Malaria has always been a major public health problem in the tropical and sub-tropical countries.

This problem worsened in the last two decades to the extent that it is responsible for 2-3 million deaths every year according to the latest WHO reports.

In Africa alone, about 1 million deaths are the toll of this deadly disease which returned with vengeance.

In Oman, we started the Malaria Eradication Programme in August 1991 by a pilot project in Sharqiya Region which was extended later on to Batinah and Muscat Regions and we managed to drop the malaria incidence by more than 90% from 1990 till January 1996 although the eradication strategy has not yet covered all he regions in Oman.

Having succeeded in reducing the malaria incidence by interrupting the transmission, we must not forget one of the top priorities which is: “to manage uncomplicated, severe and complicated malaria cases?"

Hence the importance of this manual emerged and I am sure that all those who contributed to issue the first and second editions of this manual did their best to make it informative and comprehensive in order to be a practical and easy guide to our National Anti-malarial Drug Policy which all the medical staff in our health institutions should adhere very strictly.

Even if we managed to interrupt the malaria transmission in our
country, we are still part of this small world and we shall still be importing malaria cases from abroad and we have a commitment and responsibility to receive these cases and ensure their radical cure in any of our health institutions.

This manual is the official Ministry of Health Anti-malarial Drug Policy.

Dr. Ahmed bin Abdul-kadir Al-Ghassany

H.E. The Undersecretary of Health Affairs

FOREWORD TO THE SECOND EDITION

Introduction to the Second Edition

In September 1991, the First Edition of this manual was published. It was written by

Dr. H. Mashaal, the renowned international consultant who helped, as an advisor, the

Ministry of Health to start the Malaria Eradication Programme.

After more than 4 years, it has been clear that this valuable manual should be updated so as to meet the changed epidemiology of malaria, both locally and globally. In addition, some amendments were also done. Unfortunately, Dr. H. Mashaal is not present with us due to some personal circumstances but it is our duty and responsibility to continue on in order to sustain the country’s achievements as well as strive for the complete eradication of this killer disease.

In light of the above, the Directorate of Environmental Health and Malaria Eradication committed itself to present the Second Edition
which we hope will be beneficial and a helpful guide to all the medical staff in their management of both uncomplicated and complicated cases of malaria.

**Mr. Abdullah bin Rashid Al- Mandhry**

**Director of Environmental Health and Malaria Eradication**

**PREFACE**

1st EDITION

It is estimated that 2073 million people living in more than 100 countries are exposed to the risk of malaria and that some 270 million of these are infected with malaria parasites. It is the complexity of malaria that has enabled it to survive.

Since decades and even today malaria tops the list of diseases causing high morbidity in the Sultanate of Oman.

The treatment of malaria cases and advice to travellers and pilgrims for chemoprophylaxis is the responsibility of the physicians in all health and medical institutions in the country.

This booklet on the up-to-date methodology of malaria therapy compiled by Dr H. Mashaal is coming at an opportune time, when the Ministry of Health has launched its Malaria Eradication Programme in the Sultanate. The anti-malaria staff belonging to this programme will no more attend to the treatment of malaria cases or their follow up until the incidence of this disease falls to 0.5% of the number of medical consultations. Such a reduction can be obtained by concentrating on the anti-mosquito measures for at least three
consecutive years, so that no malaria transmission occurs and the parasites in the human reservoir would eventually die out, as they do not live in the body for more than a year.

We are sure that all physicians would benefit from this guide book on malaria treatment entitled “Manual for Treatment of Malaria and Its Complications”. This manual is the Ministry of Health policy on malaria.

Director General of

Preventive Medicine

Director General of Curative Medicine

FOREWORD TO THE FIRST EDITION

This book is dedicated to His Excellency, Dr Au bin Mohammed bin Moosa, Minister of Health, Sultanate of Oman for his great interest and dedication to eradicate malaria from the Sultanate of Oman and to free the country from any malaria impediment on the various developments.

The catastrophes of malaria on development activities inspired me to write this booklet entitled “Manual for Treatment of Malaria and Its Complications “in order that all physicians and practicing doctors in all health institutions can follow the basic standard methodology of effective treatment of malaria.

The present system of involving malaria eradication staff in treating malaria cases should be stopped.

Certainly, this will relieve the staff of Malaria Eradication Programme from the treatment of malaria cases. This will enable
them to put all their efforts to implement the interruption of malaria transmission through larviciding and selective focal spraying, based on epidemiological studies. Thus, before the end of this century the Sultanate of Oman will be the first country in the Arabian Peninsula to achieve malaria eradication.

Dr. Hassan Mashaal

International Malaria Consultant

Table of Contents

| I. CLINICAL ASPECTS OF MALARIA AND LABORATORY DIAGNOSIS |
| IIL.STANDARD TREATMENT OF MALARIA CASES AMONG ALL AGE GROUPS |
| IV. MALARIA IN PREGNANCY AND THE USE OF ANTI MALARIALS |
| V. COMPLICATIONS OF falciparum MALARIA AND THEIR TREATMENT |
| VI. RARE CASES OF P.falcivarum RESISTANT TO Chloroquine Treatment |
| VIU. TREATMENT OF SEVERE AND COMPLICATED CASES OF MALARIA BY QUININE Dihydrochloride |
| VV. ROLE OF PRIMAQUINE IN MALARIA ERADICATION IN OMAN |
| IX - NURSING CARE IN SEVERE AND COMPLICATED MALARIA |
| X - THE PROBLEM OF IMPORTED MALARIA IN OMAN |
| XI. PROPHYLACTIC ANTI-MALARIA DRUGS |
INTRODUCTION

The degree of parasitaemia produced by the different species of Plasmodia differs greatly. P. vivax, probably also P. ovale, attack the youngest RBCs (reticulocytes); so that at any time not more than 2% of RBCs are invaded. On the other hand, P. malariae tends to invade the older RBCs and the infection rarely exceeds 1%. P. falciparum has affinities to attack any RBCs regardless of the age. Consequently in P. falciparum very high infection rates of the RBCs may occur.

The normal RBCs are to a certain degree deformable and therefore can pass through minute capillaries. In P. falciparum infection, the RBCs become less deformable. This consequently causes blockage of blood vessels by the parasitized RBCs.

In P. falciparum infection, both the parasitized and non-parasitized RBCs reveal an increase in haemolysis due to increased osmotic fragility. Therefore the life span of RBCs is shortened.

The parasitized RBCs adhere to the intima of blood capillaries due to reduction in the surface electrical charges and the development of knoblike protrusions in the membrane of the RBCs.

Parasitized and non-parasitized RBCs undergo haemolysis.

Moreover the parasitized RBCs before they are haemolysed carry less oxygen. This leads to anoxia.

The parasitized RBCs may release toxic substances. The toxin affects the non-parasitized RBCs, consequently the degree of anaemia is aggravated.

Circulating soluble antigens have been shown to exist in severe infections. These antigens also affect the non-parasitized cells and they are partly responsible for the degree of anaemia. Also the reticulocytes are often absent, due to bone marrow suppression by
toxin. Both the parasitized and non-parasitized RBCs are phagocytosed in large numbers by the reticulo endothelium system. As a result of these numerous factors, anaemia is severe.

Following the RBCs primary lesion, several pathological processes contribute towards impairment of liver thnction. Also severe haemolysis causing haemoglobinaemia, and in case the renal threshold is exceeded, the haemoglobin appears in the urine (haemoglobinuria). Also severe anemia leads to histo-toxic anoxia.

Other severe complications are capillaries blockage causing the increase in permeability of minute vessels and RBCs escape in the tissue (brain).

Due to failure of synthesis by the damaged hepatic cells, the albumin concentration in plasma falls; also thrombocytopenia develops. Several other complications are discussed in the text and proper guidance is given to treat and manage these cases so that lives are saved.

**II. CLINICAL ASPECTS OF MALARIA AND LABORATORY DIAGNOSIS**

When laboratory services are unavailable or results of blood films from highly clinically suspected cases are negative, reliance must be placed on clinical signs and symptoms and on the response to chemotherapy.

The diagnosis of malaria is a matter of clinical experience. The laboratory report of detection of a few parasites in the blood film of an immune or semi-immune case does not necessarily determine the actual disease which obliged the patient to seek medical help.

Malaria must be suspected amongst fever cases in endemic areas or amongst those who were recently exposed to malarious endemic areas. Clinically, the presence of intermittent fever and its recurrence
are suggestive of malaria. The regular paroxysms and fever-free intervals are quite suspicious of presence of malaria. Also the examination of the spleen, its tenderness, its enlargement and consistency provides valuable information.

**Significant Characteristics of falciparum Malaria**

P.falciparum infection varies greatly in the clinical picture. It has the tendency towards pernicious manifestations. This might be due to extraordinary rapid multiplication of P. falciparum and, therefore, the parasite density can increase to a great extent over a 48-hour period. Also the schizogony of P. falciparum has a high degree of unsynchronization. This may be attributed to the great variability in the length of the schizogonous cycle, i.e. fluctuation either way from the 48-hour period.

P. falciparum can invade any erthrocytes at any age and therefore, parasitaemia can reach a threatening level. Also schizogony has a great tendency to be only in internal capillaries, this may affect one or more organs and may lead to gross pathological lesions in several organs.

**Clinical Manifestation of P. falciparum**

In a non-immune case, the prodromal symptoms in a primary attack may occur for few hours or a few days. These are: frontal or post-ocular headache, back pain, pain in the limbs, malaise, fatigability, dizziness, prostration, feeling of chill and even shivering, hot sensations, sweating and gastro-intestinal disturbances like anorexia, nausea, vomiting, and diarrhoea. During this prodromal period, transient and minor elevation of temperature may occur.

As the situation aggravates, severe headache, pain in the back, legs, elsewhere and general malaise increase in intensity. Also, anxiety and mental confusion are common.
Chilliness is slight, the patient may feel chilly sensations or even shivering but rigors are absent or extremely mild. This is followed by a prolonged hot stage and excessive sweating. The fever is irregular and shows no distinct periodicity. Fever may be continuous or remittent or intermittent. In some cases fever is irregular in pattern. The paroxysms are prolonged and may last from 20 to 36 hours. They are irregular and more exhausting than the paroxysms of other species. The intermittent type of fever is commonly seen subsequent to the first remission or as a temporary phase during the attack.

The pulse and respiratory rates are rapid. Nausea, vomiting and diarrhoea increase in severity and there is commonly some pulmonary involvement producing cough. Also conjunctival injection, flushed face, very severe headache, abdominal discomfort and lassitude are common. The spleen is enlarged, soft and tender. The liver may also be enlarged and jaundice may develop. Anaemia is quite common.

If the treatment is not administered, the situation is aggravated, symptoms become more numerous and more severe. The lack of proper care and undernourishment aggravate the situation. Development of malignant trends and symptoms of pernicious malaria may appear suddenly. Severe complications may develop without prior warning.

**Characteristics of Malaria (Useful in the Differential Diagnosis)**

If fever returns regularly every 48-72 hours, probably the case is of malaria. Quotidian (daily) periodicity is misleading and therefore should not be taken as a necessary indication of malaria.

The combination of fever, anaemia and splenomegaly are highly suspicious in an endemic area, or when there is a history of visit to a malarious area.
Rigors with aching limbs, headache, vomiting suggest a diagnosis of malaria. Vomiting is marked as the temperature rises. When it falls, vomiting usually ceases until the next paroxysm.

The regular succession of paroxysms and fever-free (apyrexial) interval are important to suspect malaria.

Rapid release from all symptoms during apyrexial periods is also characteristics of malaria.

The characteristic symptomatology of malaria leads to an accurate diagnosis but in atypical cases other diagnostic methods are essential.

Latency and relapses are typical.

Confusion with delirium occurs in severe P. falciparum malaria but is very rare in other malarial infections.

**Blood Examination**

A certain diagnosis of active malaria infection is established on the identification of the malaria parasites in the peripheral blood. The examination of a thick blood film by an experienced technician is the best method to confirm the presence of Plasmodium and its species. Thin blood film examination is resorted to rarely whenever the microscopist cannot identify the species from thick blood film examination.

