

Diagnosis and management of severe falciparum malaria

Learner's Guide



**Communicable Diseases Cluster
Department of Control, Prevention and Eradication
Social Mobilisation and Training Unit
June 2002
Trial Edition**

The development of this training module was made possible by a grant from the World Bank.

© World Health Organization 2002

All rights reserved.

This health information product is intended for a restricted audience only. It may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means.

The designations employed and the presentation of the material in this health information product do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this health information product is complete and correct and shall not be liable for any damages incurred as a result of its use.

Table of contents

Foreword.....	3
Introduction.....	5
Learning Units	
1. Information about diagnosis and management of severe falciparum malaria in your country or place of work.....	9
2. Severe falciparum malaria	15
3. Pathophysiology of severe falciparum malaria	19
4. Guidelines for diagnosis and assessment of severe falciparum malaria	27
5. The hospital visit.....	37
6. Picture quiz	39
7. The management of severe falciparum malaria	47
8. Assessment of recovery.....	62
9. Exercises in the diagnosis and management of severe falciparum malaria	66
Case study: Patient A	67
Case study: Patient B	71
Case study: Patient C	73
Case study: Patient D	75
Case study: Patient E.....	78
Case study: Patient F.....	85
Case study: Patient G	87
Case study: Patient H	89
Case study: Patient I.....	91
Further reading.....	93
Appendix 1	95
Appendix 2.....	97
Appendix 3.....	101
Appendix 4.....	103

Foreword

This training module on the diagnosis and management of severe *P. falciparum* malaria is intended primarily for the training of physicians, nurses, medical students and other health personnel both in malarious areas of the world and in non-endemic countries.

The module consists of Part I a Learner's Guide, and Part II, a Tutor's Guide. Within the Learner's Guide learning units provide essential information on the clinical features of severe and complicated malaria and guidance on how to proceed in a logical way with diagnosis and management of the disease. The picture quiz in Learning Unit 6 helps the learner to visualize the most striking clinical manifestations of the disease and to distinguish them from similar manifestations of other infectious diseases. Learning Unit 9 is based on a problem-solving approach to learning and allows the learners to acquire the knowledge required through guided examination of several malaria patients presenting distinct features in the manifestation of the disease.

Part II, the Tutor's Guide, provides an opportunity to check step by step the learners' reasoning in the interpretation of the results of the clinical examination and laboratory investigations with the most authoritative publications. These are provided in the list of references at the end of the Learning Units, before the Annexes and Appendices. Answers are also provided for the picture quiz which could be used to promote a discussion on the signs of severe and complicated malaria. Solutions to the problems posed in Learning Unit 9 of the Learner's Guide are suggested in the Tutor's Guide.

This module is part of a series of publications in English and French prepared by the World Health Organization on the subject of severe falciparum malaria that review the latest knowledge and experience on the subject. The other publications include: *Management of Severe and Complicated Malaria, A Practical Handbook* (H.M. Gilles; 1st edition 1991), and *Management of Severe Malaria, A Practical Handbook* (D.A. Warrell *et al.* 2nd edition, 2000). While the first edition could be used as an aide-mémoire for practising physicians, the second will be helpful for those involved in clinical work and research on malaria in order to update and broaden their knowledge of the subject.

Introduction

About this course

This Learner's Guide, Part I of the module on the **Diagnosis and Management of Severe Falciparum Malaria**, is made up of teaching materials, problems and a picture quiz covering all the activities involved in diagnosing and managing severe falciparum malaria at the hospital level. This guide is based upon the problem solving approach to education, and working through the study cases presented, you will develop the competence to manage correctly cases of severe falciparum malaria. Together with Part II, the Tutor's Guide, it forms a training module which is designed to be used throughout a formal period of training and provides information, poses practical problems and suggested solutions in a simple, easily understandable form, so as to facilitate local adaptation and translation into local languages.

The Guide is designed for medical tutors, physicians, medical undergraduates and other health personnel who are, or will be responsible for the diagnosis and management of cases of severe falciparum malaria.

Objectives

At the end of the training programme based on this Learner's Guide you should have acquired the skill and competence that will enable you to:

- define what is severe falciparum malaria, predict those at high risk and recognize it when it occurs
- take a history relevant to severe falciparum malaria, conduct an appropriate physical examination and request the most urgent tests necessary for diagnosis and proper management
- assess severity of the disease in adults and children
- determine what malaria specific treatment to provide, by which route and in which doses
- provide urgent and maintenance treatment to the severely ill patient, monitor progress and modify management as necessary
- assess recovery and detect residual sequelae
- arrange for follow-up as appropriate
- write a summary of events and outcome.

How this subject will be taught

The tutor and the facilitators

The tutor has extensive experience in the management of severe falciparum malaria and is able to help you to solve a wide range of problems.

Facilitators who work with the tutor will collaborate with you to achieve the objectives outlined above. Facilitators will lead discussions and provide general help to individuals and to small groups of learners.

Presentations

Formal presentations (e.g. lectures) will usually be kept to a minimum and each session will be as short as possible. Most information that will be given in such sessions is already contained in this Guide, so there will be very little need for you to take notes. A lecture presentation will usually be combined with a demonstration.

Demonstrations

Demonstrations will either be used to illustrate some aspects of diagnosis and management of disease that you will later carry out yourself, or consist of looking at specimens and equipment that you need to know about and be able to use.

Practical sessions

There will be as many practical sessions as possible. They are intended to help you to gain as much practical experience as you can in all aspects of the diagnosis and management of severe falciparum malaria. In some, each facilitator will work with a small group of four or five learners. Because there are only a few learners in each group, the facilitator will be able to give a great deal of attention to each individual: this increases your opportunities to practise and to learn.

Small group discussions

In these exercises, a facilitator will lead discussions on particular subjects. These sessions provide good opportunities for you and the other learners to give your opinions, develop your ideas and learn from one another.

Clinical work and visits to the wards

Whenever possible, sessions will take place at the patient's bedside. This will give practical experience of real-life situations and allow you to learn about the problems you may meet in the course of your daily work.

Evaluation

Evaluation of the learner

Your progress and achievement will be evaluated by the tutor, the facilitators and yourself. This will be done through multiple-choice questionnaires.

In multiple-choice questionnaires, each question is provided with a list of possible answers from which you must select the one you think is correct. At the end of these sessions you will not necessarily be given the correct answer to each question, but the tutor will analyse the results to identify topics that were not clearly understood. The tutor may also tell you where you made mistakes and point out areas where you need to improve.

This part of the evaluation is designed to help you and the tutor to assess how well you understand the non-practical aspects of the course. Multiple-choice pre- and post-tests will be given at the beginning and at the end of this training.

Evaluation of the training by the learner

By means of a questionnaire, the tutor will ask you, the learner, how you think the training has helped you and how it might be improved. This evaluation will take place at the end of the training period in order to provide as much feedback from you as possible. You may sign the questionnaire or not, as you wish, but you should feel completely free to make suggestions for improvement on the part of the tutor and facilitators as well as in the content of the course and the training facilities.

Use of the Learner's Guide

This Learner's Guide consists of instructional materials designed to enable you to achieve the objectives stated earlier. The Guide is divided into chapters called Learning Units. You must acquire the skills and knowledge contained in one Unit before progressing to the next, otherwise you may have difficulty in achieving the objectives of subsequent Learning Units. It is a progressive step ladder learning process commencing with Learning Unit 1 where you will answer questions on what you know about the diagnosis and management of severe falciparum malaria in your country or place of work, and ending with Learning Unit 10 where you can test your knowledge with case studies on the diagnosis and management of severe falciparum malaria.

Learning Unit 1

Information about diagnosis and management of severe falciparum malaria in your country or place of work

Learning objectives

By the end of this Unit you should be able to:

- describe the situation of severe falciparum malaria in your country or place of work, and how it is managed.

In the following pages of this Learning Unit you will find a series of questions which you should answer as best you can. This is not an examination but is designed to make you think about the mechanisms believed to be responsible for the main complications of severe falciparum malaria and about how to determine appropriate treatment. Answer the questions in the sequence in which they are written. Your answers should be in respect of your country (or the country in which you are or will be working). If you cannot answer the question for the whole country but only for a part of it, please do so stating clearly to what part of the country your answers apply.

Answer clearly and briefly those questions on which you have a definite opinion. This exercise may help you to get the best out of the course that follows.

Question 1

What do you mean by "severe falciparum malaria"? What forms may malarial illness take which make it "severe"?

Question 2

Severe falciparum malaria can present with many complications. In your place of work:

a) Which complications are most common?

b) Which complications are most serious?

c) Approximately how many cases of severe falciparum malaria are seen at your place of work per month?

d) How many deaths are due to severe falciparum malaria each month?

e) Which groups of people are most affected by severe falciparum malaria in your area?

f) Is there a part of the year when most cases of severe falciparum malaria are seen?

g) In your opinion do you think that most of the cases of severe falciparum malaria among the population you serve are brought to a health facility? If not, state why.

h) Do many deaths occur at home without reaching medical care? If yes, state why.

i) What are the reasons that result in delay of patients with severe falciparum malaria reaching a health facility?

Question 3

What are some possible reasons why some attacks of falciparum malaria are "mild" (fever, headache, etc.) while others become "severe" or even fatal?

Question 4

How do you rank falciparum malaria as a cause of severe illness compared to other causes of severe illness?

What is the recommended therapy for a) uncomplicated malaria; b) severe falciparum malaria in your country or place of work?

Question 5

What other antimalarial drugs are used to treat severe falciparum malaria in your country or place of work?

Question 6

Where do people get their antimalarial drugs?

Question 7

Do you think these drugs are effective? If not, state why.

Question 8

What home, traditional or other remedies are commonly used in your area?

Question 9

What do you think are the major constraints in your country, or place of work, to a satisfactory treatment of severe falciparum malaria?

Question 10

Do people in your area use any preventive measures to reduce the risk of severe falciparum malaria?

Question 11

What do you expect from this training?

Please read carefully the next Unit on severe falciparum malaria before commencing the session to which it relates.

Learning Unit 2

Severe falciparum malaria

Learning objectives

By the end of this Unit you should be able to:

- define what is severe falciparum malaria
- identify the high risk groups likely to get severe falciparum malaria
- diagnose severe falciparum malaria
- appreciate the importance of early treatment.

What is severe falciparum malaria?

You should regard a patient as having severe falciparum malaria if there are asexual forms of *Plasmodium falciparum* in a blood film and the patient shows any of the following:

Clinical features

- a change of behaviour, confusion or drowsiness
- impaired consciousness or unrousable coma
- multiple convulsions
- deep breathing, respiratory distress
- difficulty in breathing or pulmonary oedema
- circulatory collapse or shock
- pulmonary oedema (radiological)
- jaundice
- haemoglobinuria
- a bleeding tendency
- prostration, i.e. generalised weakness so that the patient cannot walk or sit up without assistance

Laboratory findings

- hypoglycaemia
- acidosis, metabolic acidosis
- severe normocytic anaemia (packed cell volume < 20%, Hb < 7g/dl)
- haemoglobinuria
- hyperparasitaemia¹
- hyperlactataemia
- renal impairment

Please note that:

- a) Any of the clinical features are sufficiently important
- b) An individual patient may have any **one** or any **combination** of complications listed above
- c) A patient with one or some features may go on to develop others
- d) Other possible diagnoses in such a patient must be carefully looked for.

¹ Hyperparasitaemia in different places may have different meanings

Who gets severe falciparum malaria?

Any infection with *P. falciparum* can become severe if treatment is delayed or inadequate. However, people who have been repeatedly exposed to falciparum malaria develop partial immunity and are less likely to experience severe falciparum malaria. Those people who are most at risk are:

- children in areas of high endemicity - especially those aged from six months to six years
- people of all ages in areas of low endemicity
- travellers from areas where there is little or no falciparum malaria when they go into a malarious area: this may involve travel within a single country or between countries
- people returning to highly endemic areas after a few years' absence
- non immune pregnant women (at risk of all complications)
- semi-immune pregnant women, especially primigravidae (at risk of severe anaemia)

Why does severe falciparum malaria need special attention?

Because:

- severe falciparum malaria is a common cause of avoidable death
- the diagnosis is often not considered early enough
- correct early treatment and careful nursing can greatly improve the outcome
- antimalarial drugs should, if possible, be given parenterally under close supervision
- treatment should therefore be in hospital, if possible
- some methods of treatment which are still being used are dangerous or ineffective and should be abandoned.

How is severe falciparum malaria diagnosed?

Consider the possibility of severe falciparum malaria in patients with any of the clinical features and/or syndromes listed on page 12, even if the illness did not start with typical malaria symptoms.

A common reason for death in severe falciparum malaria is that the diagnosis is not thought of immediately in a patient presenting with one of the complications.

Most patients will also have fever, but this is not always so.

A correct diagnosis should be based upon a complete history of the condition, a physical examination, and laboratory investigations.

