Lesson S02: Preanesthetic Assessment of the Patient With A History of Malaria

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Needs assessment

Malaria is an infectious disease that is infrequently diagnosed in the United States. The disease process has serious consequences which are compounded by the fact that the condition is rarely suspected by clinicians practicing in areas with nearly negligible rates of infection. In several African nations, war-like conditions have forced entire populations from towns and villages to seek safety in malaria-infested jungle areas. Global travel and transport of goods permits movement of infected people and stowaway mosquitoes. Health care workers in the United States may encounter patients with a constellation of symptoms that may not be recognizable as malaria. By understanding the disease process and epidemiology of the disease, a higher index of suspicion may be realized.

Objectives

At the end of the lesson, the reader will be able to:

1. Describe the life cycle of the malarial parasite in humans.
2. List the four species of malarial parasite.
3. Understand reasons for the resurgence of malaria worldwide.
4. Offer a differential diagnosis for uncomplicated malaria.
5. Explain the hematological complications of malaria.
6. Outline a perioperative approach for a patient with malaria.
7. Write a plan for malarial prophylaxis.
8. Describe the current therapy for malaria.
9. Discuss anesthetic considerations for patients with malaria.
10. Explain the underlying pathology of cerebral malarial infection.
Case Presentation

A 30 year old man reports to an emergency room after returning from a safari in the Kruger National Park in South Africa. During the vacation, he lost his balance and fell out of a jeep landing on his elbow. He did not wish to interrupt his trip, and he medicated himself liberally with non-steroidal anti-inflammatory agents and wrapped his arm with an elastic bandage. Near the end of his trip, he developed considerable weakness and vomiting. An X-ray of the man’s arm revealed a badly displaced fracture. He was scheduled for an open reduction and internal fixation. On initial examination in the emergency department, he was found to be febrile and mildly confused, and he complained of abdominal pain. Physical inspection showed jaundice. His abdomen was tender to palpation and his urine was noted to be dark colored. Laboratory investigations revealed hemoglobin = 7 g/dl, white cell count = 12x10^9/L, platelet count = 65,000/cumm, sodium = 129 mmol/l, potassium = 3.5 mmol/l, urea = 12 mmol/l, and creatinine = 250 mmol/l. Arterial blood gas analyses on room air revealed a PaO2 = 69mmHg, PaCO2 = 31mmHg and a pH = 7.36.

The patient reported taking malaria chemoprophylaxis only once about 3 weeks before he left the United States.

Introduction

By the year 2000, more than 1.7 million people in the eastern Congo perished as a direct or indirect consequence of two years of war. Of the total of 1.7 million deaths, 200,000 were directly attributable to violence. Starvation and malaria infection claimed a significant amount of the remainder. The U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC) extrapolated these results to the population base of 18 million in the interior regions and neighboring provinces comprising the sub-Saharan region. Results showed a startling increase in malaria, cholera, meningitis and polio attributable to the destruction and abandonment of health clinics and water and sewer systems. The prevalence of HIV infection also increased because malaria victims were given required transfusions with untested blood. Facilities and reagents for proper testing of blood were unavailable after 1998. Increasing numbers of immunocompromised persons who serve as susceptible hosts to malarial infection contribute significantly to the overall increase in cases.

Epidemiology

Over 300 million people are infected with malaria annually (i.e., five times the incidence of combined cases of TB, AIDS, measles and leprosy). HIV/AIDS, malaria and tuberculosis are the most common causes of ill health and death in the poorest countries of the world. Women are four times more likely to contract the disease and twice as likely to die if they are pregnant.

A study conducted by the International Federation of Red Cross and Red Crescent Societies compared the death toll from natural disasters with the death toll attributable to AIDS, tuberculosis and malaria. Mortality due to the three infectious diseases was 160 times greater than the number of people killed by earthquakes, cyclones and floods in 1999. The Federation also published the “World Disasters Report” which showed that an estimated 150 million people died from these diseases since 1945 compared with 23 million deaths from wars that occurred during the same period.