Standard practice requires that the thick film should be examined for at least 5 minutes corresponding to approximately 100 fields under oil immersion.

In doubtful cases, the treating doctor should guide the microscopist or laboratory technician that an absence of malaria parasite (negative
slide) should not be reported before at least 200 fields of a thick blood film are examined. In these cases, repeated blood films must be taken every 4-6 hours and examined. Infalciparum, the prepatent period (the time lag until the parasites can be detected microscopically) is sometimes longer than the internal incubation period (the time lag until fever appears). The practitioner can miss the diagnosis if he depends on the results of one specimen taken in the first day of fever.

It is important to know that failure to discover parasites even after repeated examinations does not exclude the diagnosis of malaria and should not delay the start of a therapeutic trial in patients with severe disease who could have been exposed to infection.

The presence of gametocytes only is not enough to confirm the diagnosis of active malaria. This is because gametocytes may be found in the peripheral blood for weeks or months after the primary attacks has subsided or been cured. The recording of gametocytes is of great importance in our Malaria Eradication Programme since the transmission of malaria starts by an increase in the gametocytes rate together with an increase in the density and infectivity of the vector to be followed by the increase in the disease incidence. It is important to realize that the presence of malaria parasites in the blood is a proof of infection but not necessarily the cause of the diseases for which the patient seeks help. The blood of individuals, who are resident in malarious areas for many years, may reveal scanty malaria parasites but the symptoms that obliged them to seek medical help may be due to a totally different cause.

Several weeks after the termination of a malaria attack, malaria pigment may be detected in monocytes and polymorphnuclear neutrophiles. Experienced technicians may be able to detect these pigments and in this case the diagnosis is highly suggestive of a past attack.
The Estimation of Parasite Density

The rough estimation of parasite density is useful. It is always a good practice for the microscopist to give to the treating physician an idea about the density of the parasites in the thick smear.

The use of symbols to give an idea about the density is the simplest method:

+ Means 1-10 parasites per 100 microscopic field
++ Means 11-100 parasites per 100 microscopic field
+++ Means 1-10 parasites in each microscopic field
I I I I Means more than 10 parasite in each microscopic field.

To conclude the blood examination for malaria parasite, the microscopist must provide the following standard information: species of the parasite; stages of the parasite; and density of the parasites.

In severe cases, the laboratory technician should be able to establish the parasite count per microlitre of blood. This is very helpful to the treating doctor to help him monitor the response of the parasites to the line of treatment followed plus monitoring the progress of the case.

Two tally counters are used; one to count the parasites and the other to count the leukocytes (WBCs). The number of parasites relative to the leukocyte count can be used to establish the density of parasitaemia per microlitre by the following:

No. of parasites/microlitre = No. of parasites X 8000 No. of WBCs assuming that the number of WBCs/microlitre is 8000.

Usually the laboratory technician counts the numbers of parasites
relative to 500 leukocytes and multiples this number by 16.

Non-immune individuals (with no previous infection) with high parasite count (I I should be considered serious and should be given urgent management.

These patients should be admitted and hospitalized and treated under strict observation, medical, and nursing care.

**Laboratory Finding in Malaria**

In acute malaria, the detection of malaria parasite in the blood is essential.

Slight leucopenia with relative monocytosis. Pigment maybe seen in monocytes. Sometimes white blood count is normal.

Increased indirect bilirubin in the serum as well as other evidence of haemolysis.

Serum globulin is increased (especially the euglobulin fraction) but albumin decreased.

Biological false positive tests for syphilis are not infrequent.

Albuminuria and haematuria are found in nephrotic syndrome of P. malariae.

In severe infection offalciparum malaria the life span of red blood cells is shortened due to the increased osmotic fragility.

Severe haemolytic anaemia with increased bilirubin and haemoglobinuria are common in black water fever. *

Laboratory findings due to involvement of organs:

a. Liver: coagulation abnormalities resulting
from failure to synthesize clotting factors, hypo-albuminaemia an reduced metabolic clearance of many substances including alanine and lactate.


In bacterial infections, polymorphnuclear leukocytes develops.

Eosinophilia is absent.

**Prognosis infalciparum Malaria**

The presence of high parasitaemia is suggestive of complications, if not managed immediately.

Continuous fever is an indication that schizogony is increasing in density. It is also possible that the heat regulation mechanism centre in the hypothalamus may be affected through occlusion of its blood supply capillaries. The presence of continuous fever beyond 48 hours and with high parasitemia make the outlook a grave one.

The presence of debility, severe anaemia, under-nutrition, chronic illness, physical exhaustion, excess alcoholism puts the patients at a great disadvantage.

The presence of several schizonts in the peripheral blood and as well as immature gametocytaemia (sex cannot be differentiated) are usually noticed a few hours before death.

**III STANDARD TREATMENT OF MALARIA CASES AMONG ALL AGE GROUPS**

Treatment of malaria in children is essentially the same as in adults;
with the provision that some drugs (e.g. Quinine) are relatively better tolerated by children; while other drugs, e.g. intramuscular injection of Chloroquine call for greater caution.

Blackwater Fever: It is a very serious syndrome that occurs in the absence of G6PD deficiency in highly malarious areas, characterized by sudden onset, chills, fever, and intravascular haemolysis, accompanied by haemoglobinuria, and renal failure. It occurs typically In Individuals who have experienced several attacks of P. falciparum malaria.
Table: Dosage of Antimalarial Drugs for Oral Treatment of Moderately Severe Malaria in Non-immune Population
(Drug Used: Chloroquine - 1 tablet = 150mg base)
Teaspoon Syrup - 5ml = 50mg Chloroquine**

### Loading Dose (10mg/kg)

<table>
<thead>
<tr>
<th></th>
<th>0-6 Mths 5-7 Kgs</th>
<th>6-12 Mths 7-10 Kgs</th>
<th>1-3 Yrs 10-17 Kgs</th>
<th>4-9 Yrs 17-30 Kgs</th>
<th>10-14 yrs 30-45 Kgs</th>
<th>15+ Yrs 50-60 Kgs</th>
</tr>
</thead>
<tbody>
<tr>
<td>75mg, 1/2 tab</td>
<td>100mg.</td>
<td>150mg.</td>
<td>300mg.</td>
<td>450mg.</td>
<td>600mg.</td>
<td></td>
</tr>
<tr>
<td>Spoon 1 1/2 = 7 1/2ml</td>
<td>2 = 10ml</td>
<td>3 = 15ml.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Second Dose After 6 Hours (5mg/kg)

<table>
<thead>
<tr>
<th></th>
<th>0-6 Mths 5-7 Kgs</th>
<th>6-12 Mths 7-10 Kgs</th>
<th>1-3 Yrs 10-17 Kgs</th>
<th>4-9 Yrs 17-30 Kgs</th>
<th>10-14 yrs 30-45 Kgs</th>
<th>15+ Yrs 50-60 Kgs</th>
</tr>
</thead>
<tbody>
<tr>
<td>35mg, 1/4 tab</td>
<td>50mg.</td>
<td>75mg.</td>
<td>150mg.</td>
<td>225mg.</td>
<td>300mg.</td>
<td></td>
</tr>
<tr>
<td>Spoon 3/4 = 3 1/2ml</td>
<td>1 = 5ml.</td>
<td>Spoon 1 1/2 = 7 1/2ml</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Daily Dose for Next Two Days (5mg/kg) each dose

<table>
<thead>
<tr>
<th></th>
<th>0-6 Mths 5-7 Kgs</th>
<th>6-12 Mths 7-10 Kgs</th>
<th>1-3 Yrs 10-17 Kgs</th>
<th>4-9 Yrs 17-30 Kgs</th>
<th>10-14 yrs 30-45 Kgs</th>
<th>15+ Yrs 50-60 Kgs</th>
</tr>
</thead>
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<tr>
<td>35mg, 1/4 tab</td>
<td>50mg.</td>
<td>75mg.</td>
<td>150mg.</td>
<td>225mg.</td>
<td>300mg.</td>
<td></td>
</tr>
<tr>
<td>Spoon 3/4 = 3 1/2ml</td>
<td>Spoon 1 = 5ml.</td>
<td>Spoon 1 1/2 = 7 1/2ml</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: Most of Chloroquine syrup in Oman have concentration: 50mg/5ml. For radical cure of P. vivax and P. ovale, a full course of Primaquine for 14 days is followed after completion of Chloroquine. See dosage and details page 25.

** Over 60kg body weight, the dosage should be adjusted: Loading dose 10mg/kg. Second dose 5mg/kg. And daily dose for next two days: 5mg/kg.
With syrups containing active ingredient more than 50mg. per teaspoon, the dose should be adjusted accordingly.

Chloroquine is usually given in a 3-day course for the curative treatment of chloroquine sensitive P. falciparum and P. malariae and for the termination of an acute attack of j vivax or P. ovale malaria. The standard regimen consists of 10mg. base per kg. of body weight; followed by 5 mg/kg 6-8 hours later and 5 mg/kg on each of the next two days. The drug should be given after meals. There is no evidence that increasing the dose of chloroquine increases the clinical cure rate in areas of developing chloroquine resistant falciparum malaria.

No abortifacient or tetratogenic effects have been reported with chloroquine and so it may be considered safe in pregnancy.

Adverse effects related to chloroquine are rare and mild when the drug is given orally in the usual antimalarial doses. Nausea and vomiting may occur if it is taken on an empty stomach. Headache and difficulty in visual accommodation have been reported in patients receiving a therapeutic regimen of 25 mg/kg. Pruritis of the palms, soles and scalp has been reported in up to 20% of Africans using chloroquine. This is not relieved by antihistaniinics.
IV. MALARIA IN PREGNANCY AND THE USE OF ANTI MALARIALS

During the second half of pregnancy, there is multifactorial transient immuno-suppression. The presence of high adrenal steroid levels, placental chorionic gonadotrophin, alpha fetoprotein and the depression of the lymphocyte role - may play an important role in the immuno-suppression mechanism of a pregnant female.

Complications in Pre Resulting from Malaria

Abortion
Difficult delivery
Low birth weight

Acute falciparum malaria will exacerbate anaemia especially in primigravidae.
Renal insufficiency and eclampsia.
Congenital malaria: incidence is very low.
Acute pulmonary oedema. It is frequent after delivery

Hypoglycaemia due to:

- Accelerated response to starvation
- Metabolic demands of pregnancy
- Consumption of glucose by falciparum blood stage
- In case quinine is used, it
Malaria Chemo-Prophylaxis for Pregnant Women: (Not in Areas of Low Malaria Endemicity Start from 3rd to 4th month of pregnancy

Table: Chemo-Prophylaxis During Pregnancy

Drug Frequency of Administration Dose in kg base

Chloroquine Weekly 9; 300 mg *

Base OR twice weekly 150mg/dose

OR Daily (6 days/week) 100mg/dose

Equivalent to chloroquine 5 mg/kg body weight.

In areas of low malaria endemicity, the implementation of large scale malaria chemo prophylaxis is neither practical nor economic. In this case, it is necessary to establish diagnostic and treatment facilities, aiming at early detection and timely treatment of positive malaria cases among the pregnant women.

Table: Treatment of Acute Malaria (all species

<table>
<thead>
<tr>
<th>day</th>
<th>Chloroquine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>600mg (4 tablets)</td>
</tr>
<tr>
<td>6 hours</td>
<td>300 mg (2 tablets)</td>
</tr>
<tr>
<td>later</td>
<td></td>
</tr>
</tbody>
</table>
Management of Iron Deficiency Anaemia

In malarious endemic areas, the prophylactic administration of iron during pregnancy is recommended.

Management of Megaloblastic Anaemia

This is not uncommon in association with malaria in pregnancy. It is advisable to administer folate daily to prevent folate deficiency. The therapy may continue until end of pregnancy or even for few months during lactation.

**WARNING:** REGIMENS CONTAINING PYRIMETHAMINE AND TETRACYCLINES ARE CONTRA-INDICATED DURING PREGNANCY AS WELL AS DURING LACTATION.