Ideally a thick and a thin blood film should be done to demonstrate the presence of *P. falciparum* asexual parasites. But remember:

- getting a blood film done must not be allowed to delay the start of treatment unduly
- occasionally blood films may be negative even though the patient is suffering from severe falciparum malaria. Blood films should be repeated, e.g. every 6 hours: **if clinical**

features strongly suggest severe falciparum malaria, treatment may be started even if films are negative.

- a positive blood film does not prove that severe falciparum malaria is the **cause** of the severe illness. Consider and look for other possibilities as well.

Key points:

- delay in diagnosis is dangerous
- the spectrum of complications is different in children and adults
- some groups of the population are more susceptible than others.

Please read carefully the next Unit on pathophysiology before commencing the session to which it relates.

Learning Unit 3**Pathophysiology of severe falciparum malaria*****Learning objectives***

By the end of this Unit you should be able to:

- describe the mechanisms believed to be responsible for the main complications of malaria
- show how an understanding of the mechanisms of disease can help determine correct treatment.

In studying this section remember that some of the factors and theories outlined are established, while others remain speculative.

Discuss what you have read, first with your colleagues then in plenary. Try to list the ways in which understanding the pathophysiology helps in determining the correct treatment.

Mechanism of malarial disease

The possible effects of malarial infection cover an enormous range, from completely asymptomatic infection to severe fatal disease. Many factors are believed to influence the clinical manifestations of infection: some of these factors are known beyond doubt, while others remain speculative.

Factors known to influence the severity of disease in a malaria infection

- The species of parasite. Only *P. falciparum* causes severe malaria, but it also, more commonly, causes mild or asymptomatic disease.
- The immunity of the individual. Adults who have lived all their life in an endemic area are less susceptible to severe disease than:
 - adults who visit an endemic area for the first time
 - young children living in the same endemic area.
- Pregnancy
- The availability and efficacy of antimalarial drugs.
- The degree of parasite drug-resistance that prevails locally.
- Some genetically inherited conditions in the human host - e.g. sickle-cell trait, which reduce the risk of a *P. falciparum* infection leading to severe disease.

Factors that may affect the severity of illness although this is not yet proven

- The particular strain of *P. falciparum*. Are some strains more virulent than others? There is evidence to suggest that this is so, but no proof.
- The age at which first infection takes place. Perhaps very early infections - in the first 3 months of life, when maternal antibodies still convey some protection against parasite multiplication or disease - cause gradual immunization with less risk of severe disease.
- The intensity of transmission. If transmission is very intense, first infections in infants will tend to occur very early in life. There is evidence that the pattern and severity of disease in children differs according to the local transmission pattern.
- Other differences between people – some RBC abnormalities including sickle-cell trait, α -thalassemia, and probably G-6-PD deficiency, provide protection against malaria; this is also true for some HLA class I, and class II antigens.
- The extent of the individuals' response to an infection - e.g. the rate and degree of production of cytokines² such as tumour necrosis factor (TNF).
- The number of sporozoites injected by the mosquito, or by several mosquitoes.

How do parasites cause a mild form of the disease

All species of malaria parasite can cause fever, with its associated symptoms (shivering, headache, myalgia, rigors). There is now little doubt that fever is caused not directly by the parasite, but by host substances known as cytokines. These are secreted by host cells (macrophages, endothelial and other cells) in response to parasite or red cell material released when the schizont ruptures.

² A generic term for host substances released by one cell population on contact with specific antigen, which act as intercellular mediators.

How do parasites cause severe disease?

Cytokines

It is possible, but still not proven, that cytokines if produced in excess may cause severe disease in addition to fever. One cytokine known to be secreted by the individual in response to malaria is called tumour necrosis factor (TNF). Large quantities of TNF circulate in severe falciparum malaria, especially in fatal cases, and we know that TNF is capable of causing many of the symptoms, signs and complications that are typical of severe malaria - e.g. coma, hypoglycaemia, acidosis, anaemia and respiratory distress syndrome. However it is still not certain whether TNF, or other cytokines, cause malaria complications or only result from severe infection.

Sequestration

In falciparum malaria, a consistent pathological feature is the sequestration of red blood cells containing maturing parasites (schizonts, large trophozoites) in deep capillaries and venules. This phenomenon is observed in many different organs and tissues, including the brain, lungs, heart, bone marrow and gut. It seems likely, but is not proven, that sequestration is in some way responsible for complications such as altered consciousness and acidosis. We know that sequestration is not always harmful, because it occurs in mild as well as in severe falciparum malaria.

If sequestration is important in causing severe disease, how does it do so? It is unlikely that sequestration actually blocks blood vessels so that blood-flow is reduced or stopped. If sequestration had this effect, we would expect most people who recover from malarial coma to have persisting brain damage, but this is not so. Most survivors recover fully. A few - 5-10% - do have neurological sequelae such as focal brain damage, with abnormalities on CATscan pictures, so it may be that sequestration sometimes leads to obstruction of blood flow.

Alternatively, sequestered parasites, which we know to be highly active metabolically, may use up vital substances such as glucose and oxygen, so that these are not available to host cells, e.g. brain cells. The parasites may also produce waste matter, e.g. lactate or toxins, free iron, toxic oxygen radicals, that are directly injurious to local host tissues.

Another theory is that sequestration serves to concentrate schizonts in vital tissues. Rupture of schizonts may then stimulate the release of large quantities of cytokines locally with a powerful local effect even if cytokine levels in the general circulation are not particularly high.

In vitro, a parasitised cell may attract unparasitised red cells, which adhere to the surface of the parasitised cell forming a "rosette". There is still no convincing evidence that rosettes play an important part in pathogenesis *in vivo*.

Processes contributing to specific complications

- Altered consciousness or coma

It is believed that altered consciousness or coma is caused by sequestration of parasites in the brain. Ischaemia alone would not account for the excellent neurological recovery. It is worth considering that coma may be neuroprotective. Premature reversal of coma might increase the risk of neuronal damage. Other processes may cause or contribute to altered consciousness or coma. These include:

- Hypoglycaemia

Hypoglycaemia may be due to impaired production or release of glucose in the liver, and to increased intake in the tissues. In children, hypoglycaemia complicates other childhood infections in addition to malaria. Though hypoglycaemia may develop during any period of prolonged fasting, the actual mechanisms remain unclear.

Another mechanism of hypoglycaemia, most commonly but not exclusively seen in pregnant women, may develop during the course of treatment with quinine or quinidine. These drugs stimulate the pancreas to secrete insulin, and this may lead to hypoglycaemia.

- Convulsions

During a convulsion, unconsciousness occurs both during convulsion (ictal) and for a period of up to several hours after convulsion (postictal). Convulsions may be due to the direct effect of parasites in the brain or to severe accompanying metabolic disorders - e.g. profound anoxia, severe acidosis or severe hyponatraemia.

- Raised intracranial pressure

The majority of children with cerebral malaria have a high opening-pressure of the cerebrospinal fluid, indicating raised pressure in the brain and spinal column. Even when present, this may vary over time. It has also been observed in some adults. The cause of raised intracranial pressure is not clear. It is not due to cerebral oedema, although this may occasionally develop as a terminal event. Intracranial pressure may sometimes be high because of the increased mass of red cells sequestered in the brain, or because of the dilatation of vessels in the brain in response to locally generated cytokines.

Raised intracranial pressure is not the cause of coma or of death in the majority of cases. It may, however, play a part in pathogenesis or affect the course of the disease in ways that are not yet understood.

Other mechanisms of some specific complications

- Anaemia

Anaemia is partly due to the destruction of red cells that contain parasites. Several other mechanisms may accelerate the development of anaemia: non-parasitised red cells are destroyed more quickly than normal during malarial illness, and the bone marrow does not function adequately. Anaemia is worsened if there is abnormal bleeding, intravascular haemolysis or renal failure.

- Acidosis

Acidosis is probably due to a relative shortage of oxygen in tissues occupied by sequestered parasites. This shortage of oxygen is made worse when there is hypovolaemia and/or severe anaemia, as both of these conditions may impair the supply of oxygen to tissues. This lack of oxygen forces tissues to obtain energy by other biochemical pathways not dependent on oxygen; one result of this is the release of lactic acid, leading to metabolic acidosis. There is evidence that drugs containing salicylates, often given to lower the fever, may exacerbate this metabolic acidosis.

- Acute Renal failure

Acute renal failure – acute tubular necrosis – is a common complication in adults, but is rarely seen in children. It is fully reversible if the patient is kept alive for long enough, usually between a few days to 3 weeks, e.g. by peritoneal dialysis. Renal failure is most likely to develop if there has been a period of low blood pressure or shock.

- Pulmonary oedema and ARDS

Pulmonary oedema (non cardiogenic) may result from excessive fluid replacement by intravenous infusion, especially if there is renal failure. Adult respiratory distress syndrome (ARDS) appears to be due to a direct effect of parasites sequestered in the lungs, possibly through release of cytokines. Both of these complications are unusual in children in endemic areas.

- Haemoglobinuria

Haemoglobinuria results from the rapid breakdown of red blood cells (massive intravascular haemolysis) in the circulation.

- Jaundice

Jaundice is more common in adults than in children and is due partly to haemolysis and partly to liver dysfunction.

- Shock

Shock is due to inadequate cardiac output and poor tissue perfusion. In some patients it may occur concurrently with bacteraemia.

- Platelets

In falciparum malaria, the platelet count is typically low. Nevertheless, spontaneous bleeding is rare in both children and adults. When it develops it results from disseminated intravascular coagulation (DIC).

Please read carefully the next Unit on diagnosis and assessment before commencing the session to which it relates.

Learning Unit 4

Guidelines for diagnosis and assessment of severe falciparum malaria

Learning objectives

By the end of this Unit you should be able to:

- record a complete history from the patient
- conduct a physical examination of the patient looking for significant signs
- request the most urgent tests necessary for the correct diagnosis and management of falciparum malaria.

The history

Malaria may be confused with a whole variety of disease syndromes; a careful history may provide a firm basis of differentiation.

The patient's relatives should be carefully questioned in order to gain information that is of great value in establishing a diagnosis.

A complete history has two important aims:

- to look for clues to possible diagnoses other than malaria
- to assess the severity of malaria and of any of its complications.

In the course of taking a complete history, pay special attention to the elements listed in the following Table.

Table 1

Geographical history	Residence and travel within and/or outside the country
Drugs taken	Antimalarials and other drugs: <ul style="list-style-type: none"> • prior to the illness • for this illness
Symptoms: duration and time course	<ul style="list-style-type: none"> • Fever, chills, rigors. These may have preceded later developments. • Change of behaviour: relatives or guardians must be specifically asked about this - it may not be obvious to you. • Drowsiness or deteriorating level of consciousness. • Convulsion(s), when, how many, how long? Try to distinguish from unconsciousness for which the same word is used in many languages. • Very dark urine. • Breathlessness. • Inability to eat or drink, to talk, sit, stand or walk. <p>These indicate the need for admission to hospital.</p>
Previous illnesses and treatment	<p>Any recent febrile illnesses may be important. The current sickness may be a relapse, e.g. typhoid, or a complication of an infectious disease, e.g. post-measles encephalitis, cerebral abscess after pneumonia, meningitis after otitis media.</p> <p>Remember that sickle-cell anaemia crisis may resemble malaria, and may be triggered by malaria; a history of previous episodes or diagnosis may be helpful.</p> <p>Diabetes may contribute to the clinical picture, and will require special attention in a patient with malaria.</p>

Previous blood transfusions	When? Remember that: <ul style="list-style-type: none"> • hepatitis may resemble malaria • malaria itself may be transmitted by transfusion.
Pregnancy	The pregnant patient is at special risk both from malaria and from the drug treatment of malaria.
Other illnesses in the family	An identified illness in a close relative or contact may suggest an alternative diagnosis, e.g. meningococcal meningitis, measles, mumps, chicken-pox, typhoid fever, tuberculosis.

There may be other clues in the history, e.g. a dog bite in a patient with rabies, head injury in a patient developing a subdural haematoma, drug overdose, chronic alcoholism, etc. This outline suggests some common points requiring emphasis. Much other useful information may come from a complete history.

The physical examination

Like the history, the complete examination aims at:

- i) identifying other possible diagnoses; and
- ii) assessing the severity of malaria and any of its complications.

