and is associated with convulsions, delirium and coma. In un-acclimatized visitors to the tropics, it must be differentiated from heat stroke. High body temperatures (42°C and above) may cause permanent severe neurological sequelae. There is evidence that high body temperature in pregnant women contributes to fetal distress, abortion, premature labour.

Management

- Monitor body temperature frequently. If body temperature is above 39°C, apply vigorous tepid sponging and fanning, and give Paracetamol, 15 mg/kg of body weight by mouth, suppository or by nasogastric tube.
- If feasible, patient should be kept in air conditioned room
- Parenteral antipyretics (e.g. Analgesin) should be avoided.
8.11.13. Hyperparasitaemia

Clinical features

In general and especially in non-immune subjects, high parasite densities (above 5%) and peripheral schizontaemia are associated with severe disease; however, in highly endemic malarious areas, partially immune children can tolerate surprisingly high densities (20-30%) often without clinical symptoms.

Management

- An initial dose of parenteral antimalarial therapy is prudent, even if the patient can take medication by mouth.
- Some physicians recommend exchange or partial exchange transfusion (between quinine infusions) if parasitaemia exceeds 10% in a severely ill patients.
- The risks of the above procedures in the tropics, e.g. from transfusion related infections and incurred risk of bacterial infection, must be carefully assessed.
9. Management of severe malaria in special groups

9.1. Management of severe malaria in pregnancy\textsuperscript{10}

Women in the second and third trimesters of pregnancy are more likely to develop severe malaria than other adults, and in low-transmission settings, this is often complicated by pulmonary oedema and hypoglycaemia. Maternal mortality is approximately 50%, which is higher than in non-pregnant adults. Fetal death and premature labour are common.

9.1.1. Severe malaria\textsuperscript{6}

Clinical features

Pregnant women with malaria must be treated promptly, because the disease is more severe, is associated with high parasitaemia, and is dangerous for mother and fetus. Non-immune pregnant women are susceptible to all the manifestations described in above section. Moreover they have an increased risk of abortion, stillbirth, premature delivery and low birth weight of their infant. They are more likely to develop cerebral and other forms of severe malaria, and to suffer a high mortality (2-10) times higher than non-pregnant patients. They are particularly susceptible to hypoglycaemia and acute pulmonary oedema. Partially immune pregnant women, especially primigravidae, are susceptible to severe anaemia but other complications are unusual. \textit{Falciparum} malaria commonly induces uterine contractions and gives rise to premature labour. The frequency and intensity of contractions appear to be related to the height of the fever. Fetal distress is common, but frequently not diagnosed. The prognosis for the fetus is poor in severe disease. Associated infections can occur. Pneumonia and urinary tract infections are common.

Management

Pregnant women with severe malaria should be transferred to intensive care if possible. Monitoring of uterine contractions and fetal heart rate may reveal asymptomatic labour and fetal tachycardia, bradycardia, or late deceleration in relation to uterine contractions, indicating fetal distress. Once labour has started, fetal or maternal distress may indicate the need to shorten the second stage by forceps or vacuum extraction or Caesarean section.

9.1.2. Hypoglycaemia

Clinical features

Hypoglycaemia may be present in pregnant women on admission, or may occur after quinine infusion. It is commonly asymptomatic, although it may be associated with fetal bradycardia and other signs of fetal distress. In the most severely ill patients, it is associated with lactic acidosis and high mortality. In patients who have been given quinine, abnormal behavior, sweating, and sudden loss of consciousness are the usual manifestations.
Management

If the diagnosis is in doubt, a therapeutic test with 50% glucose (25-50 ml intravenously) should be used. Recurrent severe hypoglycaemia may be a problem in some cases. If injectable glucose is not available, glucose solutions can be given to unconscious patients through a nasogastric tube.

9.1.3. Pulmonary oedema

Clinical features

Pulmonary oedema may be present in pregnant women on admission, may develop suddenly and unexpectedly several days after admission, or may develop immediately after childbirth.

9.1.4. Anaemia

Clinical features

Maternal anaemia is associated with perinatal mortality, maternal morbidity and an increased risk of fetal maternal postpartum haemorrhage. Women who go into labour when severely anaemic or fluid overloaded may develop pulmonary oedema after separation of the placenta.

Management

Women with a haematocrit lower than 20% should receive a slow transfusion of packed cells and furosemide 20 mg intravenously; alternatively, they may be given exchange transfusion (in centers where this can be done safely).

9.1.5. Specific treatment for severe malaria in pregnancy

Parenteral antimalarials should be given to pregnant women with severe malaria in full doses without delay. Parenteral Artesunate is preferred over quinine in all trimesters, because quinine is associated with recurrent hypoglycaemia.

- Treatment must not be delayed; so if only one of the drugs Artesunate, Artemether or quinine is available, then it should be started immediately.
- Obstetric advice should be sought at an early stage, the paediatricians alerted, and blood glucose checked frequently.
- Hypoglycaemia should be expected, and it is often recurrent if the patient is receiving quinine.
- Severe malaria may also present immediately following delivery. Postpartum bacterial infection is a common complication in these cases.
Recommendation for the treatment of severe malaria in pregnancy

- Management of severe and complicated malaria for pregnancy is same as other adult populations – IV Artesunate. If Artesunate is not available, then IM Artemether should be used in preference to quinine.

9.2. Management of severe malaria in children

9.2.1. Severe malaria

Clinical features

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

Table 3: Differences between severe malaria in adults and in children

<table>
<thead>
<tr>
<th>Signs &amp; symptoms</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Common</td>
<td>Very common</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>5-7 days</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Resolution of coma</td>
<td>2-4 days</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Neurological signs: fits</td>
<td>&lt;5%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pretreatment Hypoglycaemia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Pulmonary Oedema</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>CSF opening pressure</td>
<td>Usually normal</td>
<td>Variable, often raised</td>
</tr>
<tr>
<td>Bleeding/ clotting disturbances</td>
<td>Up to 10%</td>
<td>Rare</td>
</tr>
<tr>
<td>Abnormality of brain stem reflexes (eg. Oculovestibular, oculocervical)</td>
<td>Rare</td>
<td>More common</td>
</tr>
</tbody>
</table>
Management

The management of severe malaria in children is generally similar to that of adults. Some specific aspects will be re-emphasized in the followings:

I. The parents or other relatives should be questioned about:
   (i) residence or history of travel;
   (ii) previous treatment with antimalarials or other drugs;
   (iii) recent fluid intake and urine output; and
   (iv) recent or past history of convulsions

II. A rapid initial examination should be carried out to assess:
   (i) hydration;
   (ii) anaemia;
   (iii) pulmonary oedema;
   (iv) level of consciousness; and
   (v) hyperpyrexia

III. Immediate tests must include:
   (i) thick and thin blood films;
   (ii) haematocrit;
   (iii) finger-prick blood glucose; and
   (iv) lumbar puncture

IV. If parasitological confirmation is likely to take more than one hour, RDT must be used for diagnosis and treatment should be started before the diagnosis is confirmed.

V. The use of a single intramuscular injection of Phenobarbital sodium 10mg/kg of body weight on admission may reduce the incidence of convulsions.

VI. If the child has a convulsion, this should be treated with paraldehyde by rectal route body weight. (The dosage is 0.3 ml/kg diluted with equal volume of olive oil or 1 in 10 with Normal Saline 0.9%. Plastic syringe can be used if the drug is administered immediately)

VII. Diazepam may also be used. (Rectal dose is 2.5 mg for under 1 year, 5 mg for 1-3 years, and 10 mg for over 3 years of age.)

VIII. Any children with convulsions should be examined for hyperpyrexia and hypoglycaemia and given appropriate treatment.

IX. Simple practical maneuver, such as tepid sponging and fanning, should be employed to try to keep the body temperature below 38.5°C.

X. Paracetamol, 15 mg/kg of body weight, may also be given as an antipyretic.
9.2.2. Cerebral malaria in children

Clinical features

- The early symptoms of cerebral malaria in children are fever (37.5°C - 41°C), inability to eat or drink. Cough and vomiting are common. The history of symptoms preceding coma may be very brief – one or two days in most cases.
- Convulsions are common before or after the onset of coma. Occasionally their presentation may be very subtle such as intermittent nystagmus, salivation, and minor twitching of a single digit or corner of the mouth and an irregular breathing pattern.
- In children with profound coma, corneal reflexes and “doll’s eye” movement may be abnormal.
- In some children opisthotonus may be observed, which may lead to a mistaken diagnosis of tetanus or meningitis.
- A child who lost consciousness after a febrile convulsion should not be considered to have cerebral malaria unless coma persists for more than half an hour after the convulsion. The depth of coma may be assessed according to the Blantyre coma scale (Annex 6b).
- Always exclude or treat hypoglycaemia.
- 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 a systolic blood pressure below 50 mmHg.
- CSF opening pressure is variable; it is raised more frequently than in adults, and is sometimes very high.
- Leukocytosis 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 from cerebral malaria have neurological sequelae which persist into the convalescent period. Sequelae may take the form of hemiparesis, cerebellar ataxia, cortical blindness, severe hypotonia, mental retardation, generalized spasticity, or aphasia.

Management of cerebral malaria in children

- Convulsions are common in children and can be treated with intravenous diazepam, 0.3 mg/kg BW (rate not exceeding 2 mg/minute) or as slow bolus (“push”) or 0.5 mg/kg BW administered intra-rectally. Alternately, paraldehyde 0.2 ml/kg BW may be administered by deep intramuscular injection or 0.4 ml/kg BW intra-rectally.
- In case of repeated convulsions, the followings are recommended:
  (a) Phenytoin sodium 0.5 mg/kg BW/minute in a non-glucose-containing fluid, preferably in isotonic saline (or)
  (b) Phenobarbitone intravenous or intramuscular loading dose of 10-15 mg/kg BW and maintenance dose of 3-5 mg/kg BW/day in divided doses twice daily.
The management of cerebral malaria in children is the same as in adults, including the modalities of careful nursing and monitoring of the unconscious patient.