PRIMA QUINE IS CONTRA INDICATED IN PREGNANCY AS WELL DUE TO ITS HAEMOLYTIC ACTION IN G6PD DEFICIENCY. THIS IS BECAUSE THE FETUS IS RELATIVELY G6PD DEFICIENT.

### V. COMPLICATIONS OF falciparum MALARIA AND THEIR TREATMENT

Cerebral malaria is the most important lethal complications of P. falciparum malaria. It occurs among non-immunes. It is a medical
emergency and an intravenous infusion of chloroquine or quinine should be commenced as soon as the diagnosis is made.

Cerebral malaria coma is non-arousable and is not attributed to other causes such as bacterial or viral meningo-encephalitides, drug intoxication, head injury, eclampsia, hypoglycaemia, and cerebrovascular accident. Headache and drowsiness are succeeded by a comatose state. Other indications of cerebral malaria are excitement, disorientation, delirium, negativism, convulsion (in children), somnolence and coma. The comatose case may resemble encephalitic lethargica. Transient monoplegia, hemiplegia, dysarthria with slurred speech, Parkinsonian posture, tremor and speech defects are occasionally observed in endemic areas.

**Svmumatolo of Cerebral Malaria**

Cerebral malaria often starts dramatically with generalized convulsion followed by persisting unconsciousness.

A short clinical examination should be performed urgently to establish the diagnosis and start immediate treatment. A second thorough examination is recommended after treatment has already started.

Fluid balance is important and the state of hydration should be carefully assessed. The pulse is rapid and pulse pressure wide. A respiratory rate greater than 30 breaths per minute may be due to high fever or indicate pulmonary oedema, aspiration pneumonia or metabolic acidosis. Splenomegaly and hepatomegaly are common. Coma should be graded and signs of meningitis excluded.

The corneal reflexes are normal except in deep coma. Abdominal reflexes are generally absent. Convulsions occur in 50 percent of cases. They are generalized and focal features are rare.

**Investigations required**
Parasite count

Haematocrit, complete blood count, platelet count

Electrolytes, blood urea, creatinine, blood glucose and blood culture.

Serum albumin is important in patients suspected of pulmonary oedema.

Test urine for specific gravity and antimalarial drugs.

Serum bilirubin, transaminases, and alkaline phosphates are useful information but not required urgently.

Lumbar puncture is very useful (not in patient with papilloedema).

The CSF is clear. Microscopy is usually normal. Neutrophil pleocytosis is not a feature of cerebral malaria and suggests pyogenic meningitis. Concentration of lactate in the CSF is raised in cerebral malaria over 2.2 mmol/l. In cases where CSF lactate concentrations are over 6 mmol/l, the prognosis is usually fatal.

**Treatment of Cerebral Malaria**

Cerebral malaria is a medical emergency and patient should be nursed properly in intensive care unit or best ward available. Majority of patients will recover if they receive outstanding professional care on first day. A rapid initial clinical assessment should be made and immediate antimalarial chemotherapy administered using optimal doses by parenteral route.

Fluid intake and volume of urine and vomit should be measured and the patient should be weighed once daily. An intake-output chart
should be maintained and fluid balance carefully assessed. Correct electrolytes and acid-base balance. Low fluid intake will initiate or aggravate renal failure. Excess fluid intake may initiate pulmonary oedema, a serious and almost fatal condition. One has to prevent complications e.g.: convulsions, hypoglycaemia, hyperpyrexia, etc. or detect them very early and treat them adequately.

**Intravenous infusion of anti-malarial drug is the most effective and safest route of administration in severe cerebral falciparum malaria as this is introduced in the blood at a known rate and can be adjusted or stopped**

Adjuvant corticosteroid therapy is contraindicated since some trials proved that it led to the prolongation of coma and an increased incidence of infection and gastrointestinal bleeding without any reduction in mortality. Adjuvant therapy with anti-coagulants is also contraindicated. (Management of Severe and Complicated Malaria, WHO, Geneva, 1991/Bruce Chwatt’s Essential Malariology, Third Edition, 1993/Dion R. Bell, Lecture Notes on Tropical Medicine, 1991/100 Clinical Problems in Tropical Medicine/Physician’s Guide to Effective Management of Cases of Malaria, 1993 by H. Mashaal)

**Chloroquiune**

Chloroquine remains very useful and the drug of choice in Sultanate of Oman where P. falciparum remains highly susceptible to this drug.

Fatal circulatory collapse following intravenous or intra-muscular chloroquine, led the previous WHO Scientific Group on the Chemotherapy of Malaria (WHO Technical Report Series No. 711 in 1984) to suggest that parenteral chloroquine should never be used. In 1990 Technical Report Series 805 by WHO Scientific Group they
realized their previous recommendation was absolutely wrong and the WHO Scientific group stated that recent studies demonstrated that “CHLOROQUINE CAN SAFELY BE GIVEN BY PARENTERAL ROUTES EVEN TO CHILDREN WITH SEVERE falciparum MALARIA” based on extensive studies.

From 1987 to 1991, the proper use of chloroquine in the treatment of cerebral malaria in susceptible areas yielded excellent results. The advantage of chloroquine over quinine are:

- fewer deaths occurred with chloroquine use than with quinine,
- it does not cause hypoglycaemia,
- it has not been associated with intravascular haemolysis, and
- it does not stimulate the pregnant uterus.

The toxic effects of chloroquine can be prevented by intravenous infusion at a slow rate as follows:

5 mg base/kg diluted in isotonic fluid given by constant rate intravenous drip over 6 hours. This is repeated five times. In other words 5 consecutive infusions, each of 5mg/kg. each given over 6 hours i.e. the total dose is 25 mg/kg given over 30 hours

If intravenous infusion is not possible, then chloroquine can be given intramuscularly or subcutaneously as follows:

3.5mg/kg base at 6 hours intervals, OR 2.5 mg/kg base at 4 hourly intervals.

Oral treatment should be substituted as soon as the patient can swallow tablets. In most cases two parenteral doses are required
before oral treatment started. Complete total dose is 25 mg base/kg.

**N.R** Some authors e.g. Hall (1982) recommend intravenous quinine in all severe and complicated cases of malaria.

In our National Antimalarial Drug Policy, the decision whether to start with quinine or chloroquine intravenously depends on the epidemiological background of the case.

If the case is a clear-cut imported case e.g. from Africa or the Indian sub-continent, where chloroquine resistance is highly suspected and in severe cases for which the origin of infection is unknown, IV quinine should be started with.

Anyway, the patient on either IV quinine or IV chloroquine will be under very strict observation monitoring the parasitic index every 6 hours to assess the response of the parasite to treatment.

**Other Severe Manifestations of P. falciparum**

**Hyperpyrexia (Hyperthermia):**

Temperatures above 38.5 C are associated with an increased incidence of convulsions especially in children.

Temperatures between 39.5 to 42 C are accompanied with delirium. Temperature above 42 C is accompanied with coma.

Malaria hyperpyrexia may be clinically indistinguishable from heat hyperpyrexia. It is thus always essential in high endemic areas to exclude malaria before a diagnosis of heat stroke can be safely made.

**Treatment of hyperpyrexia**

By tepid sponging and exposure to cool air,

Fanning, cooling
Antipyretic: Paracetemol suppositories.

**Convulsions**

Generalized convulsions may be repeated more than twice within 24 hours. Focal seizures are unusual but grand mal-seizures are common. Treatment is needed.

**Severe Anaemia and Bone Marrow Depression**

It is mainly due to haemolysis, increased osmotic fragility, bone marrow dysfunction and erythrophagocytosis but deficiency of G6PD and presence of abnormal haemoglobin further aggravates the anaemia. Anaemia reduces blood viscosity and oxygen carrying capacity and leads to an increase in cardiac output.

**Treatment of Anaemia**

If the haematocrit falls below 20%, fully cross matched whole blood or packed cells should be transfused.

Fresh blood is preferred because of the need of clotting factors and platelets. Iron and folic acid supplementation may be necessary.

**Renal Failure (Acute Renal Insufficiency)**

Renal failure is due to renal anoxia syndrome in which the operative cause is failure of the intra-renal blood flow with reduction or even cessation of glomerular filtrates and secretion of urine. The degree of tubular damage depends on the duration and intensity of renal ischaemia which must be present few hours before histological changes become detectable.

Urine Specific Gravity greater than 1.015 (conc urine) or urinary sodium less than 20 mmol/litre with normal microscopical appearance suggests dehydration.
History of oliguria (300ml. urine or less during the previous 24 hours) with vomiting suggests renal failure.

A specific gravity of urine 1.010 or less suggests acute tubular necrosis. High urinary sodium suggests that acute tubular necrosis has developed.

Uraemic complications are likely when blood urea exceeds 60 mg/dl urea nitrogen (blood urea more than 21.4 mmol/l). Blood urea rapidly rises and unless effective treatment is given, it may reach 300-400 mg/100ml blood or more.

Hyperkalaemia should be excluded. In electrocardiogram there is widening of QRS complex, shortening of QT interval and tall T wave.

Observe the respiratory rate. If increased, this suggests metabolic acidosis, pneumonia or pulmonary oedema.

**Treatment of renal failure caused by P. falciparum (applied to adults)**

The doses of chloroquine need not be reduced.

Intravenous fluid infusion: isotonic saline or glucose.

If no urine flow after fluid replacement, an established oliguric or anuric phase will follow. Take these steps:

- c. Limit water intake to 500 ml/day + an amount equal to volume of urine passed (Fluid chart)
- d. Limit protein intake to 20 g/day. Carbohydrate 200 g/day.
e. If these measures fail, give furosemide. Start with 40 mg and may increase to 150 mg then to 500 mg at half hour intervals if there is no urine flow. When giving 500 mg furosemide, it is given over 30 minutes to avoid ototoxicity.

f. If all fails, dialysis is essential.

Hyperkalaemia should be treated. Serum potassium should be kept below 7 mmol/L per litre. Give soluble insulin 20 units & glucose 50g simultaneously. The insulin/glucose regimen can be repeated until the serum potassium falls to normal level. Also intravenous calcium gluconate 10-20ml of 10% solution may be given to protect the heart from the effect of hyperkalaemia.

**Pulmonary Oedema (Acute Pulmonary Insufficiency)**

Usually it is fatal. Predisposing factors are:

(a) overhydration,
(b) pregnancy,
(c) cerebral malaria,
(d) high level parasitaemia and
(e) hypotension, hypoglycaemia, metabolic acidosis and ureaemia are commonly associated. Respiratory rate increases to 40, 60, or even 70 per minute. It is rapid and shallow. Heart rate exceed 100/minute. The sputum is tinged with copious amounts of foamy blood.

**Treatment of Pulmonary Oedema in adults (non-cardiogenic in nature):**

*
Chloroquine infusion continued.


Initially 250 ml blood can be removed rapidly.

Furosemide 40 to 120 mg intravenously.

If no improvement, vasodilator drugs can be given e.g. glyceryltrinitrate 10-200 ug/minute by intravenous infusion.
Alternatively sodium nitroprusside 10-400 ug/minute may be given. If these drugs fail or are not available, venesection of 500 mg may help.

**Bleeding and Clotting Disorders (due to P. falciparum)**

Treatment along the following lines (for adults, adjust for children):

- Transfusion of fresh whole blood or concentrate of clotting factors and platelets.

- Exchange transfusion can be used in fluid overloaded patients.

- If prothrombin or partial thromboplastin times are prolonged, give Vitamin K: 10mg very slow intravenously.

- Avoid drugs that increase the risk of gastrointestinal bleeding e.g. aspirin, cortico steroids.

- Heparin is no longer recommended. It is even dangerous.

**Algid Malaria (hypotension and shock)**

It resembles shock with very low blood pressure. If not dealt
urgently, it can lead to cellular dysfunction and organ damage.