Pointers to an alternative diagnosis

These examples are quoted because they are commonly neglected:

Table 2

In all patients	In children
<p><i>Rash</i>: rare in malaria, may suggest typhus, typhoid, measles, an arbovirus infection, relapsing fever, chicken-pox, leptospirosis or meningococcaemia.</p> <p><i>Neck stiffness</i>: note that absence of this does not exclude meningitis, and some children with severe falciparum malaria have neck stiffness (as part of generalized hypertonicity in some patients with cerebral malaria).</p> <p><i>Sepsis</i>: look for signs of sepsis.</p> <p><i>Enlarged lymph nodes</i>: trypanosomiasis, tuberculosis, AIDS-related infections and many other possibilities.</p>	<p><i>Eardrums</i>: acute or chronic otitis media.</p> <p><i>Skin</i>: rash, with fever should evoke the possibility of measles</p> <p><i>Pharynx</i>: tonsillitis, diphtheria.</p> <p><i>Bulging fontanelle</i>: suggests meningitis (in younger children).</p> <p><i>Shallow, rapid breathing with nasal flare</i>: may suggest acute respiratory infection (ARI) or pneumonia, but remember that some patients with severe falciparum malaria have abnormalities of breathing).</p> <p><i>Cough</i></p> <p><i>Increased blood pressure</i>: hypertensive encephalopathy</p>

Clinical features indicating severe falciparum malaria

Each of the clinical features and/or syndromes listed in Learning Unit 2 (page 12) that define malaria as severe falciparum malaria may be suspected on the basis of clinical assessment (history and physical signs):

Behavioural changes

May include confusion, delirium, agitation, somnolence, hallucinations, psychosis.

Differential diagnosis: typhoid, heat stroke, drug or alcohol intoxication, hypoglycaemia of any cause, encephalitis, including rabies, metabolic failure, e.g. hepatic failure, renal failure.

Coma

May be moderate or profound, gradual or sudden in onset. Coma is a usual sequel of a convulsion of any cause, but if due only to convulsions, consciousness is usually restored within a few minutes to a few hours.

Differential diagnosis - all conditions listed under behavioural changes, above.

Convulsions

Relatives may describe what they believe were convulsions, occurring before the patient came to the clinic/hospital. Ask a person who witnessed the event, and request details including movements of hands and face, biting of tongue, incontinence. Sometimes any loss of consciousness, or even drowsiness, is described by the same words used for convulsions.

In some patients, especially children, convulsions may be accompanied with very minor movements which may not be noticed unless carefully looked for. These “subtle convulsions” may be responsible for coma and require treatment with an anticonvulsant drugs.

Hypoglycaemia

Hypoglycaemia may manifest as altered behaviour, loss of consciousness, convulsions or simply vague symptoms. Do not rely on the presence of sweating, cold and clammy skin as these features are often absent, particularly in children.

Acidosis

Deep breathing (not necessarily rapid) with indrawing of the bony structures of the lower chest wall, in the absence of localizing chest signs, is a good indicator of acidosis. However the breathing pattern may be obscured by other influences - e.g. depression or excitation of the breathing centre in the brain, pulmonary oedema or chest infection. It may be possible to detect acidotic fetor (sweet smell).

Other breathing difficulties

The breathing pattern in severe falciparum malaria is influenced by many factors.

- In severe malarial anaemia, deep breathing is most commonly due to acidosis caused by tissue hypoxia
- Less commonly, breathlessness in the anaemic patient may be due to heart failure with hepatomegaly and gallop rhythm

- Central effects resulting from diseases in the brain, including irregular shallow breathing, Cheyne-Stokes breathing,³ and noisy or stertorous breathing.
- Infection – e.g. aspiration pneumonia, causing laboured breathing
- High fever which causes rapid breathing
- Pulmonary oedema – causes rapid breathing with crackles on auscultation and, in severe cases, pink frothy sputum and central cyanosis (tongue).
- Adult respiratory distress syndrome (ARDS) - indistinguishable from pulmonary oedema, but in the absence of fluid overload.

Acute renal failure

As a complication of malaria, acute renal failure is in practice confined to adults; it can be detected by monitoring urine output. If there is persistent oliguria – volume of urine produced less than 17 ml/hour in an adult or less than 0.3 ml/kg/hour in a child – despite adequate correction of dehydration or hypotension, renal failure is present or imminent. Hiccup is an indicator of advanced failure.

Severe anaemia

Severe anaemia is properly diagnosed only by measuring packed cell volume (haematocrit) and/or haemoglobin level. Suggestive signs include severe pallor of mucosae especially tongue, palms of hand and soles of feet. Severe anaemia may be accompanied by breathlessness or altered consciousness. See also above, under “Other breathing difficulties”.

Shock

There is low blood pressure, a feeble pulse, and impaired tissue perfusion with cold, clammy skin and peripheral cyanosis (nail beds, lips). In children, delayed capillary refill may be a useful sign.⁴

Haemoglobinuria

The urine is dark, tests strongly positive for blood (haemoglobin) but contains no red blood cells on microscopy. The plasma may also be dark because of the haemoglobin freed from red cells.

Jaundice

Best detected on sclerae of eyes. This is quite commonly seen in severe falciparum malaria in adults but is uncommon in children. Signs of hepatic failure are rare. Jaundice in malaria occurs at the same time as fever, unlike jaundice due to hepatitis. If jaundice is present, make sure that you look for other complications.

³ Breathing characterized by rhythmic waxing and waning of the depth of respiration with regularly recurring periods of apnoea.

⁴ Capillary refill: The health worker can check this by exercising pressure (with the nail) on the nail bed of the patient's finger and watching how long it takes for the blood to return. Capillary refill normally takes two seconds.

Bleeding tendency

In this rare complication there is spontaneous bleeding from gums or in the skin, or prolonged bleeding at venepuncture sites. Best tested for by measuring the bleeding time: pierce the earlobe with a lancet, mop every 15 seconds with filter-paper; in normal circumstances the bleeding will stop within 2 minutes.

Extreme weakness

The patient cannot sit or stand without help from others. There may be many contributing causes.

Assessing coma

A score is based on the patient's ability to move and speak in response to commands and painful stimuli. In infants who have not yet acquired speech, you can assess the cry and the child's ability to watch its mother's face, and also the response to pain. You may grade coma according to one of the following scales (Tables 3 and 4).

The Glasgow coma scale, Table 3, is suitable for adults and older children. For children aged about 9 months to 12 years, the Blantyre coma scale, Table 4, may be used.

Measurement of coma in younger infants is difficult. It is best to describe how the child responds to a standard painful stimulus.

Table 3

The Glasgow coma scale for adults and older children	
	Score
Eyes open:	4
	3
	2
	1
Best verbal response:	5
	4
	3
	2
	1
Best motor response:	5
	4
	3
	2
	1
	3-14

“unrousable coma” < 10

To calculate the Glasgow coma score, take the score for each section, then add the three figures to obtain a total score.

Table 4

The Blantyre coma scale for children aged 9 months to 12 years		
		Score
Eye movements:	directed (e.g. follows mother's face)	1
	not directed	0
Verbal response:	appropriate for age (cry)	2
	moan or inappropriate for age (cry)	1
	gasp/none	0
Best motor response:	localizes painful stimulus ^a	2
	withdraws limb from pain ^b	1
	nonspecific or absent response	0
Total		0-5

“unrousable coma” < 3

^a rub your knuckles firmly on the patient's sternum

^b press firmly on patient's thumbnail bed with the side of a horizontal pencil.

These scales can be used repeatedly to assess improvement or deterioration.

Laboratory investigations

- Thick and thin blood films for malaria parasites⁵
- Blood glucose in any patient with altered consciousness, confusion or convulsions. This is best done using a "stix" method. The test requires one drop of finger-prick blood and the result can be read within 1-2 minutes, either by eye or more accurately by reflectance meter.
- Packed cell volume (PCV).
- Lumbar puncture to exclude meningitis. Meningitis cannot be diagnosed without a lumbar puncture. Neck stiffness may be absent in meningitis, especially in children and after a convulsion; some patients with malaria have neck retraction or opisthotonos, without meningitis. A clear cerebrospinal fluid should be examined microscopically for cells, since a

⁵ For complete reference on how to prepare thick and thin blood films, staining techniques and examination of blood films for malaria parasites: *Basic Malaria Microscopy*, Part I: Learner's Guide, Part II: Tutor's Guide, Geneva, World Health Organization, 1994.

fluid may look clear with up to 300 cells/mm³. Do not wait for the cell count result if this will take more than a few minutes.

Before lumbar puncture, if possible, examine the optic fundi by ophthalmoscope. This may help in differential diagnosis; and in some patients it will show papilloedema, which is a contraindication to performing a lumbar puncture. If you are unable to examine the optic fundi, you must decide whether or not to do a lumbar puncture anyway. If the patient is deeply unconscious **and** has weak or very irregular breathing, do not do a lumbar puncture, but give antibiotics for possible meningitis. In other patients, do a lumbar puncture and examine the fluid in the usual way for cells: if there is evidence of meningitis, treat accordingly.

With these results you should initiate immediate treatment without waiting for other test results.

Other laboratory investigations if possible

These are not essential to management, but if available may be helpful or of prognostic usefulness.

- Plasma creatinine; urea is an alternative, but there is no need to measure both, as creatinine is more useful.
- Electrolytes; these may occasionally show a correctable abnormality such as hyponatraemia. Both creatinine and electrolytes are of most value when acute renal failure threatens or develops.
- Blood culture, because septicaemia may complicate severe falciparum malaria and cause shock or unresolving fever.
- Full blood cell count and differential white cell count. Sometimes these may indicate the possibility of an additional diagnosis, e.g. gross eosinophilia, or complication, e.g. profound thrombocytopenia.
- Blood gases, pH and anion gap. These help to identify acidosis and adult respiratory distress syndrome (ARDS). The main electrolytes routinely measured in plasma are sodium ions (Na⁺), chloride ions (Cl⁻), potassium ions (K⁺), and bicarbonate ions (HCO₃⁻). The sum of the measured cations (Na⁺ and K⁺) normally exceeds that of the measured anions by about 14 mmol/l (reference range 10 to 18 mmol/l). This difference is known as "anion gap" and is attributable largely to negatively charged proteins but also to phosphate, sulphate, and some organic acids. Calculation of the anion gap is principally of value in the differential diagnosis of metabolic acidosis and in following the progress of therapy. Acidosis is an indicator of severe disease, in both conscious and unconscious patients.
- Chest X-ray. May identify pulmonary oedema or lobar consolidation.
- Plasma and cerebrospinal fluid lactate concentrations. These are raised in lactic acidosis: high levels (>6 mmol/litre or above) are associated with a poor prognosis.

- Liver functions tests may be useful in distinguishing severe falciparum malaria from acute hepatitis.

Investigations during management

Some investigations will be equally, or more, valuable if repeated during the course of treatment, according to clinical indications, e.g. blood glucose for deepening coma or convulsions, creatinine and electrolytes if renal failure is suspected, or chest X-ray for possible pulmonary oedema. Some tests nearly always need repeating at intervals: blood films, packed cell volume (PCV) and/or haemoglobin concentration.

Key points:

- Take a careful history from the patient or the patient's relatives
- Make a rapid clinical assessment with special attention to level of consciousness, blood pressure, rate and depth of respiration and pallor
- Request the most urgent laboratory investigations: thick and thin blood film, blood glucose, PCV, and lumbar puncture if advisable and safe.

Please make preparations for hospital visit

Learning Unit 5**The hospital visit*****Learning objectives***

By the end of this Unit you should:

- be able to put into practice the assessment of a patient with severe falciparum malaria
- have observed how the patient with severe falciparum malaria is managed in the health facility you will be visiting.

This is a very important part of the course and there will be an opportunity to discuss these observations with your tutor at the end of the visit.

Notes from the Hospital visit

Learning Unit 6

Picture quiz

Learning Objectives

By the end of this Unit you should be able to:

- interpret physical signs of severe disease in children and adults
- decide on differential diagnoses
- determine tests that need to be carried out.