The child with cerebral malaria may also suffer from anaemia, respiratory distress (acidosis) and hypoglycaemia. These problems have to be managed accordingly.

If hypoglycaemia cannot be excluded by blood glucose examination, then all unconscious patients of malaria should be treated with intravenous glucose.

9.2.3. Severe anaemia in children

Anaemia is more common in children than adults. Children with severe anaemia may show signs of acidosis such as deep and labored breathing and grunting, hypoxic cerebral signs such as confusion, restlessness and coma, and cardiopulmonary signs such as tachycardia, dyspnoea, gallop rhythm and pulmonary oedema. 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 normochromic anemia in which dyserythropoietic changes in the bone marrow are prominent.

In other children, severe anaemia may develop rapidly in association with hyperparasitaemia. In these cases, acute destruction of parasitized red cell is responsible for this.

Management of severe anaemia in children

Indications of blood transfusion in anaemic children are the same as that for adults, a haematocrit of less than 15% (or) haemoglobin level less than 6 g/dl in a normally hydrated child is an indication for blood transfusion. Some children may require urgent blood transfusion (10 ml packed cells or 20 ml whole blood per kg body weight). A diuretic may not be indicated if the child is hypovolaemic, but many of the severely anaemic children may be in a hyperdynamic circulatory state. In such cases, furosemide 1-2 mg/kg body weight should be given intravenously before blood transfusion.

9.2.4. Hypoglycaemia in children

Hypoglycaemia is particularly common in children under three years of age and in those with convulsions or hyperparasitaemia, or in profound coma. It is easily overlooked clinically because the manifestations may be similar to those of cerebral malaria. Unconscious children should be given dextrose regularly to prevent starvation hypoglycaemia. It is most conveniently provided as 5% dextrose in saline infusion, but if volume overload is anticipated 25% dextrose diluted in an equal volume of normal saline or 10% dextrose may be infused intravenously. If this fails, 25% dextrose or any sugary solution may be given through a nasogastric tube at a dose of 1 ml/kg of body weight. Monitoring of blood glucose levels should continue even after apparent recovery, since
hypoglycaemia may recur. Unconscious children should be given adequate nasogastric tube feeding to prevent starvation and hypoglycaemia. Precaution should be taken to avoid aspiration pneumonia.

9.2.5. Metabolic acidosis in children

Rapid and deep breathing with recession of the bony structures of the lower chest wall suggests metabolic acidosis. Metabolic acidosis commonly accompanies cerebral malaria or anaemia but it may develop in a child without impaired consciousness. The risk of death is increased in either case.

Its management consists of correction of all reversible causes of acidosis such as dehydration or severe anaemia as mentioned.

9.2.6. Dehydration

Clinical features

The best clinical indications of moderate to severe dehydration in children are decreased peripheral perfusion, deep (acidotic) breathing, decreased skin turgor, raised blood urea (>6.5mmol/l), increased thirst, loss of about 5-10 % of total body weight and evidence of metabolic acidosis.

Management

Careful rehydration with isotonic saline is mandatory, with frequent examination of blood pressure and basal crepitations.

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).

9.2.7. Antimalarial drugs for children

Antimalarial drugs should preferably be given initially by intravenous infusion; this should be replaced by oral administration as soon as the patient is able to swallow drugs without vomiting. Weighing of children is mandatory and the dose of antimalarials should be calculated on the basis of body weight (mg/kg).

If intravenous infusion is impossible, quinine may be given by intramuscular injection into the anterior thigh. Do not attempt to give oral medication to unconscious children; if parenteral injection is not possible and referral is likely to be delayed, antimalarials may be given by nasogastric tube. However, nasogastric administration may cause vomiting and produce inadequate drug levels in the blood.
Recommendation for treatment of severe malaria in children\textsuperscript{10}

- For children less than 20 kg body weight, Artesunate 3.0 mg/kg and for older children 2.4 mg/kg BW IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment. Artemether, or quinine is an acceptable alternative if parenteral Artesunate is not available: Artemether 3.2 mg/kg BW IM given on admission then 1.6 mg/kg BW per day; or quinine 20 mg salt/kg BW on admission (IV infusion or divided IM injection), then 10 mg/kg BW every 8 h; infusion rate should not exceed 5 mg salt/kg BW per hour.
10. Treatment of severe *P. vivax* malaria

Although *P. vivax* malaria is considered to be benign malaria, with a very low case fatality ratio, it may still cause a severe and debilitating febrile illness. It can also occasionally result in severe disease, as in *P. falciparum* malaria. Severe *P. vivax* malaria manifestations that have been reported are cerebral malaria, severe anaemia, severe thrombocytopenia and pancytopenia, jaundice, splenic rupture, acute renal failure and acute respiratory distress syndrome. Severe anaemia and acute pulmonary oedema are not uncommon. The underlying mechanisms of severe manifestations are not fully understood. **Prompt and effective treatment and case management should be the same as for severe and complicated *falciparum* malaria.**
11. Management of malaria in complex emergencies and epidemics

11.1. Diagnosis

Rapid diagnostic tests offer the advantage of being quick to perform with less need for skilled laboratory technicians in epidemic situations. However parasitological diagnosis by microscopy is essential to know the gametocyte carrier rate among the population especially by age group. The presence of gametocytes in young children and infants indicates that the local transmission is existed and successive appearance of gametocyte among population is one of the indicators for ongoing transmission.

In all circumstances of fever, parasite-based diagnosis is needed to:
- diagnose malaria as the cause of an epidemic of febrile illness;
- monitor the epidemic curve and confirm the end of an epidemic;
- follow progress in infants, pregnant women, those with severe malaria, the severely malnourished, and suspected treatment failures.

The latter can only be done with microscopy. Microscopy capacity is also needed for field quality control of rapid diagnostic tests and it is, therefore, necessary to build this capacity as soon as possible.

11.2. Management of uncomplicated malaria in epidemics

- Most malaria patients in epidemics and emergencies are non-immune, partially immune, or otherwise vulnerable to severe disease. An active search should be made for febrile patients to ensure that as many patients as possible receive adequate treatment, rather than relying on patients to come to a fixed clinic. The principles of treatment are the same as elsewhere (See Section 6 & 7). Complete courses of treatment should always be given in all circumstances.
- During mixed *falciparum/vivax* malaria epidemics, ACTs should be used for treatment as they are highly effective against all malaria species. In areas with pure *P. vivax* epidemics, and where drug resistance has not been reported, Chloroquine is the most appropriate medicine once the cause of the epidemic has been established. In areas where resistance of *P. vivax* to Chloroquine has been reported, ACT is recommended. Use of Primaquine as gametocytocidal action is mandatory.
- The 14-day anti-relapse therapy for *vivax* malaria is impractical in most epidemic situations because of the duration of treatment and poor compliance. Moreover, it is not an effective strategy as long as the risk of re-infection is high. If adequate records are kept, anti-relapse therapy can be given in the post-epidemic period to patients who have previously been treated with blood schizonticides. Primaquine 0.25-0.5 mg base/kg body weight in two divided daily doses should be given for 14 days, as there is no evidence that shorter courses are effective.
- Appropriate health education should be provided to encourage adherence in situations where Primaquine is given without supervision.
11.3. **Management of severe malaria in epidemics**

Management of severe *P. falciparum* malaria in epidemic situations will often take place in temporary clinics or in situations in which staff shortages and high workloads make intensive case monitoring difficult. Drug treatment should, therefore, be as simple and safe as possible, with simple dosing schedules and minimal need for monitoring the treatment. The principles of treatment remains the same as already described above. Intramuscular Artesunate is the drug of choice, the use of intramuscular Artemether with its simple one-a-day regimen and ease of administration is an attractive treatment option in overburdened epidemic situations, where Artesunate is not available. Experience with Artesunate suppositories in epidemic situations is limited. Their use may be appropriate in severely ill patients who are unable to swallow oral medication when intramuscular Artesunate or Artemether is unavailable. If Artesunate suppositories are used, patients should be moved as soon as possible to a facility where intramuscular or intravenous therapy can be started. When the patient cannot be moved, continued treatment with rectal Artesunate is appropriate until oral drugs can be administered. It is essential that a full course of antimalarial treatment be completed.

If the patient is to be referred, recommendations made for “Pre-referral Treatment” must be followed.

**Summary recommendations on treatment of uncomplicated malaria in epidemic situations:**

1. The principles of treatment are the same as in section 6 & 7.
2. The following ACTs are recommended for antimalarial treatment in *P. falciparum* or mixed *P. falciparum/P. vivax* malaria epidemics:
   - Artemether plus Lumefantrine
   - Artesunate plus Mefloquine
   - Dihydroartemsinin plus Piperaquine
3. The 14-day anti-relapse therapy for *vivax* malaria patients (where applicable) should be postponed to the post-epidemic period.
4. Treatment of severe malaria:
   - Where IM Artesunate is not available, IM Artemether is an acceptable and practical alternative for treatment of severe *falciparum* malaria during an epidemic. As soon as intensive case monitoring becomes possible, Artesunate (IV) is the treatment of choice. Quinine can be used where Artemether is not available. However, timely referral is the best way if transportation of the patient is feasible.
Bibliography


8. Olumese P. *Technical Updates: WHO Guidelines on Malaria Diagnosis and Treatment* [PowerPoint slides], presentation made at inter-country meeting to address the threat of artemisinin resistance in South Asia. New Delhi, India; 2014.