Severe pulmonary oedema has recently emerged as a serious and challenging complication of acute falciparum malaria (non-cardiogenic in nature). It is a catastrophic complication of acute falciparum malaria and is rapidly fatal. Treatment is totally different from cardiogenic oedema. It can be prevented by restriction of fluid input in patients with severe falciparum malaria, usually to less than 1500 ml daily in adults to prevent pulmonary oedema.

**Treatment of Algid Malaria in Adults**

Immediate infusion of fluid to restore blood volume. In 1/2 to 1 hour, if there is no improvement in blood pressure, another litre of saline or isotonic glucose is given very slowly.

If systolic blood pressure is lower that 90-100 mm/Hg Dopamine may be needed.

After the shock has passed treat P. falciparum with chloroquine.

**Malaria Hepatic Involvement - Hepatic dysfunction**

There is considerable hyperactivity of the sympathetic nervous system which produces constriction of visceral vessels causing restriction of organ blood flow in the liver (also kidney) and this results in portal venous hypertension and degeneration of the parenchymal cells.

**Management of Malaria Hepatic Involvement**

The importance of reducing the dosage of quinine (25 to 50%) infusion and other drugs must be stressed.
In case jaundice is due to massive haemoglobinaemia (black water fever), chloroquine intravenous infusion is given instead.

General principles to treat jaundice are applied: 10% glucose intravenously. Diet is mainly restricted to carbohydrates and protein. In hypoprothrombinaemia, parenteral Vitamin K is given.

**Disturbances of Fluid, Electrolyte and Acid Base Balance**

Severely dehydrated and hypovolaemic falciparum patients who are deprived of fluids or suffer from profuse vomiting and diarrhoea will become hypotensive, oliguric, and detonate to acute renal necrosis.

Hyponatraemia might arise in a patient who has sweated profusely for days. In mild hyponatraemia, serum sodium is 125-135 mEq/litre.

Lactic acidosis may result from impaired tissue perfusion caused by micro-vascular obstruction by parasitized erythrocytes, hypovolaemia, reduced hepatic clearance of lactate and lactate production by parasites.

On the other hand, excess fluid may initiate pulmonary oedema, a serious and almost fatal condition.

**Management of Metabolic Disorder (applied to adults)**

The fluid intake and the volume of urine vomiting should be measured and the patient should be weighed once daily.

When the patient is dehydrated and hypovolaeniic, there is elevation in blood urea and creatinine. Urine output can be restored by carefi.il administration of infusion of isotonic saline. If no response, give increasing doses of slowly infused IV ftiroseamide up to total 1g. Then finally give an
infusion of Dopamine. If these fail, then restrict fluids and haemodialysis is performed.

Acidosis should be corrected only if the arterial pH falls below 7.15. The administration of sodium bicarbonate constitutes a considerable sodium load. THAM (tromethamine) is an alternative which dose not contain sodium. The usual adult dose of THAM is 300mg/kg IV as a 0.3 M solution over a period of not less than 1 hour. In children THAM is given IV in doses of 100-150mg/kg per 0.1 pH unit deviation from normal.

**Blackwater Fever**

Malaria, with severe intravascular haemolysis with haemoglobinuria, accompanied by severe manifestations of P. falciparum infection, including renal failure, hypotension and scanty parasitaemia.

**Management of Blackwater Fever**

Absolute rest. Hiccup is relieved by sucking ice. Sedatives and tranquilizers; chlorpromazine 50-100mg. IM or oral valium.

Treat vascular failure: intravenous plasma. Adjust fluid intake.

If blood count is less than 1.5 million, give citrated blood.

If plasma urea is 170-200 mg/mi., renal dialysis is required.

Glucose orally is given freely. Serum potassium is kept below 7 mEq/litre.

Alter recovery, malaria prophylaxis may prevent
Complications of Falciparum Malaria and their Treatment

2. Hypoglycaemia (plasma glucose 40mg/dl = 2.2 mmol/l)

It is a frequent complication of severe falciparum malaria. This is due to an increase glucose demand secondary to host as well as parasite anaerobic glycolysis and reduced supply because of impaired hepatic gluconeogenesis. The second process is due to quinine, if used in treatment as Quinine stimulates insulin secretion. This second process tends to occur late and it is associated with high plasma concentrations of insulin and low concentration of ketone bodies. It is common in pregnant women. The two conditions tend to overlap.

Hypoglycaemia is increasingly recognized as a complication of falciparum malaria and its treatment. Usually it is not suspected clinically because the patient is suffering from severe falciparum malaria.

Since severe hypoglycaemia may be asymptomatic in pregnant women, it must be excluded in all cases of severe malaria. In patients with severe falciparum malaria, hypoglycaemia must be suspected and excluded by repeated finger prick-testing for blood glucose, using a ‘stix’ method.

Treatment of Hypoglycaemia (in all ages)

Blood glucose should be checked immediately in severe malaria cases.

Clinical response to glucose may be dramatic in adults with the hyperinsulinaemic form of hypoglycaemia but it is less common in children.
Continuous infusion of 5 percent dextrose but avoid fluid overload.

In Sultanate of Oman, use chloroquine instead of quinine unless in very rare cases of F. falciparum-resistance to chloroquine or severe and complicated cases of malaria.

**Septicaemia**

Several types of bacterial infection are commonly associated with severe complicated falciparum malaria. Gram-negative bacteraemia presumably originates from the gastrointestinal tract or urinary tract infection. Treatment of septicaemia should be given early.

**Gastro-Intestinal Symptoms**

Nausea, vomiting, abdominal pain, and watery diarrhoea are common in malaria particularly with high fever. Malabsorption is common. Parasite sequestration in the vascular bed probably interferes with the absorptive mechanism. Gram-negative bacteria or endotoxin enter from the gut lumen.

**Treatment of Gastro-intestinal Malaria (dose given for adult)**

Patients respond well to anti-malarials

Parenteral replacement of body fluids and electrolytes is essential.

Vitamin K! (water misible) 10mg orally or Vitamin K3 (menadione) 10mg orally every day, during the acute phase.

Folic acid 1-5 mg daily for one month.

**Aspiration Pneumonia**

Aspiration pneumonia may occur in any unconscious cerebral malaria
patient. It is due to frequent vomiting. It should be treated urgently.

**Rare Complications of Falciparum Malaria**

3. Cardiac Lesions

In severe malaria myocardial failure and cardiac arrhythmia are rare. Heart failure may occur as a terminal event especially in those with severe anaemia and in women after delivery. Early antimalarial therapy and intensive care might prevent fatal complications.


5. Psychiatric Changes

Disorders reported: (i) disturbance of consciousness (ii) acute organic brain syndrome (confusion, disorientation and intellectual deterioration) (iii) movement disorders iv. focal signs. Early and improved antimalarial therapy cures the malaria psychiatric complications in a very short time.

6. Pancreatitis

Very rare. Responds well to antimalarial treatment.

**VI. RARE CASES OF P. falciparum RESISTANT TO Chloroquine Treatment**

The term resistance means the ability of a strain of Plasmodium to survive and to multiply in spite of the administration of an active drug administered in therapeutic doses or even higher. Till today, this is applied only to P. falciparum although recent reports have recorded resistance to Chloroquine and even Primaquine by P. vivax.

In the field, drug resistance is suspected when acute cases of P. falciparum do not fully and rapidly respond to proper treatment with drugs or when recrudescence of symptoms and parasites, in the blood
are seen soon after their temporary disappearance following treatment.

**Recrudesence may occur due to other causes than resistance**

There are strains of *P. falciparum* that require somewhat larger doses of certain drugs to be given over a longer period.

There may be differences between individual patients in the way they absorb and utilize drugs.

The active ingredient of the tablets given to the patient is far less than what is indicated on the label of the container.

Reports on apparent resistance of *P. falciparum* to drugs should be based on careful investigation of each case to exclude that the drug was not taken by the patient and it was not vomited. Drugs provided by unknown firms ought to be analyzed to ensure their proper contents.

**P. falciparum- resistant to Chloroquine in Oman**

Most of the resistant cases detected were imported from India or Pakistan or Africa (mainly Zanzibar). It is estimated that the number of resistant Pf cases does not exceed 0.5% of all the *P. falciparum* cases.

**Drug Regimens in falciparum Chloroquine- resistant Cases**

**A. Quinine**

Quinine is the drug of choice for the treatment of chloroquine-resistant falciparum malaria and for infections which have “broken through” chloroquine prophylaxis and for infections whose origin is
not known.

**Preparations**

Tablet Quinine bisuiphate.. 300 mg

Tablet Quinine supihate. . 300 mg (also capsules)

The content is expressed as salt and not base.

**Oral Administration**

Adult 600 mg (2 tablets) every 8 hours for 7 to 10 days.

In some strains the treatment has to be prolonged to 10-14 days.

Children 10mg/kg, every 8 hours for 7 days.

**Toxicity**

Quinine has its own characteristic side effects. Giddiness ringing in the ears, tremors and blurred vision may occur during the first few days of administration in some patients, but these symptoms usually subside when administration of the drug ceases. Idiosyncrasy to quinine with more serious symptoms occurs but is rare.

**Quinine Interaction with other Dru2s**

The concurrent use of aluminium containing antacids may delay or decrease its absorption.

Quinine can depress the hepatic enzymes system that synthesizes Vitamin K dependent factors.

The use of urinary alkalinizers as acetazolamide or sodium bicarbonate concurrently with quinine may increase quinine blood level with potential for toxicity.
The use of neuromuscular blocking agents as pancuronium succinylicholine and tubocurarine may be potentiated with quinine and result in respiratory difficulties.

**B. Pyrimethamine/Sulfadoxine = Fansidar**

This is the most widely used family of drug combination which antagonize parasite folic acid synthesis.

**Uses**

In areas where chloroquine-resistant organisms are known to occur.

In patients who, because of previous chloroquine-induced pruritis or allergic, etc., are advised not to take chloroquine.

**Treatment of resistant cases**

Quinine should be given for 1-3 days before pyrimethamine/sulfadoxine in order that:

- Quinine may accelerate reduction of parasitaemia and yield clinical improvement.
- To minimize the risk of rapidly emergence of pyrimethamine/sulfadoxine resistant strains.

**Dose of Quinine**

Quinine tablets (650 mg) 3 times daily for 1-3 days, OR: 10 mg/kg 3 times daily.

This is followed by a single dosage of pyrimethamine/sulfadoxine:

3 tablets (each tablet = Pyrimethamine 25mg. + Sulfadoxine 500mg.).
**Table: DosaEe of Pyrimethamine/Sulfadoxine in Children and Different Aae Groups**

<table>
<thead>
<tr>
<th>Years/Kg.</th>
<th>Infant 5-10kgs</th>
<th>1-3 Yrs 10-15kgs</th>
<th>4-6 Yrs 16-25kgs</th>
<th>7-10 Yrs 26-40kgs</th>
<th>11-16 Yrs 41-50kgs</th>
<th>Adult 50kgs+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>0.5 tab.</td>
<td>1 tab</td>
<td>1¼ tabs.</td>
<td>1½ tabs.</td>
<td>2 tabs.</td>
<td>3 tabs.</td>
</tr>
</tbody>
</table>

**Toxicity**

Oral sulfadoxine/pyrimethamine is very well tolerated. Minor adverse reactions are rare:

Anorexia, abdominal cramps, vomiting, ataxia, tremors, seizures and megaloblastic anaemia due to folic acid deficiency. Infrequent reactions include: granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally haemolysis may occur in G6PD deficiency.

**C. Mefloquine**

Mefloquine has been chosen as the 3rd line of treatment in case of resistance to both 1st and 2nd lines of treatment.

Mefloqume is a 4-quinoline methanol which has proved to be highly active blood schizontocide against multidrug resistant strains of P. falciparum.

Pre-clinical, toxicological, and carcinogenicity studies have been satisfactory.

It is effective against both P. falciparum and P. vivax trophozoites but it has no effect on either gametocytes of P. falciparum or tissue forms of P. vivax.