The Red Cross has identified climate change, growing urbanization, environmental damage and lack of adequate health systems as contributing factors to the increase in the incidence of infectious diseases.
The increase in the incidence of malaria followed a ban on the use of the insecticide DDT along with the emergence of DDT-resistant strains of the vector mosquito. While countries with stable economies spend about 6% of the gross domestic product on health care, poorer countries typically contribute 1% or less. As a result, malaria - once under control in countries like Azerbaijan and Tajikistan - has escalated. While 63% of the world’s population live in malaria-free areas, 29% live in regions where the incidence of malaria is now increasing after previously declining. Residents of endemic areas generally have knowledge of malarial symptoms, preventive measures and risks. One large study in Uganda showed that 30% of patients received treatment within 24 hours of symptoms with many seeking initial treatment at general stores. Often times, prescription practices did not comply with recommended guidelines. The direct and indirect costs of malaria in Africa alone are estimated to exceed $2 billion, due to decreased productivity and health care costs.

Malaria is predominantly a disease of the third world (Fig 1) with approximately 1 million deaths occurring annually in Africa alone, mostly in children under 5 years. Malaria transmission occurs in more than 100 countries throughout Africa, Asia, Latin America and the Caribbean. The incidence of malaria is also increasing in non-endemic countries such as Britain and the United States from persons who have returned from travel abroad to affected areas. (Fig 2)

**Figure 1  Malaria distribution worldwide (2006),** Source: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, GA.
Figure 2

CDC received reports of 1,324 cases of malaria, with four deaths, that occurred in 2004 in the United States. All but four cases were in persons who had traveled to a malaria-risk area. Of the four cases in persons who had not traveled to a malaria-risk area, three were caused by congenital transmission (from mother to fetus). Six more deaths were reported in 2006. Ongoing transmission occurs in part or all of more than 100 countries. Source: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, GA.

History

The symptoms of malaria are described in Chinese writings from the Nei Ching in 2700 BC. By the 4th century BC, malaria decimated villages in ancient Greece. Old Sanskrit texts attributed malaria to the bites of insects, and some Roman writers associated the disease with swamps. The Qinghao plant (Artemisia annua) was described almost 2,000 years ago as an antidote in China. This plant, the annual or sweet wormwood, is known as artemisinin and is still incorporated into antimalarial therapy. During the early 17th century, Spanish Jesuits learned from Indians in South America of an indigenous bark effective in treating malaria. When the wife of the Viceroy, the Countess of Chinchon, was cured of a fever, the tree became known as the Chinchona tree. It was later found that the extract of this Peruvian bark is quinine.

In 1880, Charles Laveran, a French army surgeon stationed in Algeria, discovered malarial parasites in the blood of a patient suffering from malaria and was awarded the Nobel Prize in 1907. Species differentiation was made in 1886 by Camillo Golgi, an Italian neurophysiologist who also received a Nobel Prize. A British officer in the Indian Medical Service, Ronald Ross, demonstrated in 1897 that malaria could be transmitted from infected patients to mosquitoes, and became the third scientist to receive a Nobel Prize for malaria-related work.

Malaria became a focus of concern during the construction of the Panama Canal. In 1906, 26,000 employees worked on the Canal with 21,000 hospitalized at some point in time from malaria. In the years that followed, an integrated program of insect control and malaria prevention was instituted by Gorgas, LePrince and Darling. By 1912, there were over 50,000 employees assigned to the construction project, and the number hospitalized for malaria decreased to 5,600.

In the United States, malaria control was formally integrated with economic development, starting with a bill signed by Franklin Delano Roosevelt in 1933 creating the Tennessee Valley Authority. Malaria affected 30% of the population in the Tennessee River Valley at that time. By 1947, the disease was eliminated in the area.
In 1955, the World Health Organization started an ambitious program to eradicate malaria worldwide by spraying houses with insecticide, providing antimalarial drug treatment and intensifying surveillance efforts. Success was reported in countries with temperate climates. Countries such as India and Sri Lanka had success initially but reduction in infection subsequently failed as efforts ceased. Most of sub-Saharan Africa was excluded from the program completely. The focus of current efforts have shifted from malaria eradication to malaria control due to the emergence of drug resistance, ongoing wars in endemic areas, population movement, lack of community participation, and limited funding sources. With the recent infusion of funds from humanitarian foundations established by wealthy individuals such as Warren Buffet and Bill Gates, efforts to fully eradicate malaria may be revived.

**Types of Infection**

Malaria may occur as an acute or chronic infection. It is caused by protozoa of the genus *Plasmodium* which are obligate intracellular parasites. There are four species of *Plasmodium*:

- *P. falciparum*, which causes 85-90% of cases in Africa, and also occurs in Southeast Asia and South America
- *P. vivax*, affecting Asia, Central Africa, and Central America
- *P. ovale*, affecting West and South Africa, and West Pacific
- *P. malariae*, which causes rare infections

*P. falciparum* infection is associated with the highest morbidity and mortality. Mixed *Plasmodium* infections are possible and result in complex treatment and recovery. *P. falciparum* can override other species. When the primary infecting protozoa is treated and eradicated, untreated *Plasmodium* of other species can dominate and create illness. While the incubation period is usually 7-14 days, the disease can remain dormant and appear many months or years after the initial infection.