Annex 1: TES sites in Myanmar

Source: Revised National Strategic Plan (2010-2016)
Annex 2: Findings of TES studies in Myanmar

<table>
<thead>
<tr>
<th>KAWTCHAUNG</th>
<th>Plasmodium falciparum</th>
<th>Coartem</th>
<th>Duocotixin</th>
<th>AS+MQ</th>
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</thead>
<tbody>
<tr>
<td>APCR</td>
<td>74 (92.5%)</td>
<td>79 (94.0%)</td>
<td>58 (100.0%)</td>
<td>76 (95.0%)</td>
</tr>
<tr>
<td>Total analysis</td>
<td>80</td>
<td>84</td>
<td>58</td>
<td>80</td>
</tr>
<tr>
<td>% parasitaemia Day 3</td>
<td>5 (6.2%)</td>
<td>7 (8.3%)</td>
<td>7 (12.1%)</td>
<td>15 (17.75%)</td>
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<table>
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<th>Duocotixin</th>
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<tbody>
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<td>APCR</td>
<td>84 (97.7%)</td>
<td>50 (98.0%)</td>
<td>72 (100.0%)</td>
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<tr>
<td>28 days finished</td>
<td>86</td>
<td>51</td>
<td>72</td>
</tr>
<tr>
<td>% parasitaemia Day 3</td>
<td>8 (10.2%)</td>
<td>1 (1.9%)</td>
<td>3 (4.2%)</td>
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</tbody>
</table>

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<th>MON, KAYIN</th>
<th>Plasmodium falciparum</th>
<th>Coartem</th>
<th>Duocotixin</th>
<th>Coartem</th>
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<tr>
<td></td>
<td>TES 28 days</td>
<td>TES 42 days</td>
<td>TES</td>
<td>Day 3 Surveillance</td>
</tr>
<tr>
<td>Kayin</td>
<td>2010/11</td>
<td>2012/13</td>
<td>2010/11</td>
<td>2013</td>
</tr>
<tr>
<td>APCR</td>
<td>65 (97.3%)</td>
<td>61 (94.0%)</td>
<td>73 (97.3%)</td>
<td>65 (97.0%)</td>
</tr>
<tr>
<td>Total analysis</td>
<td>67</td>
<td>59</td>
<td>75</td>
<td>68</td>
</tr>
<tr>
<td>% parasitaemia Day 3</td>
<td>3 (4.5%)</td>
<td>8 (13.6%)</td>
<td>17 (22.5%)</td>
<td>4 (5.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAKHINE</th>
<th>Coartem</th>
<th>Duocotixin</th>
</tr>
</thead>
<tbody>
<tr>
<td>TES 28 days</td>
<td>Day 3 Surveillance</td>
<td>TES 42 days</td>
</tr>
<tr>
<td>Kyauktaw</td>
<td>2010/11</td>
<td>2012</td>
</tr>
<tr>
<td>Butheetaung</td>
<td>67</td>
<td>79 (100.0%)</td>
</tr>
<tr>
<td>Total analysis</td>
<td>67</td>
<td>80</td>
</tr>
<tr>
<td>No. of patients recruited for Day 3</td>
<td>62</td>
<td>72</td>
</tr>
<tr>
<td>% parasitaemia Day 3</td>
<td>0</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>SAGAING (KALAY-TAMU)</td>
<td>Coartem</td>
<td>Duocotexin</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>TES</td>
<td>TES</td>
</tr>
<tr>
<td>Day 3 Surveillance</td>
<td>TES</td>
<td>TES</td>
</tr>
<tr>
<td>2009</td>
<td>2012</td>
<td>2012</td>
</tr>
<tr>
<td>2012</td>
<td>2012</td>
<td>2012</td>
</tr>
<tr>
<td>28 days finished</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>recruited for Day 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% parasitaemia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Day 3</td>
<td>(6.6%)</td>
<td>(5.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACPR (PCR corrected)</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(97.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KACHIN</th>
<th>Coartem</th>
<th>Duocotexin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TES 28 days</td>
<td>TES 28 days</td>
</tr>
<tr>
<td></td>
<td>2010/11</td>
<td>2012</td>
</tr>
<tr>
<td>28 days finished</td>
<td>59</td>
<td>52</td>
</tr>
<tr>
<td>% parasitaemia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Day 3</td>
<td>(1.7%)</td>
<td>(3.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACPR</td>
<td>60</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(98.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SHAN (NORTH)</th>
<th>Coartem</th>
<th>AS-MQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TES 28 days</td>
<td>TES 42 days</td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td>2012</td>
</tr>
<tr>
<td>28 days finished</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>% parasitaemia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Day 3</td>
<td>(7.7%)</td>
<td>(2.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACPR</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
<td>(100.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SHAN (EAST) (KYAINGTON)</th>
<th>Plasmodium falciparum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coartem</td>
</tr>
<tr>
<td></td>
<td>TES 28 days</td>
</tr>
<tr>
<td></td>
<td>2010/11</td>
</tr>
<tr>
<td>28 days finished</td>
<td>49</td>
</tr>
<tr>
<td>% parasitaemia</td>
<td>1</td>
</tr>
<tr>
<td>Day 3</td>
<td>(2.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>ACPR</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>(100.0%)</td>
</tr>
<tr>
<td>KAYAH (LOIKAW)</td>
<td>Coartem</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>TES 28 days</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>28 days finished</td>
<td>51</td>
</tr>
<tr>
<td>% parasitaemia</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(13.7%)</td>
</tr>
<tr>
<td>ACPR</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>(96.0%)</td>
</tr>
</tbody>
</table>
## Annex 3: Reports on Day 3 Parasitaemia of ACT in Myanmar (2009-2013)

<table>
<thead>
<tr>
<th>Type of Antimalarial Drug</th>
<th>Study Site</th>
<th>% of Day3 Parasitaemia of <em>P. falciparum</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2009</td>
</tr>
<tr>
<td><strong>Artemether + Lumefantrine</strong></td>
<td>Shwekyin/Bago</td>
<td>10.20</td>
</tr>
<tr>
<td>(Coartem®)</td>
<td>Kawthaung/Tanintharyi</td>
<td>6.25</td>
</tr>
<tr>
<td></td>
<td>Mon &amp; Kayin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kachin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bamaw/Kachin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MyitKyee Nar/Kachin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eastern Shan State</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kayah (Loikaw)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Northern Shan State</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muse/Northern Shan State</td>
<td></td>
</tr>
<tr>
<td><strong>Dihydroartemisinin + Piperaquine</strong></td>
<td>Kawthaung/Tanintharyi</td>
<td>18.75</td>
</tr>
<tr>
<td>(Duocotexin®)</td>
<td>Mon &amp; Kayin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kachin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MyitKyee Nar/Kachin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eastern Shan State</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kayah (Loikaw)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Northern Shan State</td>
<td></td>
</tr>
<tr>
<td><strong>Artesunate + Mefloquine</strong></td>
<td>Muse/Northern Shan State</td>
<td></td>
</tr>
</tbody>
</table>
Annex 4: WHO policy of Primaquine & G6PD deficiency

A clear policy must be in place in all countries on the use of Primaquine in the treatment of *P. falciparum* malaria to block transmission of parasites. At its meeting in September 2012, the WHO malaria policy advisory committee recommended an update in the policy on use of Primaquine as a gametocytocide to treat *P. falciparum* malaria in areas threatened by artemisinin resistance and elimination areas (Box 4).

Box 4. Updated WHO policy recommendation on use of a single dose primaquine as a gametocytocide in the treatment of *P. falciparum* malaria (October 2012)

A review of the safety and effectiveness of primaquine as a gametocytocide of *P. falciparum*, indicated that a single dose of 0.25mg base/kg body weight is effective in blocking transmission and is unlikely to cause serious toxicity in subjects with any glucose-6-phosphate dehydrogenase deficiency (G6PD) variant. On this basis, the malaria policy advisory committee recommends the following:

- A single dose of 0.25mg base/kg body weight primaquine should be given to all patients (except for pregnant women and infants <1 year of age) with parasitologically confirmed *P. falciparum* malaria on the first day of treatment, in addition to an ACT, in:
  - areas threatened by artemisinin resistance where single-dose primaquine as a gametocytocide for *P. falciparum* malaria is not being implemented; and
  - elimination areas that have not yet adopted primaquine as a gametocytocide for *P. falciparum* malaria.

- In countries already using a 0.75mg base/kg body weight single dose of primaquine in the treatment of *P. falciparum*, WHO recommends to continue with the current policy until more information on the efficacy of the lower dose is available.

Source: ERAR in the Greater Mekong Sub-region, 2013
Annex 5: ABC of Coma Management

A: Airway

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

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

B: Breathing

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

C: Circulation

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

- If dehydration is present, infuse intravenous fluids.
- Frequently check the rate of infusion to prevent overhydration.
- If patient has overhydration, stop or restrict IV fluids and give intravenous diuretics (furosemide).
- Suspected infection must be treated with antibiotics. Keep an accurate record of fluid intake and output (strict intake and output chart should be maintained). Normal urine output is approximately 1 ml/min.
### Annex 6a: The modified Glasgow Coma Scale for Adults

<table>
<thead>
<tr>
<th>Eye opening</th>
<th>Spontaneously</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To speech</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best verbal response</th>
<th>Oriented and talks</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Non-intubated)</td>
<td>Disoriented and talks</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best verbal response</th>
<th>Seems able to talk</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intubated)</td>
<td>Questionable ability to talk</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Generally unresponsive</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best motor response</th>
<th>Verbal commands</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Localizes to pain</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Withdraws to pain</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Decorticate</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Decerebrate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total score**

| Total score | 3 – 15 |

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

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

This scale can be used repeatedly to assess improvement or deterioration.
Annex 6b: Blantyre Coma Scale for Children\textsuperscript{10}

<table>
<thead>
<tr>
<th>Eye movements</th>
<th>Directed (e.g. towards mother’s face)</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not directed</td>
<td>0</td>
</tr>
<tr>
<td>Verbal response</td>
<td>Appropriate cry</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Inappropriate cry or moan</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Best motor response</td>
<td>Localises painful stimuli</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Withdraws limb from pain</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nonspecific or absent response</td>
<td>0</td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td>0 – 5</td>
</tr>
</tbody>
</table>

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

This scale can be used repeatedly to assess improvement or deterioration.
Annex 7: Antimalarial drug dosage regimens for uncomplicated *P. falciparum* malaria

1. Dosing schedule for Artemether-Lumefantrine (Coartem) + Primaquine

This is currently available as a fixed-dose formulation with dispersible or standard tablets containing 20 mg of Artemether and 120 mg of Lumefantrine2.