Because Mefloquine-resistance has already been reported every effort
is being made to protect the drug by the development of mefloquine combinations with Fansidar; by advocating its use with Primaquine as gametocytocidal drug to prevent transmission and by hopeful restricting its eventful deployment primarily for treatment, being used for prophylaxis only in special risk groups (UNDP/World Bank/WHO Update, 1983).

It is worthwhile to mention in this regard that the problem of the growing and rising multi- drug resistance by the P. falciparum strains, plus the availability of just few antimalarial drugs makes it very imperative to strictly adhere to the NATIONAL ANTI-MALARIAL DRUG POLICY TO AVOID THE EXHAUSTION OF OUR OPTIONS OF ANTI MALARIALS.

The“ failure to introduce new antimalarials reflects upon the intractability of finding new drugs rather than a lack of effort in chemotherapy research. Of more than 20,000 compounds tested in the US Army, malaria Programme less than ten have shown significant promises (Canfield, 1980) and only one. Mefloquine (WR 142.490 has been selected for extensive trials in man.” (Recent Advances in Tropical Medicine).

Forms

Tablet 250mg base (as hydrochloride).

The disadvantage is the availability of tablet forms only.

Dose

15- 25mg/kg body weight as a singl dose. To reduce GII side effects, the drug can be given in two divided doses, 12 hours apart.

N.B. Mefloquine should not be started except 12 hours after the
last dose of quinine given if the patient was treated previously with quinine.

**Adverse reactions**

Mainly dose related.

Rare effects: headache, bradycardia, rash, and pruritis

Neurological and psychiatric adverse effects have been recorded but seem to be also dose-related.

**Contra-indications**

Pregnancy

In patients taking cardioactive drugs, particularly β-adrenoreceptor and calcium-channel blocking agents.

**VU. TREATMENT OF SEVERE AND COMPLICATED CASES OF MALARIA BY QUININE DOLHYDROCHLORIDE**

All severe cases, especially those imported from outside Oman where Chloroquine resistance is rising and those with unknown origin of infection, should be treated by IV Quinine and oral Quinine should be shifted to whenever the patient becomes able to swallow.

**Loading Dose**

10mg/kg body weight in 200ml 5% glucose over a period of 4 hours.

**Maintenance Dose**
Following immediately after loading dose 5mg/kg in 200 to 600ml 5% dextrose over a period of 4 hours. This is repeated 12 hourly until the patient can swallow. Then Quinine tablets 10mg/kg 8 hourly are given to complete 7-day course.

The loading dose can be 20mg/kg by infusion in 5% dextrose saline over 4 hours and the maintenance dose 10mg/kg in 5% dextrose saline over 4 hours to be repeated every 8-12 hours.

The amount of infusion fluid (5% dextrose or isotonic solution) is adjusted as follows:

a. If the patient is overhydrated on arrival, the infusion fluid is 5ml/kg.

b. If the patient is normally hydrated or slightly dehydrated, infusion fluid volume is 1

Since cinchona alkaloids are cardioactive, it is important to determine past history of cardiac arrhythmia, heart disease and hypersensitivity to Quinine.

If after 48 hours of parenteral treatment the patient is still unable to take oral treatment or if there is evidence of renal or hepatic impairment, the maintenance dose should be reduced to half.

Hypoglycaemia caused by hyper-insulinaemia is a common side effect of Quinine. This may be prevented by continuous infusion of 5% dextrose over 24 hours.

High doses of Quinine may stimulate the pregnant uterus and cause abortion. However, normal therapeutic doses are safe.
Remember that severe falciparum malaria is worse than antimalarials.

In patients with evidence of intravascular haemolysis, Quinine should not be withheld as the evidence that it causes “blackwater fever” is not convincing.

Rarely, quinine may cause haemolysis, severe thrombocytopenia associated with quinine-dependent anti-platelet antibodies, disseminated intravascular coagulation, hypersensitivity reactions, cutaneous neutrophilic vasculitis, photosensitization and granulomatous hepatitis.

**VIII. ROLE OF PRIMAQUINE IN MALARIA ERADICATION IN OMAN**

With the increase in the incidence of *P. vivax* cases especially among the expatriate labour force, the role of PRIMAQUINE has become more prominent and important as an antirelapse measure (hypnozoitocidal). Most of the expatriate labourers come from the Indian subcontinent which lies in the ORIENTAL zoographical region in which the *P. Vivax* is predominant.

Besides, since the Ministry of Health in Oman is committed to eradicate malaria, **PRIMAQUINE** administration has become imperative as a gametocytocidal drug in *P. falciparum* malaria in order to interrupt the transmission of malaria in the community so as to avoid secondary infections originating from a single primary case of malaria.

The new notification system allows the Malaria Teams to follow-up the malaria cases and to make sure that the radical treatment of malaria cases is being given especially in case of the 14-day
treatment by Primaquine in P. vivax.

Primaquine is a bitter, colourless synthetic 8- aminoquinoline. Each tablet contains 7.5 mg or 15mg of the active base (in Oman each tablet = 7.5 mg).

**Action**

It is a hypnozoitocidal drug. It acts on the dormant liver forms called “hypnozoites” that are responsible for relapse of P. vivax and P. ovale. For the radical cure of P. vivax or P. ovale, Primaquine is administered following the last dose of standard treatment with chloroquine. It actively destroys gametocytes of all species, particularly gametocytes of P. falciparum.

**Absorption and Excretion**

Primaquine is rapidly absorbed from the intestine. After a single dose of 45mg, a peak plasma level of up to 250ug/litre is reached within 1 hour. The drug is almost completely eliminated from the body within 24 hours of its administration.

As a gametocytocide for P. falciparum, it is effective at a single dose of 30-45 mg base. If this is divided on 3 consecutive days (previously applied in the 1980s), the mean blood level will be far lower than 25ougflitre. Also there is no cumulative effect of Primaquine as It is excreted very fast (within 24 hours). Therefore the gametocytocidal effects is greatly lowered.

**Indication**

Anti- relapse treatment of P. vivax and P. Ovale cases.

As a gametocytocide for P. falciparum, it is administered as a
single dose of 30-45 mg base for adult. Dose is adjusted according to the age group.

**Dose**

As a gametocytocide for *P. falciparum* and *P. vivax*, it is effective at a single dose of 30-45 mg base (adult).

The usual dose for anti-relapse of *F. vivax* and *P. ovale* is 15 mg base daily for 14 days. For cases from South East Asia or Oceana, the same dosage is applied, but for 21-28 days instead of 14 days.

In G6PD deficiency, patients tolerate better a dose of 30-45 mg base—weekly for 8 weeks.

**Dose of Primaguine**

a: For radical treatment of *P. Vi* and *P. ovale*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Daily Dosage</th>
<th>Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-6 Years</td>
<td>7.5 mg</td>
<td>1</td>
</tr>
<tr>
<td>7-10 Years</td>
<td>10.0 mg</td>
<td>1¼</td>
</tr>
<tr>
<td>11-16 Years</td>
<td>12.5 mg</td>
<td>1½</td>
</tr>
<tr>
<td>Adults</td>
<td>15.0 mg</td>
<td>2</td>
</tr>
</tbody>
</table>

Duration of dosage for children is 10 days. For adults 14 days.

b. To destroy gametocytes of *P. falciparum* by single dose

<table>
<thead>
<tr>
<th>Age Group</th>
<th>4-6 Yrs</th>
<th>7-10 Yrs</th>
<th>11-16 Yrs</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Dose = Tablets of 7.5 mg each</td>
<td>15 mg = 2 tabs</td>
<td>22 mg = 3 tabs</td>
<td>30 mg = 4 tabs</td>
<td>37½ mg = 5 tabs</td>
</tr>
</tbody>
</table>

**Toxicity of Primaguine**
Gastr9 intestinal effects Abdominal pain or cramps are common. This can be prevented by taking Primaquine after meals.

Granulocytopenia It is produced if a potentiating factor such as concomitant use of sulfonamides.

Methaemoglobinaemia Cyanosis develops when methaemoglobin concentration exceeds 10% of the normal level of haemoglobin. The methaemoglobin levels in the majority of cases on Primaquine is less than 8.5% of the total haemoglobin.

Lymphocytic proliferative response and iminuno-suppressive activity: The lymphocyte proliferative response to malaria infection is inhibited by Primaquine. Primaquine poses potential immune-suppressive activity within the therapeutic range of its use. Since patients with malaria infection are already immuno-compromised further immuno-suppression by Primaquine may be detrimental to recovery from serious infections. Therefore it is important to administer the dose of Primaquine after the patient has passed the acute phase of this sickness.

As the lymphocyte proliferative responses to malaria are inhibited by doses of Primaquine within the range normally used to treat P. vivax infections, therefore Primaquine administration should begin ONLY after the acute phase of the disease has passed.

Haemolytic Anaemia The haemolytic action of Primaquine is increased in subjects with a genetic deficiency of the enzyme Glucose- 6- phosphate- dehydrogenase (G6PD). Primaquine
should therefore be avoided in pregnancy since every foetus is relatively G6PD deficient.

There are two variants of the enzyme (G6PD). One is fast moving on electrophoresis and is called Variant A. The other is slow moving on electrophoresis and is called Variant B. Variant A is found amongst some African while Variant B is among some Asians.

In Variant A, the G6PD deficiency is among the older RBCs therefore there is mild self limiting haemolysis. In this group the standard treatment of relapsing malaria with higher doses, acute haemolytic crisis may occur.

In Variant B (Mediterranean and Asia), even the young RBCs are deficient in G6PD and their haemolysis results in progressive haemoglobinaemia and haemoglobinuria with fatal outcome unless blood is transfused promptly.

Therefore, it is clear that there is great need in Oman to determine the prevalence and distribution of Variant A and B of G6PD- deficiency in every region of the country.

**Contra-indications**

In rheumatoid arthritis, lupus erythematosus or patients receiving drugs that depress the bone marrow activity.

**Treatment of Primaguine Poisoning**

Primaquine administration should be stopped once the urine is dark or sudden decrease in haemoglobin level occurs. In acute or chronic Primaquine poisoning, folic acid is given daily in a dose of 10-20 mg. Glucose saline may be given intravenously. Also alkaline solution by the mouth is advisable. In severe cases, blood transfusion may be necessary.
Nursing Care

The management of the patient with severe malaria is as important as chemotherapy and here the nurse has a crucial role to play:

Meticulous nursing care should be given to unconscious patients. Maintain a clear airway. Turn the patient every two hours. Do not allow the patient to lie in a wet bed. Particular attention should be paid to pressure points and the patient should be nursed on his or her side to avoid aspiration of fluid. Aspiration pneumonia is a potentially fatal complication, and must be dealt with immediately.

A careful record of fluid intake and output must be kept, the appearance of black urine noted and specific gravity measured.

The speed of infusion of fluids should be checked frequently.

Temperature, pulse, respiration, and blood pressure must be monitored regularly every 4-6 hours for at least the first 48 hours.

Changes in the level of consciousness, occurrence of convulsions or changes in behaviour of the patient must be reported immediately.

If rectal temperature rises above 390 C, vigorous tepid sponging and fanning must be applied, and paracetamol may be given.

THE PROBLEM OF IMPORTED MALARIA IN OMAN

One of the most important features of the Infectious Parasitic Diseases in Oman is the IMPORTATION of cases. Of course, this is
very obvious in case of MALARIA. Refer to Annex 3 showing the rising trend of imported malaria cases in 1995 from January to August.

**The main reasons are:**

The large number of the expatriate manpower forming 26.5% of the total population of Oman according to the last census in 01.12.1993.

- Omanis : 1,483,226
- Expatriates : 534,848
- National Total : 2,018,074

- Most of these expatriates come from malaria endemic countries e.g. India, Bangladesh, Pakistan, Sudan, and Sri Lanka.

The regular and continuous travels of Omanis to East Africa to and fro. So they are importing malaria especially the chloroquine-resistant strains of falciparum malaria.

The above two factors increase the menace of Malaria Re-establishment in areas and regions in which Malaria has been eliminated by the successful Malaria Eradication Programme.

By the large influx of imported malaria cases from abroad, the Malariogenic Potential is high.