Figure 1

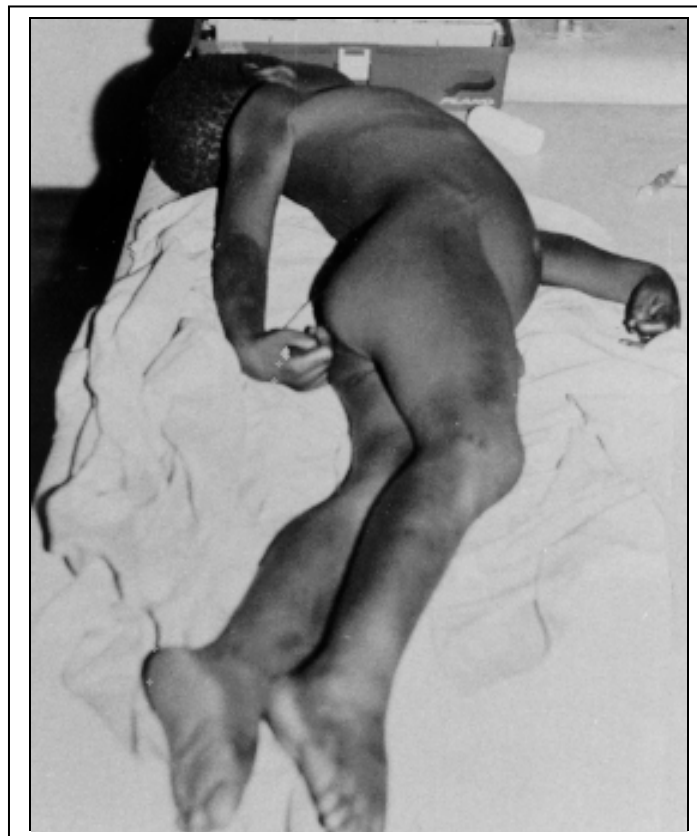


Figure 2

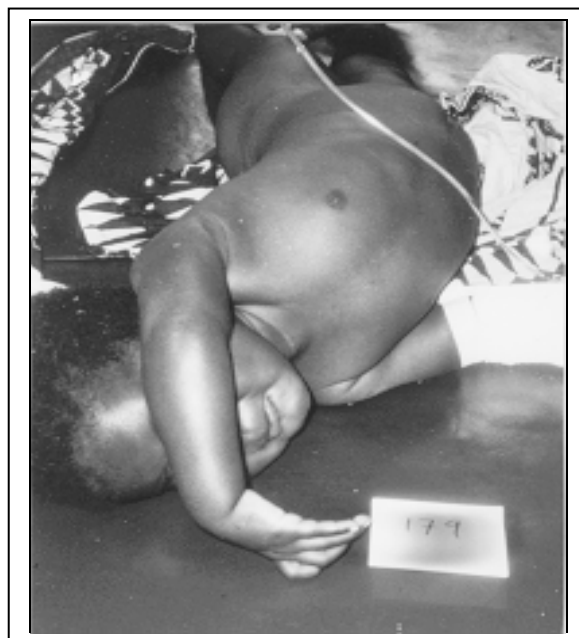


Figure 3

The children seen in Figures 1, 2 and 3 were all brought to a clinic in an area where *P. falciparum* is hyperendemic. Each child is unconscious and has a heavy *P. falciparum* parasitaemia. The children are 3 to 5 years old. They are febrile (38°C-40°C). They have been immunized against measles, diphtheria, tetanus, whooping-cough through the EPI programme.

Question 1

What do pictures 1-3 show?

Question 2

What is the differential diagnosis?

Question 3

What tests would you undertake?

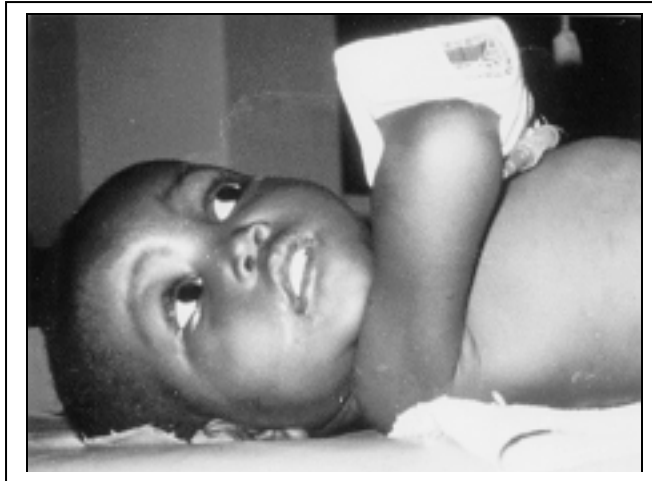


Figure 4

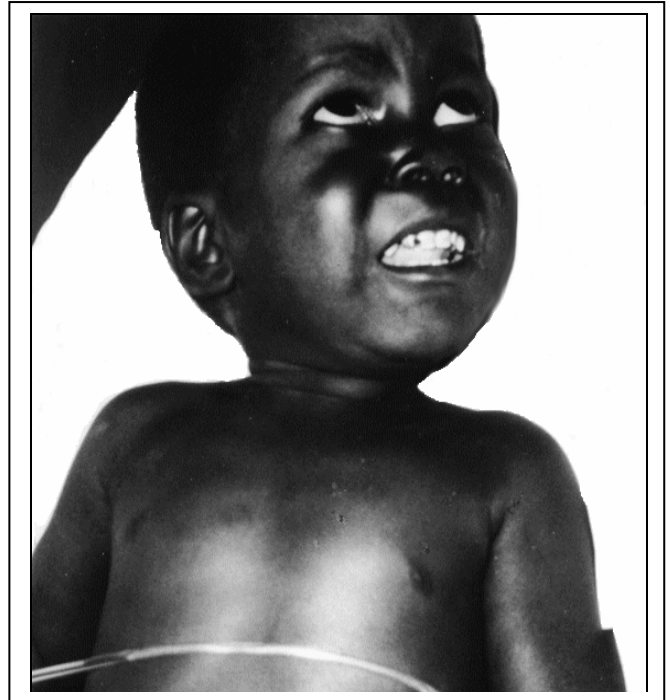


Figure 5

The children seen in Figures 4 and 5 each have a short history of fever followed by progressive loss of consciousness. Both are in deep coma and have a heavy *P. falciparum* parasitaemia. They are 3 and 4 years old. Neither has been immunized against the common childhood diseases.

Question 4

What do the pictures show?

Question 5

What could be the explanation for this?

The patient seen in Figure 6 has *P. falciparum* malaria. She was admitted in coma, treated with quinine and recovered consciousness. Two days later she had a convulsion and collapsed into coma again.



Figure 6

Question 6

What are the possible causes of the convulsion and subsequent coma?

Question 7

What investigations would you do to ascertain the causes?

Question 8

How would you manage this patient?

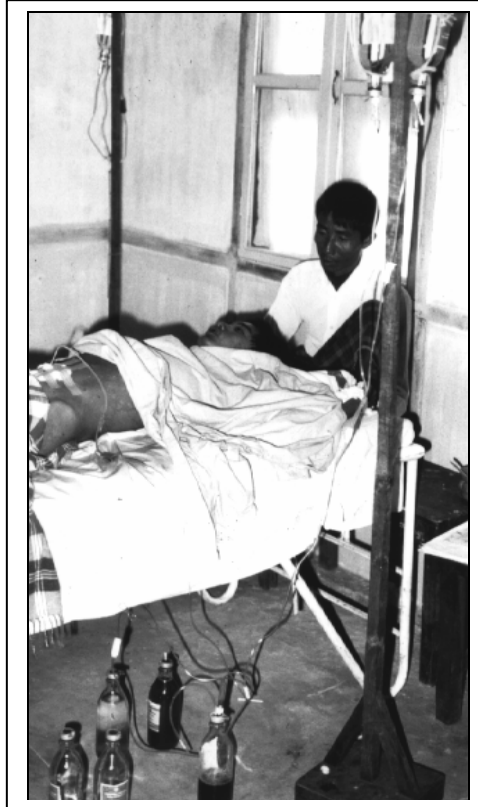


Figure 7

Figure 7 shows the supportive treatment given to a patient with severe falciparum malaria.

Question 9

What exactly does the picture show?

Question 10

What is the most frequent complication in severe falciparum malaria that leads the physician to perform this procedure?

Question 11

What are the complications to be feared in carrying out this procedure in rural hospitals?

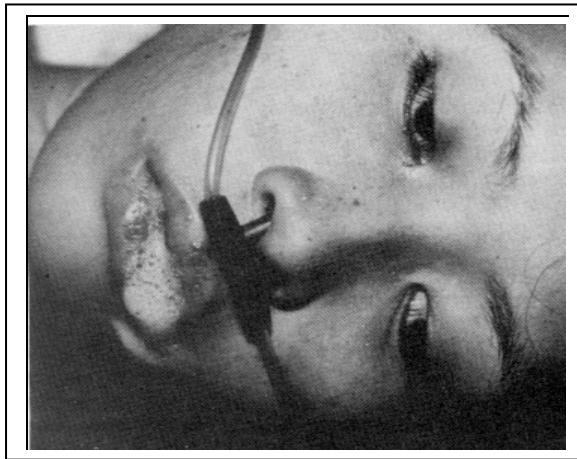


Figure 8

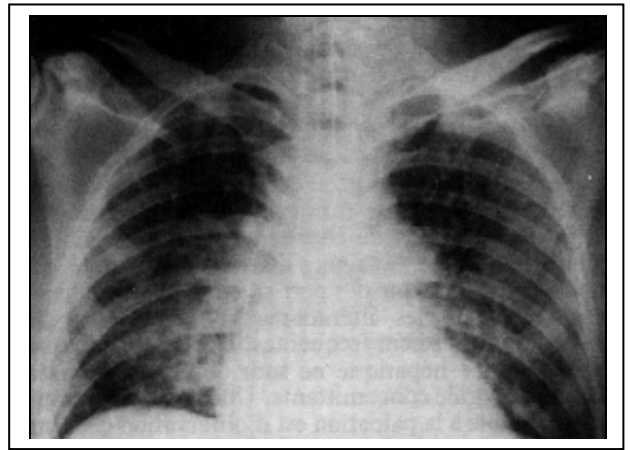


Figure 9

Figures 8 and 9 refer to the clinical and radiological presentation of a woman soon after labour.

She has severe falciparum malaria with hyperparasitaemia and the condition shown in Figures 8 and 9 was preceded by difficulty in breathing with an increased respiratory rate.

Question 12

What is the condition suggested by these pictures?

Question 13

What is the differential diagnosis for this condition?

Please read carefully the next Unit on management of severe falciparum malaria before commencing the session to which it relates.

Learning Unit 7

The management of severe falciparum malaria

Learning objectives

By the end of this Unit you should be able to:

- provide urgent treatment to a severely ill patient
- provide maintenance treatment throughout the period of illness
- arrange for regular monitoring and appropriate actions as necessary.

How is severe falciparum malaria managed?

Under ideal conditions the severely ill patient, especially one who is comatose, should be managed in an intensive care unit. This is not possible in most endemic areas. In such conditions the **nurse assures the role of the intensive care unit monitoring system**. Thus the nurse must be appropriately trained to a very high level to assure the essential role in patient management. Meticulous nursing care can be life-saving, especially in the unconscious patient. Antimalarial chemotherapy of severe falciparum malaria and dosage is indicated in Table 5.

Emergency treatment

- Start immediate resuscitation measures, paying particular attention to the airways.
- Establish an intravenous infusion.
- Correct hypoglycaemia if present by infusing dextrose over a period of 3 - 5 minutes. This can consist of any one of the following:
 - 1 ml/kg of 50% dextrose diluted with an equal volume of normal saline i.v. slowly over several minutes.
 - 5ml/kg of 10% dextrose by slow intravenous infusion
 - for other strengths of dextrose calculate accordingly.
- Re-check blood glucose 2-4 hourly during the course of treatment, particularly in the comatose patient.
- Assess the patient's fluid requirements. Look for evidence of fluid depletion or overload in order to calculate the appropriate rate of infusion. Children with severe metabolic acidosis may benefit from a resuscitation bolus of fluid, preferably a plasma expander, e.g. normal saline. The usual route for fluid infusion is intravenous; if this cannot be achieved alternatives are intraosseous or naso-gastric infusions. Intra-osseous infusion may be performed when there is life threatening hypovolaemia, under **strict sterile procedure** (see Appendix 4).
- Give an effective antimalarial drug, in the correct dose and by the appropriate route, according to the patient's weight.
- Reduce body temperature if greater than 39°C. This is best done by giving paracetamol, by mouth if possible, alternatively by suppository. In addition, remove the patient's clothes and start tepid sponging and fanning. Relatives can help with this task.
- Control convulsion: correct the hypoglycaemia if present. If the convulsions continue for more than 5 minutes give diazepam. A slow intravenous injection of diazepam (0.15 ml/kg of body weight, maximum of 10 mg for adults) can be administered. In children always calculate according to weight so as to avoid dangerous respiratory depression. Diazepam can also be given intrarectally (0.5 - 1.0 mg/kg of body weight) if injection is not possible. Monitor the breathing carefully. Alternative anticonvulsants are: paraldehyde 0.1 ml/kg i.m.⁶; phenytoin 20 mg/mg (slow i.v.) as a loading dose.

⁶ Note: Paraldehyde should, if possible, be given from a sterile glass syringe; a disposable plastic syringe may be used provided the injection is given immediately the paraldehyde is drawn up and that the syringe is never reused.

- Consider the need for blood transfusion. The most common indication for blood transfusion is severe anaemia. Assess the patients clinical condition rather than relying on the haematocrit and/or Hb level. “Does the patient need blood” is a more important question than “What is the packed cell volume (PCV)/Hb?”
 - If the patient’s life is threatened by anaemia associated acidosis, shock or the parasitaemia is so high that you can predict a critical drop - give packed cells or whole blood transfusion urgently.
 - If the patient has spontaneous bleeding give whole fresh blood if available or a platelet transfusion if possible.
- If the patient is unconscious, insert a naso-gastric tube and start the management of the comatose patient.
- Decide whether to insert a urinary catheter. This is necessary if either acute renal failure or pulmonary oedema is suspected, in order to guide fluid balance.
- Decide whether a central venous pressure line is to be set up. This is of most value where pulmonary oedema is suspected, and may be useful in the patient with shock or impending renal failure. It requires the necessary facilities, sterile procedures, expertise and a sufficient number of trained staff to use it properly.
- If facilities allow, consider the need for intubation and mechanical ventilation.