**Therapeutic dose**: The recommended treatment is a 6-dose regimen over a 3-day period. The dosing is based on the number of tablets per dose according to pre-defined weight bands (5-14 kg: 1 tablet; 15-24 kg: 2 tablets; 25-34 kg: 3 tablets; and > 34 kg: 4 tablets), given twice a day for 3 days. This extrapolates to 1.7/12 mg/kg body weight of Artemether and Lumefantrine, respectively, per dose, given twice a day for 3 days, with a therapeutic dose range of 1.4-4 mg/kg of Artemether and 10–16 mg/kg of Lumefantrine.

An advantage of this combination is that Lumefantrine is not available as a mono-therapy and has never been used by itself for the treatment of malaria. Recent evidence indicates that the therapeutic response and safety profile in young children of less than 10 kg is similar to that in older children, and Artemether-Lumefantrine is now recommended for patient ≥ 5 kg. Lumefantrine absorption is enhanced by co-administration with fat. Low blood levels, with resultant treatment failure, could potentially result from inadequate fat intake, and so it is essential that patients or caregivers are informed of the need to take this ACT with milk or fat-containing food – particularly on the second and third days of treatment.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Coartem/Lumartem/Artefan tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
</tr>
<tr>
<td></td>
<td>1stDose + PQ</td>
</tr>
<tr>
<td>&lt;1</td>
<td>½</td>
</tr>
<tr>
<td>1 – 4</td>
<td>1 – 4</td>
</tr>
<tr>
<td>5 – 9</td>
<td>2 – 4</td>
</tr>
<tr>
<td>10 – 14</td>
<td>3 – 4</td>
</tr>
<tr>
<td>15+above</td>
<td>4 – 4</td>
</tr>
</tbody>
</table>

2. Artesunate plus Mefloquine2

This is currently available as blister packs with separate scored tablets containing 50 mg of Artesunate and 250 mg base of Mefloquine, respectively. **A fixed-dose formulation of Artesunate and Mefloquine is preferable and at an advanced stage of development.**

**Therapeutic dose**: A target dose of 4 mg/kg/day Artesunate given once a day for 3 days and 25 mg/kg of Mefloquine either split over 2 days as 15mg/kg and 10mg/kg or over 3 days as 8.3 mg/kg/day once a day for 3 days. The therapeutic dose range is between 2-10 mg/kg/dose/day of Artesunate and 7-11 mg/kg/dose/day of Mefloquine.
3. Dihydroartemisinin plus Piperaquine

This is currently available as a fixed-dose combination with tablets containing 40 mg of Dihydroartemisinin and 320 mg of Piperaquine.

**Therapeutic dose.** A target dose of 4 mg/kg/day Dihydroartemisinin and 18 mg/kg/day Piperaquine once a day for 3 days, with a therapeutic dose range between 2-10 mg/kg/day Dihydroartemisinin and 16-26 mg/kg/dose Piperaquine.
Annex 8: Antimalarial drug dosage regimens for uncomplicated \textit{P. vivax, P. ovale and P. malariae} malaria infections

1. Oral Chloroquine dosage for malaria treatment for uncomplicated \textit{P. vivax, P. ovale and P. malariae} malaria infections

Dosage schedule of Chloroquine - 10mg/kg/day in Day 0 and Day 1; 5 mg/kg/day on Day 2

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Chloroquine tablets (150mg base Tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
</tr>
<tr>
<td>&lt;1</td>
<td>⅓</td>
</tr>
<tr>
<td>1 – 4</td>
<td>1½</td>
</tr>
<tr>
<td>5 – 9</td>
<td>2</td>
</tr>
<tr>
<td>10 – 14</td>
<td>3</td>
</tr>
<tr>
<td>15+above</td>
<td>4</td>
</tr>
</tbody>
</table>

Day 0 = First day of testing blood for malaria and taking treatment  
Day 1 = Second day of taking treatment  
Day 2 = Third day of taking treatment

**Primaquine as a gametocytocidal drug for \textit{falciparum} malaria**

- Primaquine 0.75 mg/kg stat is given to interrupt infectivity of malaria to \textit{Anopheles} mosquitoes and subsequent transmission to human.

2. Radical treatment should be given for confirmed \textit{P. vivax and P. ovale} infections: Primaquine (0.25mg base/kg/day for 14 days) with precautions.

- A weekly dose of Primaquine 0.75mg/kg given for 8 weeks to patients who have either mild or moderate G6PD deficiency.

- Primaquine is contraindicated during pregnancy, breast feeding mothers of <6 month, infancy (<6 months) and severe G6PD deficiency.

**Primaquine dosage for vivax malaria**

- A course of Chloroquine (as for treatment of vivax malaria) is to be followed by Primaquine at 15 mg daily for 14 days. (Primaquine at 0.25 mg per kg daily for 14 days after standard Chloroquine course)

Note: Side effects abdominal pain (common if taking on empty stomach), intravascular haemolysis (particularly in patients with G6PD deficiency)
Annex 9: Comparison of metabolic acidosis, pulmonary oedema/ARDS and pneumonia

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Metabolic acidosis</th>
<th>Pulmonary oedema/ARDS</th>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td>High/Low in late stages</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Depth</td>
<td>Deep Kussmaul’s breathing</td>
<td>Shallow</td>
<td>Variable</td>
</tr>
<tr>
<td>Effort of accessory respiratory muscles</td>
<td>Indrawing of lower chest wall, mostly in children</td>
<td>Increase effort of accessory respiratory muscle (e.g. sternocleidomastoid)</td>
<td>Variable, mostly seen in gross hypoxia</td>
</tr>
<tr>
<td>Bronchial breathing</td>
<td>Absent</td>
<td>May be present in the late stages</td>
<td>Present</td>
</tr>
<tr>
<td>Crepitations</td>
<td>Usually absent</td>
<td>Mostly present in bases</td>
<td>Present on the site of pneumonia</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>Absent</td>
<td>Present</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Mostly absent</td>
<td>Usually present in late stage</td>
<td>May be present in severe hypoxia</td>
</tr>
<tr>
<td>Jugular venous pressure</td>
<td>Not raised</td>
<td>Raised with volume overload; not raised in ARDS</td>
<td>Not raised</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Clear</td>
<td>Bilateral interstitial infiltration, hilar vessels prominent</td>
<td>Consolidation in the affected part of the lung</td>
</tr>
</tbody>
</table>
Annex 10: Pharmacology of antimalarial drugs used in Myanmar

ARTEMETHER

**Therapeutic indications**

Intramuscular Artemether is an alternative for treatment of severe malaria when parenteral Artesunate is not available. Although Artemether was superior to quinine in the treatment of severe malaria in adults (but not in children), its absorption is unpredictable, which may affect treatment responses in the most severely ill patients.

Artemether is an alternative for pre-referral treatment of severe malaria in adults when parenteral Artesunate is not available and in children when neither parenteral nor rectal Artesunate is available.

Artemether is also used in a fixed-dose oral combination with Lumefantrine for the treatment of uncomplicated malaria caused by *P. falciparum, P. vivax, P. ovale, P. malariae* or *P. knowlesi* parasites.

**Structure and mechanism of action**

Artemether is the methyl ether derivative of Dihydroartemisinin. It is two- to threefold less active than Dihydroartemisinin, its active metabolite. The ethers are metabolized to Dihydroartemisinin to a lesser extent than Artesunate. Like the other artemisinin derivatives, Artemether has broad stage specificity against blood-stage parasites, from the ring stages through to early schizonts. It also reduces gametocyte carriage, limiting malaria transmission from the treated infection.

**Pharmacokinetics**

Artemether is a water-insoluble, lipid-soluble compound and is therefore given either as an oil-based intramuscular injection or orally. It is absorbed slowly and erratically after intramuscular administration in severe malaria. Artemether is approximately 95% bound to plasma proteins. It is converted, primarily by CYP3A4 and to a lesser extent by CYP2B6, CYP2C9 and CYP2C19, into Dihydroartemisinin. While Dihydroartemisinin is responsible for most of the antimalarial action after oral administration, the concentrations of Artemether parent compound predominate after intramuscular administration in severe falciparum malaria. Artemether also undergoes auto-induction but to a lesser extent than artemisinin. Both Artemether and Dihydroartemisinin are eliminated within 7 h of administration.

**Safety**

**Adverse effects**

Artemether is generally very well tolerated after both oral and intramuscular administration. It has similar side-effects to other artemisinin derivatives, including hypersensitivity reactions (risk estimate, 1 in 3000), mild gastrointestinal disturbance, dizziness, reticulocytopenia, neutropenia and elevated liver enzyme activity. Although no electrocardiographic abnormalities were found in most studies, bradycardia and very slight prolongation of the QT interval have been reported. While
studies in experimental animals show neurotoxicity after parenteral Artemether, clinical, neurophysiological and pathological studies in humans have not shown similar findings.

**Contraindications**

Artemether is contraindicated in patients with known hypersensitivity to any artemisinin derivative.