Since the Sultanate of Oman is committed to eradicate Malaria, special interest has been given to the IMPORTATION of malaria cases.

Since 1994, the blood examination for malaria parasites (MP) has been introduced as one of the routine investigations in the Regional
Medical Check-up Centres responsible for examining all the expatriate labourers and employees in the private sector. The positive expatriates for MP are first treated and will not be eligible for a license of a labour card except after getting radical treatment and making sure their blood films for MP have become negative. This system has been initiated as a pilot study in Sharquiya and Batna Regions.

Screening of all the passengers coming from East Africa in the airport is another measure to ensure early malaria case detection and giving the treatment accordingly. Recently the involvement of private clinics has started to strengthen the passive case detection especially among the expatriates.

Blood smears are examined for malaria parasites from any fever case among expatriates and from any fever case under 10 years old among Omani. The slides are collected by the private clinics and examined in the nearest malaria laboratory. This new system is being applied gradually region by region.

The measures aim at the elimination of the reservoir of infection which will consequently help in the interruption of malaria transmission.

Impregnated mosquito bednets are given to the patient as a supplementary measure to avoid the man-vector contact.

In this regard, the responsibility of the medical practitioner for taking an accurate history of traveling abroad has become crucial.

Besides the medical practitioners all over the country should be updated about the epidemiological situation of Malaria not only in Oman but also worldwide e.g. distribution of the chloroquine resistant strains offalciparum malaria in the world.

The Directorate of Environmental Health and Malaria Eradication is
cooperating with Directorate of Health Education and Information in the Directorate General of Health Affairs to intensify the travel advice to all Omanis traveling to East Africa through pamphlets, brochures, TV spots, etc.

XI. PROPHYLACTIC ANTI-MALARIA DRUGS

Chemoprophylaxis is aimed to reduce morbidity and to prevent fatalities amongst persons at high risk for severe malaria. Basically, this covers the non-immune travelers in areas of malaria transmission as well as pregnant women.

**Drugs recommended for prophylaxis in Oman**

**Chloroquine**

It is effective for the prevention of malaria due to parasites susceptible to Chloroquine. It is well tolerated and is safe for pregnant women and children. Side effects of the daily dose are usually mild but may include headache, diplopia and gastrointestinal upset. Chemoprophylaxis is used primarily by non-immune travelers to malarious areas and for residents who are at increased risk such as pregnant women and young children.

Chloroquine-induced pruritis is uncommon among non-Africans. If Chloroquine is used for 5 to 7 years (total consumed exceeds 100 grammes), retinopathy, corneal opacity, and partial alopecia may develop.

**Proguanil**

It is used in combination with Chloroquine. It has a marked effect on the primary tissue stages of P. Falciparum, P. Vivax and P. ovale. It is very safe for prophylaxis because there are few side effects or adverse reactions. It is safe for pregnant women.
The current recommended dose for adult is 200 mg daily. This is an increase from the former dosage of 100 mg daily. Adverse occasional effects are anorexia, nausea, diarrhoea, and mouth ulcers.

**Dose of Anti-Malaria Drugs for Individual Protection**

**Two drugs given:** Chioroquine and Proguanil. Both drugs are given daily for 6 days every week.

Dtu 6- 12 Mths 1- 3 Yts. 44Th fl44 Y 15+ Th

Weight(Kg) 7- lOKgs 10- 17 kgs 17..3OKgs 3 Kgs Above 50

**Chiorofluine**

Tablet: 150mg. 15 mg. 25mg. 37mg. 50mg. ; 75mg.

1/4 Tab. 1/3 Tab .‘/2 Tab.

OR

**Chioroguine**

Syrup Teaspoon 1/4 tsp . ½ tsp. 3/4 tsp - - - -

AND

**Pro2uanil**

Tablet: 100mg 33mg . 9; 50mg. 100mg. 150mg. 200mg.

Given together 1/3 Tab. ‘/2 Tab. 1 Tab. 1 Tab. 2 Tabs.

with
Chioroguine

NB: Administration of ¼ tablet or ½ tablet of Proguanil: by dividing one tablet to 4 portions, crush the ‘/4 tablet or ‘/2 tablet in a teaspoon, mix with a bit of water, thrust in the mouth of infant who should immediately afterwards be fed on the breast.

The above table recommended dosages are to be administered starting two weeks before departure to the endemic areas as well as for 4 weeks after return.

This applies to travelers not exceeding 3 months duration in any endemic areas. For longer periods in endemic areas, consult the local authorities.

For longer period, the personal protection against mosquitoes is stressed and the traveler is asked whenever sick with fever to be examined microscopically for malaria in the nearest health institution in order to be given the appropriate treatment.

Individual Protection from Mosquito

To reduce man-mosquito contact the following is recommended:

**Use of Bed nets**: Use bed nets during the night. It is advisable to spray the outside of the net with an aerosol dispenser or hand sprayer using insecticide preparation or to use the already impregnated bed nets.

**House Screening**: Mosquito proofing of houses is practical and effective provided continuous checking is made as to the presence of any hole or tears in the screen.

**Use of Protective Clothing**: Soft leather boots protect the ankles in the evening; or a pair of thick socks rolled on the
trousers. The use of long sleeves etc. is also advised.

Pyrethrum house spj To be applied before retiring.

Mosquito coils or Joss sticks

**They contain pyrethrum and can be used as repellants.**

- **Repellants**

These are applied to skin or bed nets or clothing to repel mosquitoes. They have different qualities and different effective durations:

- Dimethyl phthalate (DMP), effective 3 hours
- Dibutyl phthalate (DBP), effective 4 hours
- N.N.diethyl toluamide (DET), effective 10 hours
- Dihydroacetone monoesters of carboxylic compound.

If this is combined with DET, their action is prolonged.
MALARIA EPIDEMIOLOGICAL SITUATION: 1990 to 1995 - SULTANATE OF OMAN

[ALL SOURCES]

MALARIA SITUATION 1990-95

- 1990: 32720 positive cases
- 1991: 19274 positive cases
- 1992: 14677 positive cases
- 1993: 10767 positive cases
- 1994: 7215 positive cases
- 1995: 1801 positive cases

Yearly trends:
- 1990: Eradication campaign started in Sharqiya region
- 1991: Eradication extended to neighbouring Qurayyat wilayat Muscat region
- 1992: Eradication extended to both Batnash regions
- 1993: Eradication extended to neighbouring Beeb wilayat Muscat region
- Intensified control in Dakhliya & Dhahir regions

S.P.R.%:
- 1990: 12.1%
- 1991: 2.7%
- 1992: 2.7%
- 1993: 2.44%
- 1994: 6.39%
- 1995: 0.0%

Annex 2
<table>
<thead>
<tr>
<th>YEAR</th>
<th>BLOOD SLIDES EXAMINED</th>
<th>POSITIVES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SURVEYS &amp; ACD</td>
<td>P.C.D.</td>
</tr>
<tr>
<td>1990</td>
<td>79703</td>
<td>191049</td>
</tr>
<tr>
<td>1991</td>
<td>47020</td>
<td>203427</td>
</tr>
<tr>
<td>1992</td>
<td>43644</td>
<td>168243</td>
</tr>
<tr>
<td>1993</td>
<td>40736</td>
<td>209282</td>
</tr>
<tr>
<td>1994</td>
<td>72146</td>
<td>223046</td>
</tr>
<tr>
<td>1995</td>
<td>126579</td>
<td>337512</td>
</tr>
</tbody>
</table>

Malaria Statistics
1990 OMAN/F-1
Annex 2 (cont.)
PERCENTAGE OF IMPORTED INTERNATIONAL CASES TO THE TOTAL CASES - 1995

<table>
<thead>
<tr>
<th>Month</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAN'95</td>
<td>12.95</td>
</tr>
<tr>
<td>FEB'95</td>
<td>23.86</td>
</tr>
<tr>
<td>MAR'95</td>
<td>23.81</td>
</tr>
<tr>
<td>APR'95</td>
<td>36.84</td>
</tr>
<tr>
<td>MAY'95</td>
<td>44.33</td>
</tr>
<tr>
<td>JUN'95</td>
<td>51.55</td>
</tr>
<tr>
<td>JUL'95</td>
<td>55.43</td>
</tr>
<tr>
<td>AUG'95</td>
<td>58.16</td>
</tr>
<tr>
<td>SEP'95</td>
<td>57.8</td>
</tr>
<tr>
<td>OCT'95</td>
<td>34.88</td>
</tr>
<tr>
<td>NOV'95</td>
<td>16.18</td>
</tr>
<tr>
<td>DEC'95</td>
<td>19.04</td>
</tr>
</tbody>
</table>
SEVERAL FACTORS HAVE COMBINED TO INCREASE THE PROBLEM OF IMPORTED MALARIA:

1) Increased Travel:
   - More malaria infections

2) Increasing Resistance of Pf and recently of Pv to drugs (chemoprophylactic drugs):
   - More infections progressing to disease

3) Inadequate or neglected travel advice
   - More infections and disease

4) Delayed Diagnosis and Treatment:
   - Progression of falciparum malaria to life threatening disease

ANNEX 4
## ANNEX 5

### DIFFERENCES BETWEEN A MALARIA CONTROL PROGRAMME AND A MALARIA ERADICATION PROGRAMME

<table>
<thead>
<tr>
<th></th>
<th>CONTROL PROGRAMME</th>
<th>ERADICATION PROGRAMME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OBJECTIVE</strong></td>
<td>The reduction of malaria to a prevalence where it is no longer a major public health problem.</td>
<td>The ending of the transmission and the elimination of the reservoir of infective cases in a campaign limited in time.</td>
</tr>
<tr>
<td><strong>AREA OF OPERATIONS</strong></td>
<td>Not necessarily covering all the area where malaria transmission takes place.</td>
<td>Must cover all the area where malaria transmission takes place.</td>
</tr>
<tr>
<td><strong>MINIMUM STANDARDS</strong></td>
<td>Good</td>
<td>Perfect</td>
</tr>
<tr>
<td><strong>DURATION OF OPERATIONS</strong></td>
<td>Without limits</td>
<td>Programme ends when certain requirements are met</td>
</tr>
<tr>
<td><strong>COST</strong></td>
<td>Constantly recurring</td>
<td>Expenditure represents a capital investment and is not a permanently recurring cost.</td>
</tr>
<tr>
<td><strong>CASE-PENDING</strong></td>
<td>Superfluous</td>
<td>Of paramount importance</td>
</tr>
<tr>
<td><strong>EPIDEMIOLOGICAL</strong></td>
<td>Superfluous</td>
<td>Necessary in the late stages</td>
</tr>
<tr>
<td><strong>INVESTIGATION OF POSITIVE CASES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPIDEMIOLOGICAL</strong></td>
<td>By usual malarriometric surveys</td>
<td>Proof of disappearance of indigenous new malaria cases</td>
</tr>
<tr>
<td><strong>EVALUATION OF RESULTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IMPORTED CASES</strong></td>
<td>Do not deserve particular attention</td>
<td>Important and dangerous when effective attack measures have been withheld</td>
</tr>
<tr>
<td><strong>TOTAL COVERAGE</strong></td>
<td>Unnecessary</td>
<td>Indispensable both for the attack measures and the case finding.</td>
</tr>
<tr>
<td><strong>ADMINISTRATION OF THE PROGRAMME</strong></td>
<td>May not be the best and still be sufficient</td>
<td>Must be fully efficient and speedy; if not, danger of failure</td>
</tr>
</tbody>
</table>

*The above table is a modification of that appearing in W.H.O., E.C.M. Sixth Report, page 9 (1957).*
**Plasmodium falciparum**

**Sporontocidal Drugs:**
1. Primaquine
2. Proguanil
3. Pyrimethamine

**Cycle in Mosquito**
- Gametocytes
- Gametocytes taken up by mosquito
- Sporozoites injected by mosquito
- Cycle in Man
  - Red blood cell
  - Mature schizont
  - Developing, in capillaries of deep circulation
  - Immature schizont
  - Early trophozoite
  - Late trophozoite
  - Ruptured cell