Treatments which are contraindicated

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

Continuing treatment

This calls for **close cooperation between medical and nursing staff**. Responsibility for various observations must be allocated according to the availability and expertise of personnel. Proper nursing care of the unconscious patient, in an intensive care unit if available, is of utmost importance in patients with cerebral malaria. Turn the patient every two hours. Do not allow the patient to lie in a wet bed. Pay particular attention to pressure points and nurse the patient on the side to avoid aspiration of fluids. Remember to provide sufficient nutritional support for the patient who has a prolonged illness.

You should have a record chart on which the important complications of the patient's illness are summarized, treatment is prescribed, and all important observations are recorded at suitable intervals.

A sample chart is provided (Table 6). Make your own modifications to this chart according to local facilities and experience.

Decide how frequently observations should be made; this should be as often as possible with the available staff, (e.g. every four hours), but will also depend on the particular circumstances of each patient and the severity, stage and complications of the illness. For example, blood glucose should be checked hourly in a comatose pregnant woman receiving intravenous quinine, but less frequently in a man whose condition is steadily improving.

Observations (see also Table 7) should be aimed at:

- controlling the delivery of drugs and infusion fluids
- detecting the development of complications of malaria
- detecting toxic and side effects of drugs being given
- documenting the patient's recovery.

Table 5. Antimalarial Chemotherapy of severe falciparum Malaria, Adults and Children*

Chloroquine-resistant malaria or sensitivity not known	Chloroquine-sensitive malaria
<p><i>Quinine (adults):</i> 20 mg dihydrochloride salt/kg of body weight (loading dose)⁷ diluted in 10 ml isotonic fluid/kg by IV infusion over 4 hours; then 8 hours after the start of the loading dose, give a maintenance dose of quinine, 10 mg salt/kg over 4 hours. This maintenance dose should be repeated every 8 hours, calculated from the beginning of the previous infusion, until the patient can swallow, then quinine tablets, 10 mg salt/kg 8-hourly to complete a 7-day course of treatment, or a single dose of 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine (maximum 1500 mg sulfadoxine – 75 mg pyrimethamine).</p> <p><i>Quinine (children):</i> 20 mg dihydrochloride salt/kg of body weight (loading dose)¹¹ diluted in 10 ml isotonic fluid/kg by IV infusion over 4 hours; then 12 hours after the start of the loading dose, give a maintenance dose of quinine 10 mg salt/kg, over 2 hours. This maintenance should be repeated every 12 hours, calculated from the beginning of the previous infusion, until the patient can swallow, then quinine tablets, 10 mg salt/kg, 8-hourly to complete a 7-day course of treatment or a single dose of 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine.</p> <p>Or</p> <p>If IV infusion is not possible, <i>quinine</i> can be given IM. If for some reason quinine cannot be administered by infusion, quinine dihydrochloride can be given in the same dosages by IM injection in the anterior thigh (<i>not</i> in the buttock). The dose of quinine should be divided between two sites – half the dose in each anterior thigh. If possible, for IM use, quinine should be diluted in normal saline to a concentration of 60-100 mg salt/ml. Alternatively, consider artemisinin/artesunate suppositories.</p>	<p><i>Chloroquine:</i> 10 mg base/kg in isotonic fluid by constant-rate IV infusion over 8 hours, followed by 15 mg/kg given over the next 24 hours.</p> <p>Or</p> <p><i>Chloroquine:</i> 5 mg base/kg in isotonic fluid by constant-rate IV infusion over 6 hours, every 6 hours, for a total of 5 doses (i.e. 25 mg base/kg continuously over 30 hours)</p> <p>Or</p> <p>(If IV infusion is not possible) <i>chloroquine</i> 3.5 mg base/kg, every 6 hours im or sc⁸</p> <p>Or</p> <p><i>Quinine or artemisinin derivative</i> (see opposite)</p>

* From: Management of Severe Malaria. A Practical Handbook, 2nd edition, WHO, Geneva, 1999.

⁷ Alternatively, the loading dose can be administered as 7 mg salt/kg by IV infusion (or pump) over 30 minutes, followed immediately by 10 mg salt/kg diluted in 10 ml isotonic fluid /kg by IV infusion over 4 hours.

⁸ Total dose 25 mg base/kg; change to oral therapy when the patient can swallow.

Or

*Artesunate*⁹ 2.4 mg/kg (loading dose) IV followed by 1.2 mg/kg at 12 and 24 hours, then 1.2 mg/kg daily for 6 days. If the patient is able to swallow the daily dose can be given orally.

Or

Artemether: 3.2 mg/kg (loading dose) im followed by 1.6 mg/kg daily for 6 days. If the patient is able to swallow, the daily dose can be given orally. If parenteral administration is not possible then suppositories of artemisinin or artesunate may be given.

Artemisinin suppositories: 40 mg/kg (loading dose) intrarectally, then 20 mg/kg 24, 48 and 72 hours later, followed by an oral antimalarial drug¹⁰.

Or

Artesunate suppositories: 200 mg intrarectally at 0, 12, 24, 36, 48 and 60 hours, may prove highly effective (trials underway). A loading dose of 4 mg/kg intrarectally followed by 2mg/kg at 4, 12, 48 and 72 hours has been used in Viet Nam. This treatment should be followed by an oral antimalarial drug¹⁰.

Or

If parenteral quinine, artemether or artesunate is not available,

Quinidine: 15 mg base/kg (loading dose) by IV infusion over 4 hours, then 8 hours after the start of the loading dose, give 7.5 mg base/kg over 4 hours, 8-hourly, until the patient can swallow, then quinine tablets (dosage as above for adults and children) to complete a 7-day course of treatment, or a single dose of 25 mg/kg sulfadoxine and 1.25 pyrimethamine.

⁹ Artesunic acid, 60 mg per ampoule is dissolved in 0.6 ml of 5% sodium bicarbonate diluted to 3.5 ml with 5% dextrose and given immediately by IV bolus ("push") injection.

¹⁰ For example, mefloquine 25 mg/kg in two divided doses 8-24 hours apart.

Some important points to note in relation to Table 5.

In areas where a seven day course of quinine is not curative (e.g. in Thailand) add an **oral** course of tetracycline 4 mg/kg four times daily or doxycycline 3 mg/kg once daily, for 3-7 days, as soon as the patient can swallow, except for children under 8 years and pregnant women; or clindamycin 10 mg/kg twice a day, for 3-7 days, as soon as the patient can swallow.

In patients requiring more than 48 hours of parenteral therapy, reduce the quinine or quinidine maintenance dose by one-third to one-half (i.e. 5-7mg **salt**/kg of body weight every 8 hours).

Total daily doses of intravenous quinine are as follows:

Adults:

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

day 1: 30 mg **salt**/kg of body weight

day 2 and subsequent days: 15 mg **salt**/kg of body weight

Children:

day 0 (first day of treatment): 20-25 mg **salt**/kg body weight

day 1: 20 mg **salt**/kg body weight

day 2 and subsequent days: 10 mg **salt**/kg of body weight

It is unusual to have to continue intravenous infusions of quinine for more than 4-5 days. If it is more convenient, quinine may be given by continuous infusion. Infusion rates should not exceed 5 mg **salt**/kg of body weight/hour.

If quinine cannot be administered by infusion, quinine dihydrochloride can be given in the same dosage by intramuscular injection in the anterior thigh. The dose of quinine should be divided between two sites – half the dose in each anterior thigh. If possible, for intramuscular use, quinine should be diluted in normal saline to a concentration of 60 mg/ml.

When quinine is not available but quinidine is, the latter may be used. Because of the possible cardiotoxic effect of quinidine this drug should be used only if the cardiac function can be monitored.

Quinine : Salt-Base Equivalents

	Salt (mg)	Base (mg)
Quinine bisulphate	508	300
Quinine dihydrochloride	366	300
Quinine ethylcarbonate	366	300
Quinine hydrobromide	366	300
Quinine hydrochloride	405	300
Quinine sulphate	363	300

Surveillance form during hospital

**Table 6. MANAGEMENT OF SEVERE MALARIA: OBSERVATION DAILY SHEET
(Acute Phase)**

Date of admission:/...../.....

Time (hour/min):/.....

Name of patient:

DATE: DAY

Record No. Age: Sex: M F Weight Drugs given before admission including OPD	Hours	1			4																
	Real time (Hours/min)																				
	QUININE diHcl	2	0	m	k	g															10
Investigations done on admission Parasite count Haemotocrit / Hb Blood Sugar Urine analysis CSF Grouping of blood	Temperature (2x/day)																				
	Pulse (2x/day)																				
	Respiratory rate (2x/day)																				
	Blood pressure (2x/day)																				
	Blantyre coma scale (3x/day)																				
	Convulsions (Y/N)																				
	Able to drink (Y/N)																				
	Able to sit (Y/N)																				
	Parasite count																				
	Haemotocrit / Hb																				
	Blood sugar																				
	IV quinine in mg																				
	IV fluids – dextrose saline																				
	Other drugs e.g. IV Diazepam / antibiotics																				
	Urine volume																				
Blood transfusion																					

MANAGEMENT OF SEVERE MALARIA: OBSERVATION SHEET (Convalescence Phase - Discharge)

Date of admission:/...../.....

Time (hour/min):/.....

Name of patient:

Record No.	Frequency of observations	DAY		DAY		DAY		DAY		DAY ...		Outcome and follow up visits
	Hours	0	12	0	12	0	12	0	12	0	12	
	Real time (hour/min)											
Rectal temperature °C	12 hourly											100% recovery / with sequelae (specify) / death / evasion Fever clearance (day/h) / Coma recovery time (day/h) / Parasitaemia clearance (day/h)
Level of consciousness (Blantyre coma scale)	12 hourly											
Pulse per minute	12 hourly											
Respiratory rate (per minute)	12 hourly											
Blood pressure (mm Hg)	once in 24 hours											
Haematocrit (%) or Hb (g/dl)	on Day 3 and 7											
Parasite count per mm ³	Day 3, Day 7											
Oral quinine (mg)	3 times daily											
Sulfa-pyrimethamin (SP tablet)	After 3 days quinine											
Other medication (specify)												
Brief comments												

Table 7 indicates some of the important observations during treatment and their implications. Table 8 indicates some of the errors that can be encountered in case management of severe falciparum malaria.

Table 7. Observations during treatment

Regular observations	Possible abnormality	Appropriate actions
A. Clinical		
Breathing	Increased rate or difficulty Deep breathing in children	Review urine output and fluid balance. Assess lung, heart and liver size. Chest X-ray if available. If pulmonary oedema is demonstrated, or seems likely, treat acidosis if diagnosed.
Rectal temperature	>39°C	Give paracetamol (rectal or oral) if not given within past 4 hours. Tepid sponging and fanning - get relatives to help with this.
	If temperature remains high or rises despite 24 hours of antimalarial therapy	Reconsider your diagnosis, while continuing treatment
Blood pressure	Falls: <80 mm Hg systolic in an adult, and <50 mm Hg in infants and children. In children, BP is not always reliable: check for peripheral perfusion, looking at nailbed refill.	Review fluid balance, urine output, quinine infusion rate and haematocrit. Give plasma or saline infusion if indicated - i.e. if hypovolaemic. Look for haemorrhage. Take blood for bacteriological culture if facilities are available. Give broad spectrum antibiotic for possible sepsis.
Fluid balance (use input and output chart); weigh patients as accurately as possible. Catheterize if acute renal failure or pulmonary oedema is suspected.	Oliguria: <17 ml/hour in an adult or <0.3 ml/kg/hour in infants and children	Review adequacy of hydration and infusion. Correct deficit if necessary. Prevent or manage acute renal failure if suspected.
Coma score	Deterioration	Immediately check blood glucose. Reconsider other diagnoses.

Convulsions (Subtle convulsions can be easily missed)	These can recur, or develop for the first time during treatment. They may be due to malaria, to high fever, abnormal blood glucose levels, electrolyte imbalance, or be part of the disease spectrum - Often they herald coma.	Check rectal temperature if >39°C, manage as above. Check blood glucose; check fluid balance; check electrolytes if possible: risk of hyponatraemia. Correct any cause; give anticonvulsant drug (page 46).
Prolonged bleeding from vein puncture sites or spontaneous haemorrhage	Disseminated intravascular coagulation (DIC)	Check bleeding time ¹⁰ (see page 29). Crossmatch blood. Give whole fresh blood for platelet infusion as needed to correct blood loss and bleeding tendency.
B. Laboratory		
Blood glucose	Falls <2.6 mmol/l (40 mg/dl)	Review infusion; a child will become hypoglycaemic if deprived of glucose for more than 12-24 hours. Give i.v. 50% dextrose (1ml/kg) diluted with an equal volume of normal saline.
Packed cell volume	Falls <20%	Cross-match blood: consider need for transfusion, but give only if clinically indicated, using packed cells. Repeat haematocrit at regular intervals.
Parasitaemia	Remains high for 2-3 days, or remains positive for > 5 days. Commonly remains at the initial level for 12-24 hours, even if drugs are fully effective; then falls.	Review adequacy of antimalarial drug and dosage. Consider alternative or give an additional drug.