**Cautions**

A marked increase in the concentration of Artemether in the cerebrospinal fluid of patients with meningitis was observed, prompting researchers to advise caution in treating patients with signs of meningitis. Patients with acute renal failure have higher maximum concentrations, higher exposure, a lower volume of distribution and a longer elimination half-life of Artemether than people without renal failure.
**ARTEMETHER–LUMEFANTRINE**

*Therapeutic indications*

Artemether–Lumefantrine is indicated for the treatment of uncomplicated *P. falciparum* or *P. vivax* malaria and is considered effective against *P. ovale, P. knowlesi* and *P. malariae*.

Artemether–Lumefantrine may also be used as follow-on, but not initial, treatment in severe malaria when the patient is well enough to take oral medication.

Artemether–Lumefantrine is not indicated for malaria prophylaxis.

*Structure and mechanism of action*

Lumefantrine (benflumetol) is a fluorene derivative belonging to the aryl amino-alcohol group of antimalarials, which includes quinine, halofantrine and mefloquine. It is thought to work similarly to the other members of the group by preventing haem detoxification within the parasite food vacuole, thus causing accumulation of the toxic haem complex. Lumefantrine is not available as and has not been used as monotherapy, which should slow the selection and spread of resistance to this drug.

*Pharmacokinetics*

Artemether is more lipophilic than other artemisinin derivatives and is readily absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 2 h of oral administration. It is then converted, primarily by CYP3A4 and to a lesser extent by CYP2B6, CYP2C9 and CYP2C19 enzymes, into Dihydroartemisinin which is responsible for most of the antimalarial action. Artemether also undergoes auto-induction. Both Artemether and Dihydroartemisinin are eliminated rapidly.

Lumefantrine is highly lipophilic and is more readily absorbed when co-administered with fatty foods or milk. Its bioavailability and the time to reach maximum concentrations vary within and between individuals, primarily due to fat-dependent absorption. The absorption of Lumefantrine is close to saturation at currently recommended doses, so increasing the dose does not result in a proportional increase in exposure; similar non-linear relations between dose and bioavailability are well described for other highly lipophilic drugs. Lumefantrine exhibits high plasma protein binding (99.7%) and has an elimination half-life of ~3 days. It is extensively metabolized in the liver, primarily by the CYP3A4 enzymes. Its active metabolite is desbutyl-lumefantrine.

*Safety*

*Adverse events*

Artemether–Lumefantrine has a wide therapeutic index and is generally well tolerated, with reported side-effects such as nausea, dizziness and headache that are not easily distinguishable from symptoms of acute malaria. Artemether–Lumefantrine does not significantly prolong the QTc interval.
Contraindications

Artemether–Lumefantrine should not to be administered to patients with known hypersensitivity to either Artemether or Lumefantrine.

Cautions

Artemether–Lumefantrine has not been studied extensively in patients > 65 years or children weighing < 5 kg, so these patients should be monitored closely when taking this medication.

The manufacturer advises against administration to patients with congenital or clinical conditions resulting in QTc prolongation, a family history of congenital long QT syndrome or sudden death or those with electrolyte abnormalities such as hypokalaemia or hypomagnesaemia, which may affect cardiac conductivity, although there is no evidence for iatrogenic toxicity in these groups.

Dosage recommendations

Formulations currently available: Dispersible or standard tablets containing 20 mg of Artemether and 120 mg of Lumefantrine in a fixed-dose combination formulation. The flavored dispersible tablet pediatric formulation facilitates use in young children.

Dose optimization: To evaluate the feasibility of dose optimization, a population model of the pharmacokinetics of Lumefantrine was constructed at the Mahidol–Oxford Tropical Medicine Research Unit from pooled concentration–time data for 1390 patients in four countries (Papua New Guinea, Thailand, Uganda, United Republic of Tanzania). Body weights from 8 to 70 kg were well represented. A saturation model was used to describe the dose-limited absorption. The current dose recommendations resulted in similar day-7 Lumefantrine plasma concentrations in all non-pregnant patients, except for the smallest children (weighing 5–14 kg). Because of dose-limited absorption, however, it is uncertain whether increases in individual doses would result in predictably higher Lumefantrine exposure in these young children. Extended or more frequent dosing regimens should be evaluated prospectively in this age group.
ARTESUNATE

Therapeutic indications

Parenteral (intravenous or intramuscular) artesunate is indicated for the initial treatment of severe malaria.

Rectal artesunate is indicated as pre-referral treatment for severe malaria.

Artesunate–Mefloquine is indicated for the treatment of acute uncomplicated *P. falciparum, P. vivax, P. ovale, P. knowlesi* or *P. malariae* malaria.

Structure and mechanism of action

Artesunate is a hemisuccinate derivative of Dihydroartemisinin, which is obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide. In vivo, artesunate is rapidly converted to its active metabolite Dihydroartemisinin. The mechanism of action of the artemisinin derivatives is not well-defined but involves cation-mediated generation of reactive intermediates and reduction of the peroxide bridge.

Artesunate, like other artemisinin derivatives, kills all erythrocytic stages of malaria parasites, including the ring stages and early schizonts, as well as the gametocytes responsible for continuing transmission, although it has only partial activity against the mature stage V gametocytes. It is essentially inactive against extra-erythrocytic forms, sporozoites, liver schizonts and merozoites. Artesunate is more water-soluble than other artemisinins and therefore can be administered intravenously. It can also be given orally, rectally or by the intramuscular route.

Pharmacokinetics

Artesunate is rapidly absorbed and biotransformed into its active metabolite Dihydroartemisinin by plasma esterases, with a possible contribution from CYP2A6 enzymes. While Dihydroartemisinin accounts for nearly all the antimalarial activity of oral artesunate, Artesunate contributes more significantly to the antimalarial effect after intravenous administration. Peak concentrations of artesunate are reached within a few minutes of parenteral administration; thereafter, artesunate is rapidly eliminated. Plasma protein binding of Dihydroartemisinin is approximately 93%. Dihydroartemisinin is metabolized in the gut and liver by glucuronidation and is excreted in the urine.

Safety

Pregnancy

In experimental animals, dose-dependent fetal toxicity was observed after administration of artesunate in the first trimester and was more likely to occur with increased duration of treatment. There is no evidence that artemisinin derivatives are teratogenic in humans, but experience is still limited. While the possible risk for teratogenicity limits the use of artemisinin derivatives in the treatment of uncomplicated malaria in women in the first trimester, treatment of severe malaria
with artesunate is recommended as it is potentially life-saving for the mother. Artesunate has been successfully and safely administered in the second and third trimesters of pregnancy.

**Adverse events**

Artesunate is generally well-tolerated and has a better safety profile than quinine in severe malaria. It has similar side-effects to other artemisinin derivatives, including hypersensitivity reactions (risk estimate, 1 in 3000), gastrointestinal disturbances, cough, rash, arthralgia, dizziness and delayed haemolysis. Clinically, the most significant effect is haemolysis, which has been reported up to weeks after treatment. Dose-dependent neutropenia was observed in Cambodia, where an oral dose of 6 mg/kg bw artesunate for 7 days resulted in significantly lower neutrophil counts than in those patients given 2 or 4 mg/kg bw. Other adverse effects observed in animal models, such as hepatotoxicity and neurotoxicity, have not been observed in clinical studies at therapeutic doses. Although there is a theoretical concern about bradycardia and QTc prolongation associated with artemisinin derivatives, particularly at high doses, this has not been seen with artesunate.

**Contraindications**

Artesunate is contraindicated in patients with known hypersensitivity to Artesunate or artemisinin derivatives.

**Cautions**

As lower plasma concentrations of artesunate and Dihydroartemisinin are reported in young children with severe anaemia, it is important to monitor their response to treatment closely.

While use of artesunate in patients with renal or hepatic impairment has not been studied extensively, the limited data available (and the known metabolism and excretion of drug) do not suggest that artesunate would be toxic to renally or hepatically impaired individuals. Nevertheless, caution is advised in treating these patients.

**Dosage optimization**

For the treatment of uncomplicated malaria, the target dose of artesunate remains 4 mg/kg bw daily, with a daily dose range of 2–10 mg/kg bw. Children weighing < 25 kg with severe malaria had lower exposure to intravenous or intramuscular artesunate and its active metabolite Dihydroartemisinin than older children and adults given the same dose of 2.4 mg/kg bw, which was attributed to an increased clearance rate in younger children. This may increase the risk for treatment failure, which can be fatal in severe malaria. The Mahidol–Oxford Tropical Medicine Research Unit performed nonlinear mixed-effects population pharmacokinetics modelling in order to inform WHO dosage recommendations for ensuring equivalent exposure to the drug for all target populations. These models confirmed that young children (< 25 kg/5 years) should receive a slightly higher dose of 3 mg/kg, which is still within the therapeutic range prescribed by the manufacturer and does not raise safety concerns.
CHLOROQUINE

Therapeutic indications

Chloroquine is indicated for the treatment of uncomplicated malaria due to *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*.

Chloroquine is no longer recommended for prophylaxis against *P. falciparum* but may be used to prevent *P. vivax* infections.

Structure and mechanism of action

Chloroquine is a 4-aminoquinoline that inhibits intraparasitic haem detoxification; it may also interfere with the biosynthesis of nucleic acids. Chloroquine reaches high concentrations in the parasite’s food vacuole. Chloroquine resistance is associated with genetic mutations in genes encoding trans-membrane proteins of the parasite’s food vacuole (PfCRT and PfMDR).

Pharmacokinetics

Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration. Plasma protein binding is approximately 55%. Chloroquine is extensively distributed in body tissues and fluids, including the placenta and breast milk. It is metabolized in the liver by CYP2C8 and CYP3A4 enzymes, mainly to monodesethylchloroquine, which has similar antimalarial activity (17). The drug is eliminated slowly from the body, with ~55% eliminated via the kidneys.