**Tissue Schizontocidals:**
1. Proguanil
2. Pyrimethamine

**Gametocytocidal:**
- Primaquine

**Blood Schizontocidals:**
1. Chloroquine
2. Quinine
3. Fansidar
4. Mefloquine
PLASMODIUM VIVAX

SPORONTOCIDAL DRUGS:
1. Proguanil
2. Pyrimethamine

CRUCIAL STAGES OF GROWTH:
- Gametocytes
- Macrogametocyte and microgametocyte
- Female and male gametes
- Fertilization
- Eggs

CYCLE IN MOSQUITO:
- Eggs injected into human
- Eggs develop into infective stages
- Mosquito bites infected individual

CYCLE IN MAN:
- Insecticide treated nets
- Blood smear for diagnosis
- Chloroquine (gametocytocidal in Pv)
- Anti-relapse (hypnozoitocidal):
  1. Primaquine
  2. WR238,605

GROWTH STAGES OF OOCYST:
- Sporozoites
- Salivary glands
- Ruptured oocysts
- Fertilization
- Gametocytes taken up by mosquito
- Mosquito bites infected individual

BLOOD SCHIZONTOCIDAL:
- Chloroquine
- (gametocytocidal in Pv)
## ANNEX 8

### VARIETY OF ANTIMALARIAL DRUGS EFFECTIVE AT VARIOUS STAGES

**THE MALARIA PARASITE CYCLE**

<table>
<thead>
<tr>
<th>ANOPHELES</th>
<th>HUMAN HOST (LIVER)</th>
<th>HUMAN HOST (BL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sporontocidal Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Primaquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Proguanil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Pyrimethamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Causal Prophylactic Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Proguanil } $p.f.$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Pyrimethamine } $p.f.$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antirelapse Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Primaquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemosuppressive Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Chloroquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Amodiaquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Fansidar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Maloprim</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Schizontocidal Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Quinine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Chloroquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Amodiaquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Mefloquine} in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Fansidar } combin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Qinghaosu: Artesunate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gametocytocidal Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Primaquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Chloroquine } $p.v.$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Amodiaquine } $p.m.$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$p.f.$ = *P. falciparum*

$p.v.$ = *P. vivax*

$p.m.$ = *P. malariae*
PROGNOSTIC INDICATORS

The major indicators of a poor prognosis in children and adults with severe malaria are listed below:

**Clinical Indicators**

Age under 3 years

Deep coma
Witnessed or reported convulsions

Absent corneal reflexes

Decerebrate rigidity

Clinical signs of organ dysfunction (e.g. renal failure, pulmonary oedema)

Retinal hemorrhages.

**Laboratory Indicators**

Hyperparasitaemia (>250,000/ or >5%)

Peripheral schizontaemia

(Comments: These previous indicators show the great responsibility of the laboratory technician to record the density of parasitaemia plus the stages of parasites as well as the great responsibility of the treating doctor to ask for that, e.g. Pfr++++. sch++. g).

Peripheral leokocytosis (>12,000/pl)

Packed cell volume less than 20%

Haemoglobin less than 4.4 mmol/l(<7. lgIdl)

Blood glucose less than 2.2 mmoJl(<4OmgIdl)

Blood urea more than 21.4mmolll (>60mg of urea nitrogen per dl)

Low CSF glucose

Creatinine more than 265 gmol/l (>3.0mg/di)

High CSF lactic acid (>6 mmol/l)

Raised venous lactic acid (>6 mmol/l)
More than 3-fold elevation of serum enzymes (aminotransferases)

Increased plasma 5”- nucleotidase

Low antithrombin III levels

**ANNEX 10**

**COMMON ERRORS IN DIAGNOSIS AND MANAGEMENT**

The common errors in the diagnosis and management of severe malaria are listed below:

**Errors in diagnosis**

Failure to take a travel history

Misjudgment of severity

Faulty parasitological diagnosis and laboratory management

Failure to diagnose other associated infections

Missed hypoglycaemia

Failure to carry out an ophthalmoscopic examination for the presence of retinal hemorrhages.

Misdiagnosis (e.g. influenza, viral encephalitis, hepatitis, scrub typhus, etc).

**Errors in Management**

Inadequate nursing care

Errors in fluid and electrolyte replacement
Delay in starting anti-malarial therapy

Use of inappropriate drug (e.g. Chloroquine in areas of resistance)

Unjustified withholding of an anti-malarial drug

Dosage not correctly calculated

Inappropriate route of administration

Failure to elicit a history of recent chemotherapy

Unjustified cessation of treatment

Failure to control the rate of intravenous infusion

Failure to prevent cumulative effects of anti-malarial drugs

Failure to switch patients from parenteral to oral therapy as soon as they can take oral medication

Unnecessary continuation of chemotherapy beyond the recommended length of treatment

Unnecessary endotracheal intubation

Failure to prevent or control convulsions

Failure to recognize and treat severe anaemia

Use of potentially dangerous ancillary therapies

Delay in considering obstetrical intervention in late pregnancy

Failure to recognize and manage pulmonary oedema, aspiration pneumonia, and metabolic acidosis
Delay in starting peritoneal dialysis or haemodialysis

Failure to review anti malarial treatment in a patient whose condition is deteriorating

**Annex 11**

**Ancillary Therapies to be Avoided in the Management of Severe falciparum Malaria**

- Corticosteroids
- Other inflammatory agents
- Other agents given for cerebral oedema (urea, invert sugar)
- Low molecular weight dextran
- Epinephrine (Adrenaline)
- Heparin
- Epoprostenol (Prostacycline)
- Pentoxiphylline (Oxpenti!)
- Hyperbaric oxygen
- Ciclosporin (Cyclosporin A)

**Management of Severe and Complicated Malaria By H. M. Gilles WHO, Geneva, 1991**

**Bruce- Chwatt’s Essential Malariology, 1993**
The Regional Malaria Officer should be informed about any preliminary information of any confirmed malaria case within ONE HOUR by telephone or any other means to help him start immediately his investigation and mobilize his teams accordingly.

The notification form should be completely filled and sent by FAX as per the system, within 24 hours.

**Density of malaria parasitaemia in the THICK BLOOD FILM (TBF)**

<table>
<thead>
<tr>
<th>Density</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>1 - 10 asexual forms of parasites per 100 microscopic fields of a TBF.</td>
</tr>
<tr>
<td>++</td>
<td>11 - 100 asexual forms of parasites per 100 microscopic fields of a TBF.</td>
</tr>
<tr>
<td>+++</td>
<td>1 - 10 asexual forms of parasites per ONE microscopic field of a TBF.</td>
</tr>
<tr>
<td>++++</td>
<td>More than 10 asexual forms of parasites per ONE microscopic field of a TBF.</td>
</tr>
</tbody>
</table>

**THE ANTI-MALARIAL DRUGS**

- **First Line Drug**: Chloroquine (Schizontocidal)
- **Second Line Drug**: Quinine (Schizontocidal, short course)
- **Third Line Drug**: Fansidar (Schizontocidal), Mefloquine (Schizontocidal)

**N.B.**
1. PRIMAQUINE: GALEMETOCYTICIDAL in *falciparum* malaria
2. ANTI-RELAPSE in vivax/ovale malaria

**REMEMBER THAT:** IN ALL CASES OF SEVERE MALARIA, PARENTERAL ANTIMALARIAL CHEMOTHERAPY SHOULD BE STARTED IMMEDIATELY.

**PROGNOSTIC INDICATORS**

The major indicators of a poor prognosis in children and adults with severe malaria are listed below:

**Clinical Indicators**
- Age under 3 years
- Deep coma
- Witnessed or reported convulsions
- Absent or normal reflexes
- Deoorate rigidity
- Clinical signs of organ dysfunction (e.g., renal failure, pulmonary edema)
- Retinal hemorrhages.

**Laboratory Indicators**
- Hyperparasitaemia (≥250,000/l or >5%)
- Peripheral schizontocitia
  - **(Comments)**: These previous indicators show the great responsibility of the laboratory technician to record the density of parasitaemia plus the stages of parasites as well as the great responsibility of the treating doctor to ask for that, e.g., Smear, etc.
- Peripheral leucocytosis (>12,000/μl)
- Fasted cell volume less than 20%
- Hemoglobin less than 6.4 mmol/l (≤7.1 g/dl)
- Blood glucose less than 2.2 mmol/l (<40 mg/dl)
- Blood urea more than 11.4 mmol/l (≥60 mg of urea nitrogen per dl)
- Low CSF glucose
- Creatinine more than 360 μmol/l (>4.0 mg/dl)
- High CSF lactic acid (≥6 mmol/l)
- Raised venous lactic acid (≥6 mmol/l)
- More than 3-fold elevation of serum magnesium (anisotransferases)
- Increased plasma UCP oxidases
- Low antiheparin III levels

**COMMON ERRORS IN DIAGNOSIS AND MANAGEMENT**

**Errors in diagnosis**
- Failure to take a travel history
- Misjudgment of severity
- Faulty parasitological diagnosis and laboratory management
- Failure to diagnose other associated infections
- Misused hypoglycemia
- Failure to carry out an ophthalmologic examination for the presence of retinal hemorrhage
- Malaria (e.g., influenza, viral meningitis, leptospirosis, scrub typhus, etc.)

**Errors in Management**
- Inadequate nursing care
- Errors in fluid and electrolyte replacement
- Delay in starting anti-malarial therapy
- Use of an inappropriate drug (e.g., chloroquine in areas of resistance)
- Unjustified withholding of an anti-malarial drug
- Dosage not correctly calculated
- Inappropriate route of administration
- Failure to solicit a history of recent chemotherapy
- Unjustified cessation of treatment
- Failure to control the rise of intravenous infusion
- Failure to prevent cumulative effects of anti-malarial drugs
- Failure to switch patients from parenteral to oral therapy as soon as they can take oral medication
- Unnecessary continuation of chemotherapy beyond the recommended length of treatment
- Unnecessary anti-malarial intoxication
- Failure to prevent or control convulsions
- Failure to recognize and treat severe anemia
- Use of potentially dangerous ancillary therapies
- Delay in considering obstetric intervention in late pregnancy
- Failure to recognize and manage pulmonary edema, aspiration pneumonia, and metabolic acidosis
- Delay in starting perinatal dialysis or hemodialysis
- Failure to review antimalarial treatment in a patient whose condition is deteriorating
FREQUENT TRAVEL AND MALARIA

A British businessman who had visited several sub-Saharan African countries every year for 26 years returned from one visit with fever and chills. He had not taken chemoprophylaxis, believing that by now he was immune to malaria. He delayed reporting his fever for three days, developed cerebral malaria with renal failure, and required three weeks in intensive care.
BLOOD FILMS AND MALARIA

**Thick Blood Films** - A British laboratory technician developed fever during a week’s leave from his hospital post in East Africa. By the same evening he was prostrated and delirious. Thin blood films were negative for malaria, but thick film revealed occasional *P. Falciparum* rings. Treatment was started immediately. He made a full recovery.

**Negative Films** - A British doctor working in an African hospital developed fever and rigors. Thick and thin blood films were negative for malaria parasites. Suggestive symptoms continued the next day, when blood films revealed a 1% *P. falciparum* parasitaemia.

**Parasitaemia on Blood Films** - A girl aged 12 years accompanied her family to Britain from West Africa, where she has always lived. After a week she developed progressive fever with headache, malaise, and constipation. Blood films revealed *P. Falciparum* (1% of red cells), but there was no improvement on antimalarial treatment. *Salmonella typhi* was grown from blood and stool cultures.
FEVER AND MALARIA

Case 1 - An Indian woman aged 58 developed a dry cough and feverishness one week after arrival in Britain. Two general practitioners on successive days diagnosed an upper respiratory tract infection. She was admitted to hospital a week later with multiorgan failure complicating falciparum malaria, and died after two weeks in intensive care.