¹⁰ If facilities allow platelets count, prothrombin or partial thromboplastin times should be checked.

Table 8. Errors in management

- Inadequate nursing care
- Errors of fluid and electrolyte replacement
- Delay in starting antimalarial therapy
- Use of an inappropriate drug (e.g. chloroquine in areas of resistance)
- Unjustified withholding of an antimalarial 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 identify or treat metabolic acidosis
- Failure to prevent cumulative effects of antimalarial 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
- Unduly delayed endotracheal intubation (when it is indicated and possible)
- Failure to prevent or control convulsions
- Failure to recognize minor (“subtle”) convulsions
- Failure to recognize and treat severe anaemia
- Use of potentially dangerous ancillary therapies
- Delay in considering obstetrical intervention in late pregnancy
- Failure to recognize and manage pulmonary oedema
- Undue delay in starting peritoneal dialysis or haemodialysis
- Failure to review antimalarial treatment in a patient whose condition is deteriorating
- Failure to pass a nasogastric tube to prevent aspiration pneumonia
- Failure to cover with antibiotics if the decision is taken to delay lumbar puncture.

Key points:

- Severe falciparum malaria is a medical emergency requiring nursing, medical and laboratory staff to be alert at all times. Prompt action is especially important for high-risk groups such as young children and pregnant women.
- The management of the patient is as important as chemotherapy and here the nurse has a crucial role to play.
- Regularly monitor the core temperature, respiration (rate and depth), blood pressure, level of consciousness and other vital signs. These observations will make it possible to identify the late onset of important complications such as hypoglycaemia, metabolic acidosis, pulmonary oedema and shock. Record urine output.
- Laboratory measurements should include regular checks on PCV, glucose, urea or creatinine (electrolytes and arterial blood gases when possible).

Read the next Unit on assessment of recovery before the session to which it relates.

Learning Unit 8

Assessment of recovery

Learning objectives

By the end of this Unit you should be able to:

- assess the extent to which the patient has recovered
- record any residual sequelae
- arrange for follow-up
- write a summary of the events and outcome.

How do you assess the patient's recovery?

This is an extension of the previous learning unit. Your records and observations will provide some indications of patient recovery - e.g. falling temperature, falling parasite count, and an improving coma score.

In addition, also record the patient's ability to:

- drink
- eat
- talk
- sit
- stand
- walk

When a patient has recovered, assess for possible sequelae of the disease or the treatment. In particular you should:

Perform a neurological examination

Especially assess the patient's functional capacity to hold and use objects, ability to feed, gait and posture. Try to determine whether the patient can do the things that he or she was able to do before the illness began. For a young child this requires asking parents or guardians about the child's previous activities.

Assess vision and hearing

Use the best available methods. You can use simple bedside measures, especially for infants and children (e.g. does the child turn its head towards a noise? does the child watch the mother when she moves?). Use audiometry and vision charts if these are available.

Repeat packed cell volume (PCV) and blood films

Ideally these should be repeated on day 7 and day 14 after recovery and again one month later. Also make sure that on day 7 the haemoglobin is not continuing to fall. If so there may be another cause of anaemia that needs to be looked for. By day 14 full recovery should have occurred.

Review and synopsis

When you are discharging the patient, summarize the events of the patient's illness. Indicate the distinguishing features of the illness and the patient's responses to treatment. A form to enter this information could be attached to the other record sheets.

Key points:

- A proportion of children (about 10%) who survive cerebral malaria have neurological sequelae which persist into the convalescent period.
- It is important to retest PCV and Hb one month after discharge, especially if the patient was anaemic.

Read the next Unit on exercises in diagnosis and management before the session to which it relates.

Learning Unit 9

Exercises in the diagnosis and management of severe falciparum malaria

Learning objectives

By the end of this Unit you should be able to:

- assess the severity of the disease in adults
- assess the severity of the disease in children
- determine what malaria specific treatment to provide by which route and in which doses
- decide which investigations need to be carried out and when
- interpret correctly the results of special investigations
- provide appropriate management of the patient for various complications of severe falciparum malaria.

Case study: Patient A

The place: a country where *P. falciparum* malaria is transmitted in forested areas but not in the main cities.

A woman aged 25 years is brought to the outpatient department of the central hospital in the capital. She is a local resident, the wife of a business executive, and is in the seventh month (28 weeks) of her first pregnancy.

The patient became ill five days ago, with chills, sweating and headaches. An antibiotic was prescribed and her condition seemed to improve, but yesterday she developed rigors and persistent vomiting. A blood film at the local clinic showed malaria parasites, and oral quinine (600 mg every 8 hours) was prescribed. She took two doses.

Today she has been referred to your hospital because of restlessness and increasing mental confusion. Examination shows a semiconscious woman, who is unable to speak. She withdraws her hand from a painful stimulus but cannot localize a stimulus applied to the sternum or forehead. There is no neck stiffness, jaundice, pallor or rash. Axillary temperature is 39°C, pulse 90 beats/min., blood pressure 110/70 mmHg. The uterine fundus is palpable (26-28 weeks), and the foetal heart can be heard.

Question 1

What tests are urgently required?

Question 2

If the blood glucose is 1.2 mmol/l (22 mg/dl) what treatment will you give?

Question 3

If the blood film shows *P. falciparum* rings "++++", and the cerebrospinal fluid is normal except for low glucose, then:

a) what antimalarial drug will you administer and by which route?

b) Would you prefer an alternative to quinine because the patient is pregnant?

c) Would you give a loading dose of quinine? Justify your answer.

d) What nursing procedures are important during this treatment?

e) If you were in a health unit without facilities for parenteral therapy, what alternative treatment could you consider?

Question 4

After six hours the patient becomes increasingly restless. The respiratory rate increases to 40/minute. The blood glucose level is normal. Under these conditions, what diagnostic steps would you take?

Question 5

A chest X-ray gives the picture shown (Figure 10). What is the diagnosis and treatment?

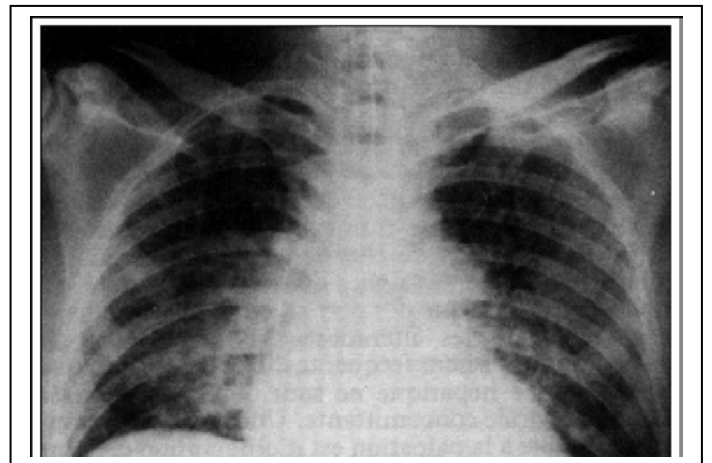


Figure 10

Question 6

What other observations are particularly important in this patient?

Question 7

What other questions would you ask this patient's relatives?

Case study: Patient B

The place: a rural clinic in a hyperendemic *P. falciparum* area. Various antimalarial drugs are available, but intravenous infusions cannot be given.

A child aged 20 months became feverish two days ago and has vomited several times today. One hour ago the child had a convulsion, described by the mother as a repetitive twitching of limbs and mouth, followed by unresponsiveness for a few minutes. The child is now febrile (39.3°C), conscious, and able to localize and respond to a painful stimulus. A thick blood film shows *P. falciparum* rings "++++". The child repeatedly vomits any antimalarial drug given by mouth.

Question 1

a) Does the child have cerebral malaria?

b) What should you do about the convulsions?

Question 2

The district hospital is 30 km away; the journey will probably take several hours by bus.

a) Should the patient be referred to hospital?

b) What treatment will you give in the meantime?

Question 3

The child successfully took the second and third doses of quinine by mouth and was brought back to the clinic the next day; there had been little change; the child was still febrile, and the parasitaemia was unchanged.

Does this suggest that the child has drug-resistant malaria?

Question 4

The child was well and aparasitaemic on the third day, and went on to complete a seven-day course of oral quinine. At the end of that time a further blood test showed gametocytes "+".

What should be done about the gametocytes present in the blood after treatment?

Case study: Patient C

The place: a country where *P. falciparum* is hyperendemic.

The patient, a 28-year-old male economist, was born and brought up locally, but attended university in Northern Europe for five years. He returned home last month.

One week ago he developed fever. He decided this could not be malaria because he had grown up in a malarious area and believed he was therefore immune. Two days ago he became confused, especially at night. He stayed in bed and was attended by a servant who today called the doctor because the patient was increasingly confused. The last urine he had passed was a small volume of very dark fluid 24 hours ago.

On examination, the patient was a well nourished adult man. He was afebrile with a rectal temperature of 36.5°C. He was restless but could give brief appropriate answers to questions, and could localize the site of a painful stimulus. He was jaundiced and his mucous membranes were pale. There was some bleeding from the gums, and there were a few retinal haemorrhages in each eye.

Question 1

a) What is the differential diagnosis?

b) Was the patient right to think he was immune to malaria? Justify your answer.

Question 2

The thick blood film shows *P. falciparum* rings "++++" and the thin blood film shows that 26% of red cells are parasitized.

a) What else would you look for in the thin blood film?

b) What other tests would you require to investigate the bleeding tendency?

c) What treatment is needed for the bleeding?

Question 3

The patient has not passed urine for 24 hours. What kind of investigations and actions are appropriate?

Question 4

15 ml of dark brown urine was obtained by catheter. The urine 'stix' tests showed albumin "++", blood "++++", conjugated bilirubin "++", urobilinogen "++". Microscopy of the urine showed no cells and a few casts.

How do you interpret the results of the urine test?

Question 5

Acute renal failure is confirmed. Is it possible that the kidneys may recover?

How should quinine therapy be given to this patient with acute renal failure?

Case study: Patient D

The place: a country with hyperendemic *P. falciparum* malaria in low-lying areas but no malaria transmission on the high central plateau.

A nineteen-year old woman was brought to a clinic in the malaria-endemic area. The medical officer recorded that the patient gave a history of fever for the past three days with rigors and vomiting. On examination she was febrile with an axillary temperature of 39.1° C and slightly jaundiced. She was fully conscious. Because she had never been out of the country, the doctor considered it unlikely that she was suffering from *P. falciparum* malaria, but nevertheless checked a thin blood film. No malaria parasites were seen on the film so he diagnosed hepatitis and advised rest and a fat-free diet.

Question 1

Do you think the medical officer was right to decide that this patient did not have malaria? Justify your answer.

Could the doctor have done better with:

a) the history?

b) the investigations?

Question 2

Two days later the patient was brought back to the clinic by anxious relatives. She had become drowsy and was not answering questions properly. On examination the patient was afebrile, slightly jaundiced and confused. She could not answer questions but could withdraw her hand from a painful stimulus. The possible diagnoses considered were fulminant hepatitis, sickle-cell crisis, relapsing fever and cholecystitis. Malaria was ruled out because she was apyrexia. Treatment was started urgently with tetracycline intravenously and enemas to empty the large bowel. She remained unconscious and her temperature rose to 38°C; a blood film now showed scanty *P. falciparum* parasitaemia. This was considered "probably incidental" because low-grade parasitaemia was common among young adults in the area, but "to cover malaria", chloroquine was prescribed: 600 mg intravenously, to be followed by 300 mg intravenously every eight hours.

What errors were made:

a) in clinical judgement?

b) in the treatment of the patient?

Question 3

The next day the patient was increasingly febrile and the parasitaemia had increased, so quinine 20 mg base/kg was given to run intravenously over one hour in normal saline, to be repeated 8-hourly. Twenty-four hours later the patient became increasingly breathless. There were no signs in the chest but pneumonia was diagnosed and treated with penicillin. After a further twelve hours the patient was still breathless and suddenly had a convulsion. Her level of consciousness deteriorated and she died ten hours later.

a) What errors were made in administration of quinine?

b) What errors were made in diagnosis of clinical complications?

Case study: Patient E

A four-year-old girl is brought to the outpatient department of your hospital by her mother, late in the evening.

The child was well until yesterday morning (36 hours ago), when she began to have fever. Yesterday she took meals but seemed indifferent; today she has refused food, but has drunk a little. The mother says the child had a "fit" this morning; she regained consciousness immediately. For the past few hours the child has been increasingly drowsy, and for the last hour has been unconscious.