Safety

Pregnancy

At the doses used for treatment or prophylaxis of *P. vivax*, *P. ovale* or *P. malaria*, chloroquine is considered safe in pregnancy. The chloroquine concentrations achieved are reportedly lower during pregnancy, particularly in the second and third trimesters, although one studies showed no such difference. The response of pregnant patients to treatment should be monitored closely.

Adverse effects

Chloroquine is generally well tolerated at therapeutic doses. Large doses used for the treatment of rheumatoid arthritis are associated with a higher frequency of adverse events than the lower doses used in malaria. Pruritus is a common side effect and is more severe in dark-skinned individuals. Other less common side effects include headache, hepatitis, elevated liver enzyme, various skin eruptions and gastrointestinal disturbances, such as nausea, vomiting and diarrhoea. Taking chloroquine with food helps to avoid gastrointestinal intolerance. Chloroquine causes slight widening of the QRS complex and QT intervals in electrocardiography but has not been associated with conduction disturbances or arrhythmia at therapeutic doses. More rarely, central nervous system toxicity, including convulsions and mental changes, may occur. Chronic use (> 5 years continuous use as prophylaxis) may lead to eye disorders, including keratopathy and retinopathy. Other uncommon effects include myopathy, reduced hearing, photosensitivity and hair loss. Blood disorders, such as aplastic anaemia, are extremely uncommon.
Acute overdosage is very dangerous, and death can occur within a few hours. The patient may progress from feeling dizzy and drowsy with headache and gastrointestinal upset, to sudden visual loss, convulsions, hypokalaemia, hypotension and cardiac arrhythmia. Overdosed patients require intensive care.

Contraindications

Chloroquine is contraindicated in patients with known hypersensitivity to chloroquine or any aminoquinoline compounds.

Caution

Use with caution in patients with psoriasis, neurological (e.g. epilepsy), retinal, or gastrointestinal disorders, as chloroquine may exacerbate these underlying conditions. The drug should also be administered with caution to patients with retinal or visual impairment or hepatic impairment.
CLINDAMYCIN

**Therapeutic indications**

Clindamycin is used in combination with artesunate or quinine for severe or uncomplicated malaria.

**Structure and mechanism of action**

Clindamycin is a lincosamide antibiotic derived from lincomycin. Its mechanism of action involves inhibition of microbial protein synthesis by preferential binding to the 50S ribosomal subunit and interference with peptide chain initiation.

**Pharmacokinetics**

Clindamycin is rapidly absorbed after oral administration, with an oral bioavailability of approximately 90%. It is widely distributed in body fluids and tissues, including bone, but insignificant levels are reached in cerebrospinal fluid. Clindamycin also crosses the placenta and appears in breast milk. It is about 90% bound to plasma proteins and accumulates in leukocytes, macrophages and bile. The half-life of clindamycin may be prolonged and clearance reduced in neonates and patients with renal impairment. Clindamycin is metabolized by CYP3A4 enzymes in the liver into the active N-demethyl and sulfoxide metabolites and some inactive metabolites. About 10% of a dose is excreted in the urine as active drug or metabolites and about 4% in faeces; the remainder is excreted as inactive metabolites. Excretion is slow and takes place over many days. Although clearance is reduced slightly in patients with markedly reduced renal function, dose modification is not considered necessary. Clindamycin is not effectively removed from the body by dialysis.

**Safety**

Studies of reproductive toxicity with clindamycin in experimental animals revealed no evidence of impaired fertility or harm to the fetus. Although data on its use during pregnancy in humans are limited, clindamycin is regarded as safe for use in pregnancy.

**Adverse events**

Clindamycin is generally well tolerated after oral administration. Its major disadvantage is its potential to cause antibiotic-associated diarrhoea, leading to overgrowth of *Clostridium difficile* and pseudomembranous colitis. Other adverse effects include nausea, vomiting, abdominal pain or cramps, rash or pruritis. High doses of clindamycin may cause a metallic taste in the mouth. Rarely, clindamycin therapy has been associated with anaphylaxis, blood dyscrasias (leukopenia, agranulocytosis, eosinophilia, thrombocytopenia), erythema multiforme, polyarthritis, jaundice, raised liver enzymes and hepatotoxicity. Some parenteral formulations contain benzyl alcohol, which may cause fatal “gasing syndrome” in neonates.

**Contraindications**

Clindamycin is contraindicated in patients with known hypersensitivity to clindamycin or lincomycin.
Cautions

Clindamycin should be used with caution in patients with gastrointestinal diseases as they may be at greater risk for pseudomembranous colitis. Caution is also advised in administering clindamycin to severely ill elderly patients, who may be more likely than younger patients to develop diarrhoea. The longer elimination half-life of clindamycin in neonates means that its plasma concentration may be significantly higher than in older children. For this reason, close monitoring of organ function is required when clindamycin is administered to neonates, particularly if they were premature. Clearance of clindamycin is reduced in patients with moderate-to-severe liver disease, so dosage modification (increasing the interval between doses) may be needed.

Greater bioavailability, higher serum protein binding, lower plasma drug clearance and a smaller steady-state volume of distribution have been found in patients with HIV/AIDS than in healthy volunteers. Although the clinical significance of these findings has not yet been established, close monitoring of these patients is recommended.
DIHYDROARTEMISININ–PIPERAQUINE

Therapeutic indications

Dihydroartemisinin–piperaquine is indicated for the treatment of uncomplicated *P. falciparum* or *P. vivax* malaria and is likely to be very effective in *P. ovale*, *P. knowlesi* and *P. malariae* malaria. It may also be used as follow-on treatment in severe malaria once the patient is well enough to take oral medication.

Structure and mechanism of action

Dihydroartemisinin is a sesquiterpene peroxide and an active metabolite of artesunate and Artemether. The mechanism of action of the artemisinin derivatives is not known but involves cation-mediated generation of reactive intermediates and reduction of the peroxide bridge.

Piperaquine is a bisquinoline compound of the 4-aminoquinoline group of antimalarial drugs that include chloroquine. Piperaquine is thought to act similarly to chloroquine, which accumulates inside the parasite food vacuole and inhibits parasite-mediated haem detoxification, causing accumulation of the toxic haem complex.

Piperaquine is also effective against chloroquine-resistant malaria parasites. In chloroquine resistance, mutation in the genes encoding trans-membrane parasite food vacuole proteins are thought to result in efflux of chloroquine, so that it cannot accumulate at its site of action. These mutated parasite membrane proteins are considered to be unable to efflux the bulky bisquinoline structure.

Pharmacokinetic parameters

Dihydroartemisinin–piperaquine is readily absorbed from the gastrointestinal tract, with peak plasma concentrations reached within 1–3 h for Dihydroartemisinin and 3–6 h for piperaquine. Piperaquine is extensively distributed throughout the body, with more than 99% bound to plasma proteins.

Dihydroartemisinin has a smaller volume of distribution and plasma protein binding of 44–93%. Elimination of Dihydroartemisinin is much more rapid (elimination half-life, about 1 h) than that of piperaquine (2–4 weeks).

Safety

Adverse events

Overall, Dihydroartemisinin–piperaquine was well tolerated in large randomized controlled trials. The adverse effects reported included nausea, diarrhoea and vomiting, as well as anorexia, anaemia, dizziness, headache, sleep disturbance and cough.

Although there was no evidence of cardiotoxicity in large randomized trials and extensive use of Dihydroartemisinin–piperaquine, piperaquine does prolong the QT interval on electrocardiography (reflecting ventricular repolarization) by approximately the same amount as chloroquine (but by less
than quinine). In a study in healthy volunteers, Dihydroartemisinin–piperaquine increased the QTc interval by 45.2, 35.5 and 21.0 ms in people who took each dose with a high (~1000 kcal) or low (~400 kcal) fat/calorie meal and in fasting conditions, respectively; none had a QTc interval greater than 500 ms (2). Significant prolongation of the QTc interval may cause potentially life-threatening ventricular tachyarrhythmia, but there is no evidence that this has occurred with piperaquine, despite its extensive use.

**Contraindications**

Dihydroartemisinin–piperaquine should not be administered to patients with known hypersensitivity to either Dihydroartemisinin or piperaquine. It should not be used in patients with congenital QTc prolongation or who have a clinical condition or are on medication that results in QTc interval prolongation.

**Cautions**

In view of the lack of evidence on the safety of Dihydroartemisinin–Piperaquine in patients > 70 years of age, in infants weighing < 5 kg and in patients with renal or hepatic impairment, patients in these populations should be monitored closely when this combination is administered.

**Dosage recommendations**

The previous edition of the WHO Guidelines for the treatment of malaria recommended target oral doses of 2–10 mg/kg Dihydroartemisinin and 16–26 mg/kg Piperaquine to be taken daily for 3 days. The dosing schedule recommended by the manufacturers, however, indicates that some individuals at the upper end of the weight range receive much lower doses of piperaquine and Dihydroartemisinin than this target. Furthermore, the weight-adjusted dosage recommendation for Dihydroartemisinin–piperaquine was the same for all age groups, even though their pharmacokinetic parameters do not scale linearly with weight. Children aged <5 years have higher body weight-adjusted oral clearance of Piperaquine than other age groups (8,14,33) and therefore have lower exposure to piperaquine, placing them at increased risk for treatment failure.