Case 2 - A British woman aged 49 had lived in Malawi for 27 years. She developed left iliac fossa pain and fever, with diarrhoea. Diverticular disease was diagnosed and shown on barium enema. Antibiotics failed to stop repeated episodes of fever and abdominal pain. P. Falciparum was identified by chance on a blood film, and both fever and pain disappeared within one day of starting antimalarial drugs.

BMJ, Volume 306
01 May 1993, page 1176
JAUNDICE AND MALARIA

A Nigerian student who had been resident in the United Kingdom for 10 years visited his family in Nigeria. Ten days after returning to Britain he developed malaise, anorexia, and fever, with jaundice. Hepatitis was diagnosed. Blood films revealed a 5% P. Falciparum parasitaemia. Liver enzymes were marginally raised. He recovered fully after antimalarial treatment.

BMJ, Volume 306
01 May 1993, page 1176

Annex 13 (cont.)
# TABLE OF NORMAL RANGES

<table>
<thead>
<tr>
<th><strong>PLASMA OR SERUM</strong></th>
<th><strong>SI Units</strong></th>
<th><strong>Conventional Units</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine transaminase ALT (SGPT)</td>
<td>0.20 U/l</td>
<td>0 - 20 U/l</td>
</tr>
<tr>
<td>Albumin</td>
<td>35 - 45 g/l</td>
<td>3.5 - 4.5 g/100 ml</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>100 - 330 nmol/l</td>
<td>2.5 - 12 ng/100 ml</td>
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<tr>
<td>Alkaline phosphatase</td>
<td>20 - 100 U/l</td>
<td>3 - 12 King-Armstrong U/100 ml</td>
</tr>
<tr>
<td>Anti-Diuretic Hormone (ADH)</td>
<td>4 - 8 ng/l</td>
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<tr>
<td>Aspartate transaminase AST (SGOT)</td>
<td>0 - 25 U/l</td>
<td>0 - 25 U/l</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>22 - 28 mmol/l</td>
<td>22 - 28 mEq/l</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>2 - 17 µmol/l</td>
<td>0.1 - 1 mg/100 ml</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.25 - 2.62 mmol/l</td>
<td>9 - 10.6 mg/100 ml</td>
</tr>
<tr>
<td>Chloride</td>
<td>93 - 108 mmol/l</td>
<td>93 - 108 mEq/l</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>3.6 - 7.2 mmol/l</td>
<td>145 - 280 mg/100 ml</td>
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<tr>
<td>Cortisol:</td>
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</tr>
<tr>
<td>9 AM</td>
<td>170 - 720 nmol/l</td>
<td>6 - 26 µg/100 ml</td>
</tr>
<tr>
<td>Midnight</td>
<td>170 - 220 nmol/l</td>
<td>6 - 8 µg/100 ml</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&lt; 100 µmol/l</td>
<td>&lt; 100 mg/100 ml</td>
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<tr>
<td>Creatinine phosphate kinase (CPK)</td>
<td>&lt; 80 µmol/l</td>
<td>1.0 mg/100 ml</td>
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<tr>
<td>DNA Binding</td>
<td>&lt; 25 µl</td>
<td>&lt; 25 µl</td>
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<tr>
<td>Growth hormone</td>
<td>&lt; 10 ng/ml</td>
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<tr>
<td>Glucose (fasting)</td>
<td>3.6 - 6.6 mmol/l</td>
<td>65 - 120 mg/100 ml</td>
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<tr>
<td>Immunoglobulins:</td>
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<tr>
<td>IgA</td>
<td>1.25 - 4.25 g/l</td>
<td>125 - 425 mg/100 ml</td>
</tr>
<tr>
<td>IgG</td>
<td>5 - 16 g/l</td>
<td>500 - 1600 mg/100 ml</td>
</tr>
<tr>
<td>IgM</td>
<td>0.5 - 1.7 g/l</td>
<td>50 - 170 mg/100 ml</td>
</tr>
<tr>
<td>Iron:</td>
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<td></td>
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<tr>
<td>Males</td>
<td>16 - 30 µmol/l</td>
<td>90 - 170 g/100 ml</td>
</tr>
<tr>
<td>Females</td>
<td>11 - 27 µmol/l</td>
<td>60 - 150 g/100 ml</td>
</tr>
<tr>
<td>Iron binding capacity (TIBC)</td>
<td>45 - 72 µmol/l</td>
<td>150 - 400 g/100 ml</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.65 - 1 mmol/l</td>
<td>1.3 - 2.0 mEq/l</td>
</tr>
<tr>
<td>Osmolality (plasma)</td>
<td>285 - 295 mmol/l</td>
<td>285 - 295 (mossmols/l)</td>
</tr>
<tr>
<td>pCO₂</td>
<td>4.7 - 6.0 kPa</td>
<td>35 - 45 mmHg</td>
</tr>
<tr>
<td>pO₂</td>
<td>12 - 13.3 kPa</td>
<td>90 - 100 mmHg</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 - 7.45</td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.8 - 1.4 mmol/l</td>
<td>2.5 - 4.3 mg/100 ml</td>
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<tr>
<td>Potassium</td>
<td>3.5 - 5.0 mmol/l</td>
<td>3.5 - 5.0 mEq/l</td>
</tr>
<tr>
<td>Proteins (total)</td>
<td>58 - 72 g/l</td>
<td>5.8 - 7.2 g/100 ml</td>
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<tr>
<td>Serum hydroxy-butyric-dehydrogenase (SHBD)</td>
<td>50-170 U/l</td>
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<tr>
<td>Sodium</td>
<td>133 - 145 mmol/l</td>
<td>133 - 145 mEq/l</td>
</tr>
<tr>
<td>Thyroxine (T4)</td>
<td>70-160 nmol/l</td>
<td>5.5 - 12.5 µg/100 ml</td>
</tr>
<tr>
<td>T3 Resin uptake</td>
<td>88 - 110%</td>
<td></td>
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<tr>
<td>Thyroid stimulating hormone (TSH)</td>
<td>0.8 - 3.6 U/l</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>3.3 - 7.0 mmol/l</td>
<td>20 - 42 mg/100 ml</td>
</tr>
<tr>
<td>Urates:</td>
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<tr>
<td>Male</td>
<td>0.24 - 0.44 mmol/l</td>
<td>4.0 - 7.5 mg/100 ml</td>
</tr>
<tr>
<td>Female</td>
<td>0.21 - 0.37 mmol/l</td>
<td>3.5 - 6.2 mg/100 ml</td>
</tr>
<tr>
<td>Faecal fat</td>
<td>0 - 17 mmol/24 hr</td>
<td>0 - 59/24 hr</td>
</tr>
</tbody>
</table>

### URINE

| **Coproprotein** | < 0.1 mg/24 hr | |
| **Hydroxy-methoxy-malonic acid** | 5 - 35 µmol/24 hr | 1.7 mg/24 hr |
### Table of Normal Ranges

(Continued)

<table>
<thead>
<tr>
<th></th>
<th>SI Units</th>
<th>Conventional Units</th>
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<tbody>
<tr>
<td><strong>HAematological</strong></td>
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<tr>
<td>Haemoglobin (Hb):</td>
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</tr>
<tr>
<td>Males</td>
<td>13.5 - 18.0 g/dl</td>
<td>13.5 - 18.0 g/100 ml</td>
</tr>
<tr>
<td>Females</td>
<td>11.5 - 16.5 g/dl</td>
<td>11.5 - 16.5 g/100 ml</td>
</tr>
<tr>
<td>Red blood cell count:</td>
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<tr>
<td>Males</td>
<td>4500 - 6500 x 10^9/l</td>
<td>4.5 - 6.5 million/mm³</td>
</tr>
<tr>
<td>Females</td>
<td>3900 - 5600 x 10^9/l</td>
<td>3.9 - 5.6 million/mm³</td>
</tr>
<tr>
<td>Packed cell volume (PCV):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.4 - 0.54</td>
<td>40 - 54 per cent</td>
</tr>
<tr>
<td>Females</td>
<td>0.35 - 0.47</td>
<td>35 - 47 per cent</td>
</tr>
<tr>
<td>Mean corpuscular haemoglobin (MCH)</td>
<td>27 - 32 pg</td>
<td>27 - 32 µg</td>
</tr>
<tr>
<td>Mean corpuscular haemoglobin concentration (MCHC)</td>
<td>32 - 36 g/dl</td>
<td>32 - 36 per cent</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV)</td>
<td>76 - 98 fl</td>
<td>76 - 98 µm³</td>
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<tr>
<td>Reticulocyte count</td>
<td>0.2 - 2 per cent</td>
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<tr>
<td><strong>White blood count (WBC)</strong></td>
<td>X10^9/l</td>
<td>/mm³</td>
</tr>
<tr>
<td>Total</td>
<td>4.0 - 11.0</td>
<td>4000 - 11000</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>2.5 - 7.5</td>
<td>2500 - 7500</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.5 - 3.5</td>
<td>1500 - 3500</td>
</tr>
<tr>
<td>Eosinophiles</td>
<td>0.04 - 0.44</td>
<td>40 - 440</td>
</tr>
<tr>
<td>Basophiles</td>
<td>0.0 - 1.0</td>
<td>0 - 100</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.2 - 0.8</td>
<td>200 - 800</td>
</tr>
<tr>
<td>Platelets</td>
<td>X10^9/l</td>
<td>/mm³</td>
</tr>
<tr>
<td></td>
<td>150 - 400</td>
<td>150,000 - 400,000</td>
</tr>
<tr>
<td><strong>Vitamin B12</strong></td>
<td>200 - 800 ng/ml</td>
<td>200 - 800 µg/ml</td>
</tr>
<tr>
<td><strong>Leucocyte Alkaline Phosphatase (LAP)</strong></td>
<td>20 - 70/100 neutrophils</td>
<td></td>
</tr>
<tr>
<td><strong>ESR (Westergren) all ages, both sexes</strong></td>
<td>&lt; 25 mm/hr</td>
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</tr>
<tr>
<td><strong>Prothrombin Time (PT)</strong></td>
<td>14 seconds</td>
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</tr>
<tr>
<td><strong>PT Ratio (Test/control)</strong></td>
<td>&lt; 1.2</td>
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<tr>
<td><strong>Activated Partial Thromboplastin Time (PTT)</strong></td>
<td>15 seconds</td>
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</tr>
<tr>
<td><strong>Kaolin Cephalin Clotting Time (KCCT)</strong></td>
<td>40 seconds</td>
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<tr>
<td><strong>Arterial Blood</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCO₂</td>
<td>4.7 - 6.0 kPa</td>
<td>35 - 45 mmHg</td>
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<tr>
<td>pO₂</td>
<td>12 - 13.3 kPa</td>
<td>90 - 100 mmHg</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 - 7.45</td>
<td>7.36 - 7.45</td>
</tr>
<tr>
<td><strong>Cerebrospinal Fluid</strong></td>
<td></td>
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</tr>
<tr>
<td>Glucose</td>
<td>2.7 - 4.1 mmol/l</td>
<td>48 - 73 mg/100 ml</td>
</tr>
<tr>
<td>Protein</td>
<td>0.15 - 0.4 g/l</td>
<td>15 - 40 mg/100 ml</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faecal Fat</td>
<td>&lt; 17 mmol/24h</td>
<td>&lt; 5g/24h</td>
</tr>
<tr>
<td>Xylose</td>
<td>23% of oral dose in 5 h more than half within the first 2 h</td>
<td></td>
</tr>
</tbody>
</table>
ANNEX 15

References to Amendments of Second Edition

1- Manual on Clinical malariology of falciparum Malaria in the Arabian Peninsula by Dr. M.A. Fand

2- Manual on Malaria Microscopy by Dr. M.A. Farid

3- Clinical Malariology by H.A.H. Mashaal, 1986

4- Physician’s Guide to Effective Management of Cases of Malaria by H.A.H. Mashaal, 1993


6- Lecture Notes on Tropical Medicine

7- Management of Severe and Complicated Malaria by WHO, Geneva.

8- Recent Advances in Tropical Medicine
9- A Textbook of Malaria Eradication, by Emilio Pampana, 1963