At the examination the child is well-nourished, unconscious, and not dehydrated. The axillary temperature is 40.2°C; pulse 120/beats/min, regular; blood pressure 90/70 mmHg. No neck stiffness. The pupils are equal; a few retinal haemorrhages seen; no papilloedema. Some yellowish sticky fluid is seen filling the left external auditory meatus. Reflexes are normal. No rash.

Question 1

If facilities are limited, which laboratory tests are essential for this child as a guide for immediate action?

Question 2

a) Among the possible tests, you should have included blood glucose. Why does this have priority in this case?

b) In this patient 2 ml venous blood was taken into a fluoride oxalate sample tube and sent to the laboratory to determine the blood glucose. However, two hours is too long to wait. Should you wait for the result of the blood glucose test if it will take 2 hours?

c) If not, what should you do?

Question 3

In this child the blood glucose level was 1.0 mmol/l (18 mg/dl). 50% dextrose was given intravenously, but the child remained unconscious.

What does this suggest?

Question 4

Figure 11 is the thick blood film from this patient as seen under the high power microscope (magnification x700).

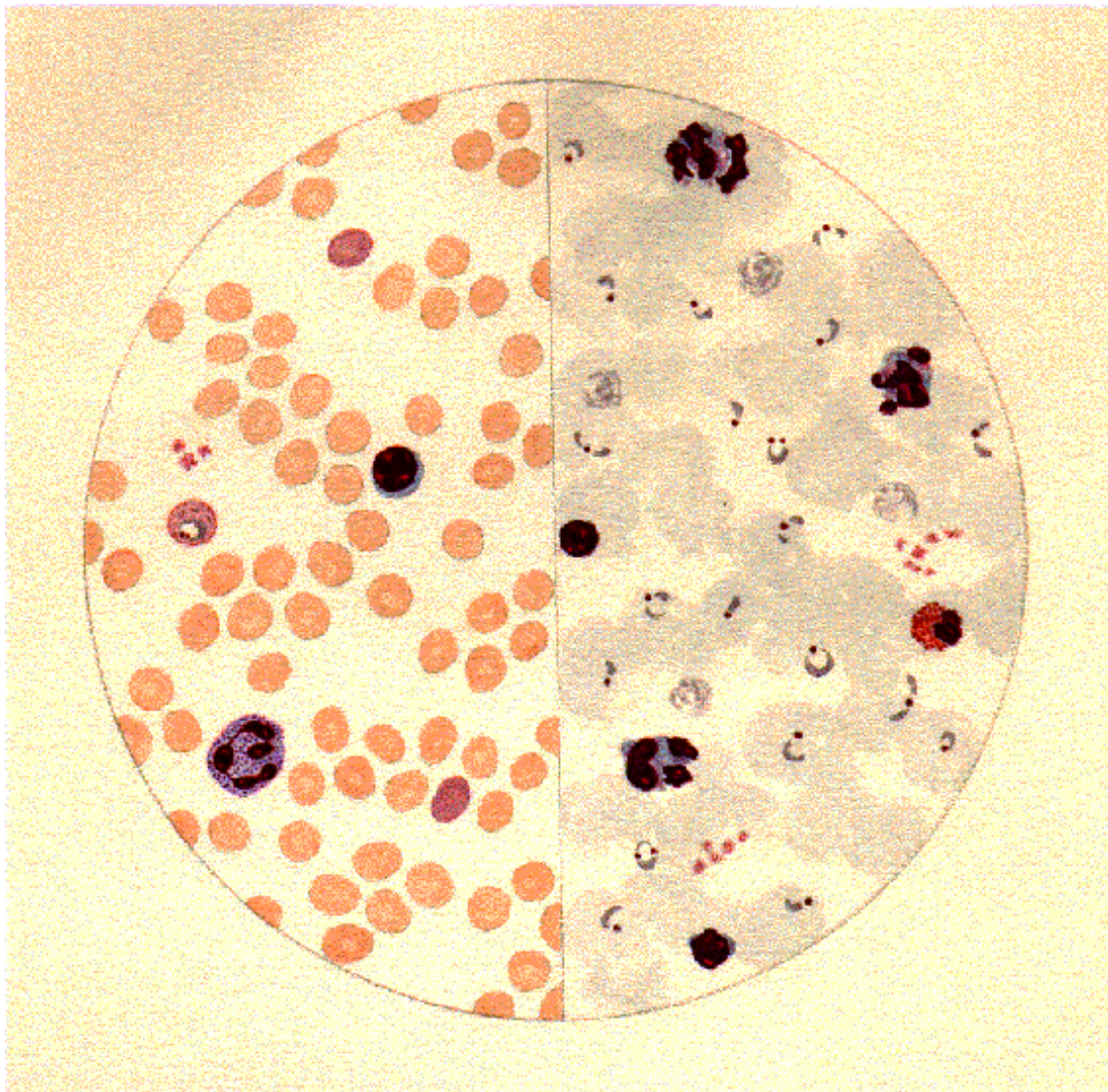
a) What does the film show?

b) What species of parasite is present?

c) How heavy is the infection?

d) How could you quantify it more accurately?

Figure 11 – Thick blood film



Question 5

If a child has *P. falciparum* parasitaemia "++++" with hypoglycaemia:

a) Does this exclude a diagnosis of meningitis?

b) Neck stiffness was assessed in this patient. Is it still necessary to do the lumbar puncture?

c) Does clear colourless cerebro spinal fluid exclude meningitis?

Question 6

In this patient microscopy of the cerebrospinal fluid showed 3 wbc/mm³ and 7 rbc/mm³ (normal).

a) Could the ear discharge be important in this patient?

b) What should be done about it?

Question 7

What is your decision on how to proceed with antimalarial treatment?

a) Which drug(s) to use?

b) By which route?

c) What is the correct dosage and schedule?

Question 8

Apart from antimalarial drug(s), is any other drug therapy indicated for this patient?

Question 9

How should fluid replacement be given?

Question 10

The haematocrit is 19%. What are the implications of the levels of parasitaemia and haematocrit in this patient?

a) Would you transfuse?

b) If blood transfusion is or becomes necessary, how would you give the blood?

Question 11

What clinical observations would you make during the course of treatment in this patient?

Question 12

What laboratory tests would you repeat (and when) during treatment?

Question 13

What should be followed up after the child has recovered?

Case study: Patient F

The place: a country with hyperendemic *P. falciparum* malaria.

A sixteen-year old man was brought to a clinic in a malaria-endemic area. His friend told the doctor that the patient had a history of fever for the past 7 days. Two days before admission, the patient went to a private clinic and was diagnosed with influenza. He was given some medication but did not improve. On examination the patient was febrile and jaundiced. He was stuporous. Blood smear showed *P. vivax* malaria.

Question 1

Do you think that cerebral malaria could be the cause of the patient's stupor?

Question 2

What will you investigate in this patient?

Question 3

What is your management if repeated blood smears show only *P. vivax* malaria while blood glucose and lumbar puncture are normal?

Question 4

If the patient had a haematocrit/packed cell volume (PCV) of 18%, what would you do?

Question 5

If the patient had glucose-6-phosphate dehydrogenase deficiency, when could you give him primaquine?

Question 6

What further antimalarial treatment will this patient require?

Question 7

What precautions would you take for this treatment?

Case study: Patient G

The place : a city where there is no *P. falciparum* malaria transmission.

The patient, a 24-year-old woman who made a 2-month visit to a part of the country where malaria is endemic. For malaria prophylaxis she took mefloquine (250 mg weekly), but discontinued this on return to the city. Twelve days later she felt tired and had a mild headache. The following evening she became febrile and began to vomit. Her general practitioner referred her to hospital. On examination, she was well but febrile with a temperature of 39.5° C. There were no other abnormalities. Thick and thin blood films showed *P. falciparum* trophozoites with 20% parasitized erythrocytes. Quinine was immediately started by intravenous route (loading dose of quinine 20 mg salt/kg given in 4 hours, followed by 10 mg salt/kg every 8 hours for a total of 10 days) to attempt a rapid reduction of the parasitaemia. During the second infusion a nurse reported that the patient could not communicate with them. On examination, she was conscious with open eyes but unable to speak. Although there was no spontaneous movement of her limbs. The reflexes were normal and the plantar responses flexor. There was no neck stiffness or retinal haemorrhage.

Question 1

What is the neurological lesion?

Question 2

What important investigations should be carried out immediately?

Question 3

Is it possible that any person who has mefloquine prophylaxis may get malaria?

Question 4

Will you use dexamethasone in this patient? Justify your answer.

Case study: Patient H

The place: a country where *P. falciparum* malaria is transmitted in forested areas but not in the main cities.

A man aged 30 years is brought to hospital because of stupor. One month before admission he had a holiday in the forest. The patient became ill seven days ago, with chills, sweating and headache. He went to a private clinic and was diagnosed with upper respiratory tract infection. He was prescribed an antibiotic and his condition seemed to improve, but yesterday he developed rigors and persistent vomiting. A blood film at the private clinic showed *P. falciparum* malaria with 10% parasitaemia, and oral quinine (600 mg every 8 hours) was prescribed. He took 3 doses. Today he is referred to your hospital because of stupor. His temperature is 39° C, pulse 100/min, and blood pressure 120/80 mmHg.

Question 1

What tests are urgently required?

Question 2

Blood glucose was 30 mg/dl, then the doctor gave him 50 ml of 50% dextrose. After dextrose infusion, the patient became alert. Would you give him a loading dose of quinine?

Question 3

If the patient had renal failure and was not given quinine before admission, will you give him a loading dose of quinine?

Question 4

If the patient had jaundice and renal failure, how do you adjust dose of quinine?

Question 5

If the patient's consciousness does not improve after dextrose infusion and he has convulsions, what will you do?

Case study: Patient I

The place: A country where *P. falciparum* malaria is hyperendemic.

A 30-year-old woman was admitted to hospital because of high fever with dyspnoea. Twenty days before admission, she had fever which did not subside after taking paracetamol. Today she developed dyspnoea and came to the hospital. On examination, her temperature was 38° C, pulse rate 120/min, respiratory rate 28/min, and blood pressure 130/88 mmHg. The chest film showed increased interstitial shadowing and a normal heart size compatible with noncardiogenic pulmonary oedema. Blood smear showed *P. falciparum* malaria.

Question 1

What is the possible cause of tachypnoea in this patient?

Question 2

The patient was given furosemide (30 mg) and oxygen therapy via nasal canula (with oxygen flow 5 l/min). Half an hour later, the patient was not improved and arterial blood gas showed PaO₂ 48 torr. What should you do?

Question 3

When will you start the patient on positive-end expiratory pressure (PEEP) assisted ventilation?

Question 4

If central venous pressure (CVP) is measured to evaluate the patient's volume status, what level of CVP should be maintained?

Question 5

What other severe malaria manifestations or complications are often associated with pulmonary oedema?

Further reading

Basic Malaria Microscopy. Part I: Learner's Guide. Geneva, World Health Organization, 1991. ISBN 92 4 154430 9

Basic Malaria Microscopy. Part II: Tutor's Guide. Geneva, World Health Organization, 1991. ISBN 92 4 154431 7

Bench aids for the diagnosis of malaria infections. 12 colour plates. Geneva, World Health Organization, 1991. ISBN 92 4 154524 0

International travel and health: Situation as on 1 January 2002. Geneva, World Health Organization, 2002. ISBN 9241580275 (updated annually).

WHO model prescribing information: drugs used in parasitic diseases, second edition, Geneva, WHO, 1995. ISBN 9241401044

WHO. *Practical chemotherapy of malaria : report of a WHO scientific group.* Technical Report Series, No 805, 1990. ISBN 9241208058

WHO. *Management of severe falciparum malaria: A practical handbook.* Second edition, Geneva, World Health Organization, 1998. ISBN 924154523 2

World Health Organization (2000). Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 94, supplement 1 (especially pages S1/20-S1/30).

WHO: *The use of antimalarial drugs: report of a WHO informal consultation, 13-17 November 2001.* WHPO/CDS/RBM/2001.33, http://whqlibdoc.int/hq/2001/WHO_CDS_RBM_2001.33.pdf

Appendix 1

Enumeration of malaria parasites

In addition to definitive diagnosis of malaria and differential diagnosis of the species of malaria parasites, microscopical examination also enables their number in a unit volume of blood to be determined. Knowledge of the degree of parasitaemia may be of diagnostic and prognostic value in the case of severe *P. falciparum* malaria infection and also helps in following up the changes produced by treatment.