The WorldWide Antimalarial Resistance Network analysed pooled data from individual patients to determine the influence of dosing schedules on the clinical efficacy of Dihydroartemisinin–piperaquine. Twenty-four published and two unpublished studies (with a total of 7072 patients) were included in the analysis. After correction for reinfection by parasite genotyping, the Kaplan–Meier estimates of cure rates were high 97.7% (95% CI, 97.3%–98.1%) at day 42 and 97.2% (95% CI 96.7%–97.7%) at day 63. Overall, 28.6% (979/3429) of children aged 1–5 years received a total dose of piperaquine < 48 mg/kg (the lower limit previously recommended by WHO), giving a risk that was 2.3–2.9-fold greater than that of other age groups. This sub-optimal dosing was associated with reduced efficacy at day 63 (94.4%; 95% CI, 92.6–96.2%; p < 0.001). After adjustment for confounding factors, the mg/kg bw dose of piperaquine was found to be a significant predictor of recrudescence, the risk increasing by 13% (95% CI, 5.0–21%) for every 5-mg/kg bw decrease in dose (p = 0.002). In a multivariable model, increasing the target minimum total dose of piperaquine for children aged 1–5 years from 48 mg/kg bw to 59 mg/kg bw was predicted to halve the risk for treatment failure and to cure more than 95% of these young patients. The increased exposure was not associated with gastrointestinal toxicity in the 10 studies in which this could be assessed.
On the basis of the evidence of sub-optimal dosing of young children, the Mahidol–Oxford Tropical Medicine Research Unit performed nonlinear mixed-effects population pharmacokinetics modelling in order to inform WHO dosage recommendations for ensuring equivalent piperaquine exposure for all target populations. Selection of the published models included for simulating the target exposure in adult patients was based on use of an appropriate structural pharmacokinetic model, sufficient data collection and adequate predictive performance. Exposure to piperaquine was then simulated with the population pharmacokinetic estimates and between- and within-patient variation reported for each of the pediatric data sets available (unpublished data from the WorldWide Antimalarial Resistance Network). The results were reported as medians and interquartile ranges for day-7 concentrations. Peak concentrations for 1000 patients were simulated for each body weight.

The revised WHO dosage recommendations selected ensure that the Piperaquine exposure of young children \((C_{\text{max}}, \text{day-7 concentration})\) is equivalent to that of older children and adults, while using as few weight bands as possible and minimizing the use of half-tablets. Equivalent exposure in all weight groups is achievable with increases in mg/kg bw dosage of up to 20% in some weight bands; importantly, this will not result in higher maximum \((C_{\text{max}})\) or day-7 concentrations of piperaquine than those already observed in adult patients given the doses currently recommended by the manufacturer. Any further simplification of these recommendations will require a prospective study of the safety of slightly higher mg/kg doses in young children.
MEFLOQUINE

Therapeutic indications

Mefloquine is indicated for the chemoprophylaxis of malaria caused by all species. In combination with artesunate, it is also recommended for treatment of uncomplicated malaria.

Structure and mechanism of action

Mefloquine, a 4-methanolquinoline, is structurally related to quinine and belongs to the aryl aminoalcohol group of drugs. Mefloquine has two racemic forms, erythro- and threo-, each composed of a pair of enantiomers, of which the racemic mixture of the erythro- enantiomers is the most active against malaria parasites. Its mechanism of action is not fully understood but is thought to involve inhibition of parasite-mediated haem detoxification, a common mechanism of action of quinoline antimalarials. A more recent proposal is that it inhibits endocytosis of the cytosol by the parasite. Mefloquine has approximately the same stage specificity of action as quinine, killing primarily the large ring and trophozoite asexual parasites. It has no significant pre-erythrocytic activity.

Pharmacokinetics

Inter-individual differences in absorption result in different times to reach maximum concentrations. The pharmacokinetic parameters of mefloquine are altered in malaria: patients with malaria have higher plasma concentrations and eliminate mefloquine more rapidly than healthy volunteers, possibly because of interruption of entero-hepatic cycling. The pharmacokinetic parameters of mefloquine are also highly stereospecific. Mefloquine is extensively distributed in the body; it crosses the blood–brain-barrier and the placenta and is found in breast milk. It accumulates in erythrocytes, with an erythrocyte-to-plasma ratio of about 2:1. Approximately 98.2% of mefloquine is bound to protein. In the liver, it is metabolized by CYP3A4, largely to an inactive metabolite. Mefloquine has a long elimination half-life (≤ 3 weeks). Excretion occurs primarily via the bile and faeces as unchanged drug and metabolites, with a small proportion excreted unchanged in the urine.

While mefloquine has no effect on the pharmacokinetics of Dihydroartemisinin, concomitant administration of artesunate decreases the maximum concentration and increases the clearance rate and volume of distribution of mefloquine. Delaying the dose of mefloquine to the second day of artesunate administration increases its estimated oral bioavailability substantially, probably as an indirect effect of rapid clinical improvement. Administration with food does not alter the kinetics of artesunate–mefloquine.

The pharmacokinetic parameters of mefloquine are similar in children and adults. Peak mefloquine concentrations in whole blood are lower during pregnancy than in non-pregnant individuals. As the overall efficacy of the drug does not appear to be affected, however, dosage adjustment is not warranted for pregnant women.
Safety

Adverse events

Although mefloquine is associated with higher incidences of central nervous system and gastrointestinal adverse effects than other ACTs, it is generally well tolerated when given in combination with artesunate for the treatment of uncomplicated malaria. Mefloquine has been associated with seizures, anxiety, irritability, dizziness, paranoia, suicidal ideation, depression, hallucinations and violence in patients treated for malaria and in people on long-term mefloquine prophylaxis. Such neuropsychiatric adverse effects generally resolve after discontinuation of mefloquine. The estimated incidence of seizures, encephalopathy or psychotic reactions ranges from 1 in 10 000 healthy people receiving chemoprophylaxis, 1 in 1000 malaria patients in Asia, 1 in 200 malaria patients in Africa to 1 in 20 patients recovering from cerebral malaria. Mefloquine should therefore not be given to patients who have had cerebral malaria. Mefloquine prophylaxis should be avoided in travellers who require fine motor coordination or in whom sudden onset of dizziness or confusion may be hazardous, such as pilots and drivers. Travellers and their companions should be advised to monitor for adverse effects such as restlessness, anxiety, depression or confusion, and, if these occur, to discontinue mefloquine and seek medical attention.

The most frequently reported adverse effect with treatment is vomiting or gastrointestinal disturbances, which tend to affect adherence and efficacy. Early vomiting was a predictor of treatment failure in patients given mefloquine for uncomplicated malaria. Mefloquine has been associated rarely with hepatitis, polyneuropathy, thrombocytopenia, pneumonia, skin rashes or irritation, sinus bradycardia and visual impairment. Adverse events appear to be associated with high concentrations of the (−)-enantiomer rather than of the drug overall and to be more frequent in women than men.

Contraindications

Mefloquine is contraindicated in patients with known hypersensitivity to Mefloquine or related compounds (e.g. quinine and quinidine). It should not be prescribed for follow-up treatment after cerebral malaria or for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia or another major psychiatric disorder, or with epilepsy or a history of convulsions.

Caution

Given the lack of evidence on the safety of mefloquine in severe hepatic impairment, such patients should be monitored carefully because of a potential increase in the risk for adverse events. Clinical trials show no or only small, clinically insignificant alterations in the electrocardiogram after administration of mefloquine; however, caution should be exercised in administering mefloquine to patients with cardiac disease.

The teratogenic and embryotoxic effects of mefloquine observed in experimental animals and the high rate of spontaneous abortions seen in one small study of mefloquine prophylaxis in pregnant women have raised concern about the safety of mefloquine in pregnancy. Large clinical studies have not, however, revealed such adverse outcomes, allaying concern that mefloquine might be
associated with stillbirth. Prophylactic doses of mefloquine in the second and third trimesters of pregnancy also appear to be effective and are not associated with adverse maternal or fetal outcomes. However, gastrointestinal side-effects, including nausea and vomiting, are more common in pregnant women treated with mefloquine than those treated with SP.

**Dose optimization**

For the treatment of uncomplicated malaria in combination with artesunate, the recommended total dose of mefloquine is 25 mg/kg bw, which gives a higher cure rate than the previously recommended dose of 15 mg/kg bw. A pharmacokinetics model predicted that initial use of the lower (15-mg/kg bw) dose of Mefloquine resulted in a greater likelihood of selecting resistant mutants than *de novo* use of the higher (25-mg/kg bw) dose. Giving mefloquine in two or three doses improves its tolerability and oral bioavailability. The fixed-dose combination of artesunate + mefloquine given daily for 3 days is preferred.
**PRIMAQUINE**

*Therapeutic indications*

Primaquine is indicated for radical cure of *P. vivax* or *P. ovale* malaria; for presumptive anti-relapse therapy (terminal prophylaxis) in people extensively exposed to *P. vivax* or *P. ovale*; to reduce onward transmission of *P. falciparum* malaria in programmes to eliminate *P. falciparum* malaria and in areas threatened by resistance of *P. falciparum* to artemisinins; and as an alternative for primary prophylaxis against all malaria species.

Except in primary prophylaxis, Primaquine is used in conjunction with an effective blood schizonticide: either ACT, or chloroquine for vivax or ovale malaria.

*Structure and mechanism of action*

Primaquine is an 8-aminoquinoline, which is highly active against the exoerythrocytic forms (hypnozoites) and the sexual stages of malaria parasites (gametocytes). It has weak activity against the asexual blood stages of *P. vivax* and has negligible activity against *P. falciparum*. Although *P. falciparum* gametocyte clearance takes days, gametocytes are sterilized within hours; therefore, the effect of Primaquine on oocyst and sporozoite formation (and thus onward transmission of the treated infection) precedes its effect on gametocyte carriage.

Hepatic metabolism of Primaquine produces reactive intermediate metabolites that generate toxic intracellular oxidative species. The parent compound itself is relatively inactive. The precise mechanism of action of Primaquine is not fully understood, but it is thought that the reactive intermediates disrupt the metabolic processes of plasmodial mitochondria and interfere with electron transport in the parasite. There is no evidence for acquired resistance to its hypnozoitocidal or gametocytocidal activities.