Methods of counting malaria parasites in thin blood films

To count parasites as a percentage of red cells on the thin film, use two tally counters, one for red cells and the other for parasites. Count all the red cells in an oil immersion field, then all the parasites in the same field. Repeat the exercise until 500 red cells have been counted. Percentage parasitaemia is then the total number of parasites x 100 divided by the total number of red cells counted.

$$\text{Percentage of parasitaemia} = \frac{\text{Number of parasites counted (total)} \times 100}{\text{Number of red blood cells counted (total)}}$$

Methods of counting malaria parasites in thick blood films

I. Parasites per μl (microlitre)

The following is a practical method of adequate accuracy. It is based on the number of parasites per μl of blood in a thick film, these being assessed in relation to a predetermined number of leukocytes. An average of 8000 leukocytes per μl is taken as the standard. Despite inaccuracies due to variations in the number of leukocytes between individuals in normal health and greater variations in ill health, this standard allows for reasonable comparisons. Before counting begins, the equivalent of 0.25 μl of blood (100 fields, using a 7 x ocular and a 100 x oil-immersion objective) should be examined in the thick film to determine the parasite species and stages that may be present. When this has been established, a suitable counting method for positive blood films is:

1. To count parasites and leukocytes separately using two tally counters.
2. (a) If, after 200 leukocytes have been counted, 10 or more parasites have been identified, record the results in the record form, showing parasites per 200 leukocytes;
 - (b) If, after 200 leukocytes have been counted, 9 or less parasites have been counted, continue counting until 500 leukocytes have been counted and record the parasites per 500 leukocytes.

3. In each case, the parasite count in relation to the leukocyte count can be converted to parasites per μl by the simple mathematical formula:

$$\frac{\text{No. of parasites counted} \times 8000}{\text{No. of leukocytes counted}} = \text{parasites per } \mu$$

This means that if 200 leukocytes are counted, the parasites are multiplied by 40, and if 500 leukocytes are counted the parasites are multiplied by 16.

4. It is normal practice to count all the species present and to include both sexual and asexual parasites together. Occasionally a separate count is made of the gametocytes of *Plasmodium falciparum* but when this is done, they should still be included in the general parasite count. It is rarely possible to separate the gametocytes of *P. vivax* or *P. malariae* from the asexual parasites with sufficient accuracy to justify a gametocyte count.

II. The Plus System

A more simplified method of enumerating parasites in thick blood films is to use the plus system. This indicates the relative parasite count and entails using a code of from one to four pluses, as follows:

+	=1-10 parasites per 100 thick film fields	(4-40 parasites per mm^3)
++	=11-100 parasites per 100 thick film fields	(40-400 parasites per mm^3)
+++	=1-10 parasites per one thick film field	(400-4000 parasites per mm^3)
++++	=more than 10 parasites per one thick film field	(4000-40000 parasites per mm^3)

This system should be used only when it is not possible to undertake the more acceptable parasite count per μl of blood.

Appendix 2

Antimalarial Chemotherapy of severe falciparum Malaria, Adults and Children*

Chloroquine-resistant malaria or sensitivity not known	Chloroquine-sensitive malaria
<p><i>Quinine (adults)</i>: 20 mg dihydrochloride salt/kg of body weight (loading dose)¹¹ diluted in 10 ml isotonic fluid/kg by IV infusion over 4 hours; then 8 hours after the start of the loading dose, give a maintenance dose of quinine, 10 mg salt/kg over 4 hours. This maintenance dose should be repeated every 8 hours, calculated from the beginning of the previous infusion, until the patient can swallow, then quinine tablets, 10 mg salt/kg 8-hourly to complete a 7-day course of treatment, or a single dose of 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine (maximum 1500 mg sulfadoxine – 75 mg pyrimethamine).</p> <p><i>Quinine (children)</i>: 20 mg dihydrochloride salt/kg of body weight (loading dose)¹¹ diluted in 10 ml isotonic fluid/kg by IV infusion over 4 hours; then 12 hours after the start of the loading dose, give a maintenance dose of quinine 10 mg salt/kg, over 2 hours. This maintenance should be repeated every 12 hours, calculated from the beginning of the previous infusion, until the patient can swallow, then quinine tablets, 10 mg salt/kg, 8-hourly to complete a 7-day course of treatment or a single dose of 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine.</p> <p>Or</p> <p>If IV infusion is not possible, <i>quinine</i> can be given IM. If for some reason quinine cannot be administered by infusion, quinine dihydrochloride can be given in the same dosages by IM injection in the anterior thigh (<i>not</i> in the buttock). The dose of quinine should be divided between two sites – half the dose in each anterior thigh. If possible, for IM use, quinine should be diluted in normal saline to a concentration of 60-100 mg salt/ml. Alternatively, consider artemisinin/artesunate suppositories.</p>	<p><i>Chloroquine</i>: 10 mg base/kg in isotonic fluid by constant-rate IV infusion over 8 hours, followed by 15 mg/kg given over the next 24 hours.</p> <p>Or</p> <p><i>Chloroquine</i>: 5 mg base/kg in isotonic fluid by constant-rate IV infusion over 6 hours, every 6 hours, for a total of 5 doses (i.e. 25 mg base/kg continuously over 30 hours)</p> <p>Or</p> <p>(If IV infusion is not possible) <i>chloroquine</i> 3.5 mg base/kg, every 6 hours im or sc¹²</p> <p>Or</p> <p><i>Quinine or artemisinin derivative</i> (see opposite)</p>

* From: Management of Severe Malaria. A Practical Handbook, 2nd edition, WHO, Geneva, 1999.

¹¹ Alternatively, the loading dose can be administered as 7 mg salt/kg by IV infusion (or pump) over 30 minutes, followed immediately by 10 mg salt/kg diluted in 10 ml isotonic fluid /kg by IV infusion over 4 hours.

¹² Total dose 25 mg base/kg; change to oral therapy when the patient can swallow.

Chloroquine-resistant malaria or sensitivity not known	Chloroquine-sensitive malaria
<p>Or</p> <p><i>Artesunate</i>¹³ 2.4 mg/kg (loading dose) IV followed by 1.2 mg/kg at 12 and 24 hours, then 1.2 mg/kg daily for 6 days. If the patient is able to swallow the daily dose can be given orally.</p> <p>Or</p> <p><i>Artemether</i>: 3.2 mg/kg (loading dose) im followed by 1.6 mg/kg daily for 6 days. If the patient is able to swallow, the daily dose can be given orally. If parenteral administration is not possible then suppositories of artemisinin or artesunate may be given.</p> <p><i>Artemisinin suppositories</i>: 40 mg/kg (loading dose) intrarectally, then 20 mg/kg 24, 48 and 72 hours later, followed by an oral antimalarial drug.¹⁴</p> <p>Or</p> <p><i>Artesunate suppositories</i>: 200 mg intrarectally at 0, 12, 24, 36, 48 and 60 hours, may prove highly effective (trials underway). A loading dose of 4 mg/kg intrarectally followed by 2mg/kg at 4, 12, 48 and 72 hours has been used in Viet Nam. This treatment should be followed by an oral antimalarial drug.¹⁴</p> <p>Or</p> <p>If parenteral quinine, artemether or artesunate is not available,</p> <p><i>Quinidine</i>: 15 mg base/kg (loading dose) by IV infusion over 4 hours, then 8 hours after the start of the loading dose, give 7.5 mg base/kg over 4 hours, 8-hourly, until the patient can swallow, then quinine tablets (dosage as above for adults and children) to complete a 7-day course of treatment, or a single dose of 25 mg/kg sulfadoxine and 1.25 pyrimethamine.</p>	

¹³ Artesunic acid, 60 mg per ampoule is dissolved in 0.6 ml of 5% sodium bicarbonate diluted to 3.5 ml with 5% dextrose and given immediately by IV bolus ("push") injection.

¹⁴ For example, mefloquine 25 mg/kg in two divided doses 8-24 hours apart.

Some important points to note in relation to the Table

In areas where a 7-day course of quinine is not curative (e.g. in Thailand) add an **oral** course of tetracycline 4 mg/kg four times daily or doxycycline 3 mg/kg once daily, for 3-7 days, as soon as the patient can swallow, except for children under 8 years and pregnant women; or clindamycin 10 mg/kg twice a day, for 3-7 days, as soon as the patient can swallow.

In patients requiring more than 48 hours of parenteral therapy, reduce the quinine or quinidine maintenance dose by one-third to one-half (i.e. 5-7mg **salt**/kg of body weight every 8 hours).

Total daily doses of intravenous quinine are as follows:

Adults:

- day 0 (first day of treatment): 30-40 mg **salt**/kg of body weight
- day 1: 30 mg **salt**/kg of body weight
- day 2 and subsequent days: 15 mg **salt**/kg of body weight

Children:

- day 0 (first day of treatment): 20-25 mg **salt**/kg body weight
- day 1: 20 mg **salt**/kg body weight
- day 2 and subsequent days: 10 mg **salt**/kg of body weight

It is unusual to have to continue intravenous infusions of quinine for more than 4-5 days. If it is more convenient, quinine may be given by continuous infusion. Infusion rates should not exceed 5 mg **salt**/kg of body weight/hour.

If quinine cannot be administered by infusion, quinine dihydrochloride can be given in the same dosage by intramuscular injection in the anterior thigh. The dose of quinine should be divided between two sites – half the dose in each anterior thigh. If possible, for intramuscular use, quinine should be diluted in normal saline to a concentration of 60 mg/ml.

When quinine is not available, quinidine may be used. Because of the possible cardiotoxic effect of quinidine this drug should be used only if the cardiac function can be monitored.

Quinine : Salt-Base Equivalents

	Salt (mg)	Base (mg)
Quinine bisulphate	508	300
Quinine dihydrochloride	366	300
Quinine ethylcarbonate	366	300
Quinine hydrobromide	366	300
Quinine hydrochloride	405	300
Quinine sulphate	363	300

Appendix 3

Setting up an intra-osseous infusion

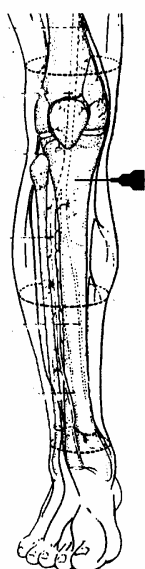
When it is impossible to set up an intravenous infusion e.g. in a shocked patient, or one in whom accessible veins have already been used – an intra-osseous infusion can be lifesaving.

An intra-osseous infusion can be used to administer anything that would otherwise be given intravenously, i.e. fluids, whole blood, packed cells, drugs.

Equipment

- alcohol swabs
- a small syringe and fine needle for giving local anaesthetic
- an 18-gauge needle with trochar (special needles are made for intra-osseous infusion; alternatively a bone-marrow aspiration needle, or even a standard 17-21 g disposable needle can be used, with care)
- IV bottle and drip-set, or 50 ml syringe containing fluid for infusion.

Procedure (with full sterile precautions)



- Choose a point for insertion of the infusion needle, in the middle of the wide flat part of the tibia, about 2 cm below the line of the knee joint (see diagram).
- Do not use a site where there is a fracture or where there is any overlying skin sepsis.
- If the patient is conscious, anaesthetize the skin and underlying periosteum at the chosen point.
- With the needle vertical to the skin, press firmly with a slight twisting motion until the needle enters the marrow cavity with a sudden "give".
- Attach a 5 ml syringe, aspirate to confirm that the position is correct. The aspirate can be used for blood films, blood culture, and blood glucose measurement.

Possible complications

Sepsis. Do not leave an intra-osseous line in one site for more than 6-8 hours – after that time, sepsis is increasingly likely to develop.

Compartment syndrome. If the needle is allowed to pass entirely through the tibia, fluid may be infused into the posterior compartment of the leg causing swelling and eventually impairing circulation. Check the circulation in the distal leg at regular intervals.

Notes

- You can place an infusion in each leg, either simultaneously or in sequence, if necessary.
- An alternative site for an intra-osseous infusion is the antero-lateral surface of the femur, 2-3 cm above the lateral condyle.
- An infusion allowed to drip through the needle in the usual way (by gravity) may go very slowly. For urgent administration use a 50 ml syringe to push in the required fluid as a bolus.

Appendix 4

Prevalence

The number of instances of illness or of persons ill, or of any other event such as accidents, in a specified population, without any distinction between new and old cases. Prevalence may be recorded at a stated moment (point prevalence) or during a given period of time (period prevalence). *WHO Bulletin*, 1966, **35**: 783-784.

The prevalence rate (P) for a disease is calculated as follows:

$$P = \frac{\text{Number of cases or events or conditions at the specified time}}{\text{total population at risk at the specified time}}$$

Incidence

The number of instances of illness commencing, or of persons falling ill, during a given period in a specific population. *WHO Bulletin*, 1966, **35**: 783-784.

Incidence rate (I) is calculated as follows:

$$I = \frac{\text{Number of people who get a disease in a specified period}}{\text{Average total population at risk in the same area in time}}$$

Malaria specific mortality rate

The number of malaria deaths in a given period, usually one year, for a given population, usually 100 000.

Malaria case fatality rate (CFR)

The number of malaria deaths in a time period, divided by the number of malaria cases in the same period. The ratio is usually multiplied by 100, to express CFR as a percentage.