*Pharmacokinetics*

Primaquine is rapidly absorbed from the gastrointestinal tract, reaching peak concentrations within 1–4 h, with a bioavailability of about 96%. Primaquine is biotransformed by two main routes: by monoamine oxidase to the predominant, but inactive, metabolite carboxyprimaquine, which is relatively slowly eliminated; and via CYP2C19, CYP2D6 and CYP3A4 in the liver, which generate the reactive intermediates responsible for antimalarial effects and haemolytic toxicity. Genetic polymorphisms that decrease CYP2D6 enzyme activity reduce bioactivation of Primaquine and may result in treatment failure. Primaquine is extensively distributed in the body. About 75% of Primaquine in plasma is bound to proteins, and high concentrations occur in erythrocytes. Primaquine crosses the placenta, but it is uncertain whether significant amounts occur in breast milk.

Both Primaquine and carboxyprimaquine are excreted mainly through the biliary tract and can be found in faeces within 24 h of administration. Primaquine is also excreted in the urine as unchanged drug. Conflicting results have been reported on the effects of gender on the disposition of Primaquine, some studies reporting increased exposure and hence greater side-effects in women and others reporting no effect of gender. In view of the relatively small samples in each of these
studies, the findings should be interpreted cautiously. The pharmacokinetics of a single oral dose of 15 mg did not appear to be altered in patients with severely impaired renal function and end-stage renal dysfunction.

**Safety**

**Adverse events**

While Primaquine is generally well tolerated, it may cause dose-related gastrointestinal discomfort, including abdominal pain, nausea and vomiting. Administration with food improves tolerability. Hypertension and cardiac arrhythmia have been reported rarely. The most important adverse effect is haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and the degree of haemolysis is proportional to the dose, duration of exposure, and degree of G6PD deficiency. Leukopenia, methaemoglobinemia with cyanosis and granulocytopenia may also occur. Fortunately, Primaquine is eliminated rapidly, so that haemolysis stops once the drug is stopped. Patients should discontinue Primaquine if they pass red or black urine, or have symptomatic anaemia.

**Contraindications**

Primaquine is contraindicated in patients with known hypersensitivity to Primaquine or related compounds and in patients with severe G6PD deficiency or severe nicotinamide adenine dinucleotide (NADH) methaemoglobin reductase deficiency. Primaquine crosses the placenta and may cause haemolysis in a G6PD-deficient fetus; it is therefore not recommended for use during pregnancy or during breastfeeding unless the G6PD status of the infant is known. Use of Primaquine in infants < 6 months is not advised because of lack of data on its safety.

**Caution**

The different variants of G6PD deficiency are associated with significantly different risks for haemolysis. The African A–variant is at the less severe end of the spectrum of severity, and the Mediterranean variant (which predominates in southern Europe, the Middle East and Central Asia) is at the more severe end. Administration of a single dose of 0.25 mg base/kg bw as a gametocytocide is considered to confer no significant haemolytic risk in people with any of the variants; therefore, testing for GDPD deficiency is not required before this single dose administration. The regimens necessary for radical cure may, however, cause significant, occasionally life-threatening haemolysis in G6PD-deficient patients; therefore, testing for G6PD deficiency is recommended before radical cure regimens. Unfortunately, testing is not widely available, so an individual decision on whether to prescribe radical a curative regimen depends on an assessment of the potential risks of haemolytic toxicity and the benefits of preventing relapse. This assessment must be based on knowledge of the prevalence and severity of G6PD deficiency in the patient’s ethnic group and the risks and impact of vivax relapse in the area. Caution is also advised in treating patients with systemic diseases associated with an increased risk for granulocytopenia, such as rheumatoid arthritis and systemic lupus erythematosus.
Dose optimization

The dosages recommended for radical cure of *P. vivax* or *P. ovale* malaria, presumptive anti-relapse therapy (0.25 mg base/kg bw per day for 14 days for “temperate strain infections” and 0.50 mg base/kg bw per day for 14 days for tropical, frequently relapsing infections) and primary prophylaxis (0.5 mg/kg bw base up to maximum oral dose of 30 mg daily) remain unchanged. WHO now recommends a single, low dose (0.25 mg/kg bw) to reduce onward transmission of *P. falciparum* malaria in programmes to eliminate *P. falciparum* malaria and in areas threatened by resistance of *P. falciparum* to artemisinins. This lower dose is safer and was considered to be as effective in reducing transmissibility on the basis of the limited available data from assessments of direct transmission blocking in mosquito feeding studies, which is considered therapeutically more relevant than gametocyte clearance. The feasibility of achieving this lower dosage in young children would be enhanced by the availability of a pre-qualified 3.75-mg Primaquine tablet.
QUININE

Therapeutic indications

Parenteral quinine is indicated for the treatment of severe malaria. Oral quinine is used in the treatment of uncomplicated malaria, particularly in the first trimester of pregnancy, or as an alternative treatment when an effective ACT is not promptly available.

Structure and mechanism of action

Quinine is an alkaloid derived from the bark of the cinchona tree that belongs to the aryl amino alcohol group of drugs. It is one of four antimalarial cinchona alkaloids and is the L-stereoisomer of quinidine. Quinine kills large ring and trophozoite asexual parasites and is gametocytocidal against *P. vivax*, *P. ovale* and *P. malariae* but not *P. falciparum* malaria. The mechanism of action of quinine is not clearly understood, although it is thought to involve inhibition of parasite haem detoxification inside the food vacuole.

Pharmacokinetics

Quinine is rapidly absorbed after both oral and parenteral administration. It is widely distributed throughout the body and is detectable in cerebrospinal fluid, breast milk and the placenta. Quinine undergoes extensive hepatic biotransformation, predominantly via CYP3A4 enzymes as well as CYP2C9, CYP1A2 and CYP2D6, into several metabolites. Quinine is both a substrate and an inhibitor of CYP2D6. The initial metabolite, 3-hydroxyquinine, contributes approximately 10% of the antimalarial activity of the parent compound. Up to 20% of administered drug is excreted unchanged by the kidneys, and small amounts may appear in bile and saliva.

The pharmacokinetics of quinine is altered significantly by malaria infection. Both the apparent volume of distribution and systemic clearance are reduced in proportion to disease severity, resulting in higher plasma quinine levels in patients with severe malaria. As a result, quinine accumulates with standard maintenance dosing regimens (10 mg salt/kg bw every 8 h), unless the patient starts to recover. As a consequence, if there is no clinical recovery within 48 h, the dosage is reduced by one third (to 10 mg salt/kg bw every 12 h). In patients who are in acute renal failure, quinine clearance is determined by the overall disease severity and hepatic function. In addition, plasma-protein binding, mainly to the acute-phase protein α1-acid glycoprotein, increases from about 80% in healthy subjects to around 90% in patients with malaria.

The exposure of pregnant women to quinine was generally lower and elimination more rapid than that in non-pregnant patients. The disposition of quinine changes with age, with slightly higher concentrations observed in children < 2 years. In children with protein energy malnutrition, clearance is significantly reduced, the elimination half-life is significantly longer but the maximum concentration significantly lower than in controls. Quinine pharmacokinetics, including total clearance normalized to ideal body weight, is not significantly altered in obese patients; thus, the maintenance dose of quinine in these patients should be based on ideal body weight rather than on total body weight. Quinine clearance is significantly lower in elderly patients, posing a potential risk for drug accumulation and toxicity.
Safety

Adverse events

Because of its narrow therapeutic index, quinine has frequent adverse effects. The side-effects commonly seen after administration of treatment doses are referred to as “cinchonism”. Mild forms are characterized by tinnitus, slight impairment of hearing, headache, nausea, dizziness, dysphoria and sometimes disturbed vision. Impairment of high tone hearing is usually concentration-dependent and reversible. More severe manifestations include vertigo, vomiting, abdominal pain, diarrhoea, marked auditory loss and visual symptoms, including loss of vision. An important side-effect of quinine is hyperinsulinaemic hypoglycaemia, which is particularly common in young children, pregnant women and elderly patients. Quinine also causes prolongation of the QTc interval (typically by about 10%), although cardiotoxic effects are much less frequent than those of quinidine. Hypotension and cardiac arrest may occur if the drug is given too rapidly (such as in an intravenous bolus); intravenous formulations should therefore be given by infusion not exceeding a rate of 5 mg/kg bw per hour. Venous thrombosis may occur after intravenous administration, while pain, necrosis and abscess formation may occur with acidic intramuscular injections. Hypersensitivity reactions to quinine have also been reported, including urticaria, bronchospasm, flushing of the skin, fever, antibody-mediated thrombocytopenia, haemolytic anaemia and haemolytic–uraemic syndrome. Hepatic injury and psychosis occur very rarely.

Quinine has been used as an abortifacient, but there is no evidence that it causes abortion, premature labour or fetal abnormalities (28, 34). Quinine therefore remains the drug of choice during the first trimester of pregnancy. It may also be used safely in the second and third trimesters of pregnancy, although poor compliance because of 7-day treatment course and low tolerability may compromise its efficacy, and there is a high rate of hyperinsulinaemic hypoglycaemia.

Overdosage of quinine may cause oculotoxicity, including blindness from direct retinal toxicity, and cardiotoxicity, and can be fatal. Cardiotoxic effects include conduction disturbances, angina and hypotension leading to cardiac arrest. Treatment is largely supportive, with particular attention to maintenance of blood pressure, glucose and renal function and to treating any arrhythmias.

Contraindications

Quinine is contraindicated in patients with known hypersensitivity to quinine or any of the cinchona alkaloids.

Caution

Although caution should be exercised when administering quinine to patients who have heart rhythm disorders or heart disease, there is little evidence of cardiotoxicity in patients with malaria. Quinine metabolites may cause oxidative haemolysis in people with G6PD deficiency. Caution is also advised in treating patients with kidney or liver disease, as the drug may accumulate.