**Pathophysiology**

Malaria is transmitted by the bite of an infected female *Anopheles* mosquito. In humans, the parasite multiplies in two stages, first in the liver and then in blood cells. Sporozoites, which form the infective stage of the parasite, are injected from the salivary glands of the mosquito into the host's blood stream. Sporozoites enter the liver where asexual multiplication occurs to produce thousands of merozoites within a tissue schizont. One infected cell in the liver can produce 10,000 *P. vivax* merozoites and 30,000 *P. falciparum* merozoites.

The schizont in the liver ruptures 6-16 days after the initial infection and releases merozoites into the bloodstream. The merozoites then invade the erythrocytes forming trophozoites that exist initially in small and rounded ring forms. The ring-stage trophozoite matures to create a schizont that ruptures to release merozoites into circulation. The ring-stage trophozoite may also differentiate into sexual erythrocytic cells called gametocytes.

For some species of *Plasmodium* (*P. vivax, P. ovale*), the liver stage of the parasite can become dormant and re-emerge after 1-18 months. Because parasites are capable of living at very low levels in the blood for extended periods of time, *P. falciparum* can reemerge one year after infection, and *P. malariae* can occur up to 50 years after infection.

Gametocytes in the bloodstream of the host are ingested by other feeding mosquitoes. They are fertilized in the stomach to form ookinetes which are forced through the gastric wall to the body
cavity. Sporozoites soon develop and settle in the salivary glands of the mosquito where they are ready for injection into a human host.

**Figure 3:** Following the injection of sporozoites from the bite of the mosquito, merozoites are created in the liver establishing endless proliferation of merozoites and gametocytes in the bloodstream of the host.

The blood stage parasites are responsible for the majority of clinical manifestations of the disease. Trophozoite and schizont-infected erythrocytes can adhere to the capillary endothelium, a process known as sequestration. Red cells containing matured *P. falciparum* parasites develop knolls that contain histidine-rich proteins. The phenomenon enhances microvascular obstruction and removes mature *P. falciparum* from the circulation, leaving only the early asexual erythrocyte stages, such as rings, detectable on peripheral blood smears.

Although sequestration is still believed to be a primary pathogenetic mechanism, the role of cellular mediators (cytokines) released from infected erythrocytes is now thought to be of equal or greater importance. Circulating levels of tumor necrosis factor (TNF) are elevated in patients with cerebral malaria and correlate with an increased risk of death. Massive release of TNF into systemic circulation can cause hypotension, lactic acidosis, septic shock, mucosal gut damage, increased pulmonary microvascular permeability and neutrophil aggregation in the lung. TNF also plays a key role in triggering the release of other cytokines, notably IL-1, IL-6, and IL-9.

**Clinical Features**

The clinical features of uncomplicated malaria are generally non-specific consisting of fever, malaise, weakness, chills, dizziness, diarrhea, myalgia and headache. Presenting symptoms in children may include cough, tachypnea, and convulsions. Hypoglycemia is not uncommon. Although a very high
temperature (>40°C) is typically associated with malaria, it is remitting and the patient is often afebrile when examined. Fever often results from the release of toxins when infected cells rupture. Hepatomegaly or splenomegaly is found in approximately one third of patients. Anemia is caused by destruction of both infected and uninfected cells. Renal failure develops when capillaries clot and toxic wastes can no longer be filtered by the kidneys.

For the clinician, it is of paramount importance to distinguish between patients with uncomplicated disease and those with severe malarial infection, as the latter are at considerable risk of mortality. Features indicative of severe disease are outlined in Table 1.

Differential diagnosis should consider such diseases as influenza, typhoid, dengue fever, meningitis, viral hepatitis, leptospirosis, Japanese encephalitis and septic shock from other sources. Fever and thrombocytopenia are common in dengue and leptospirosis. Coagulopathy is common to leptospirosis and viral hepatitis. Hepatorenal syndrome occurs in leptospirosis and scrub typhus. Diagnosis is made by demonstration of antibodies in serum and clinical observation.

A definitive diagnosis of malaria can be made only by detection of parasites in the peripheral blood. Optical microscopy is considered the gold standard. Thick blood films enable better detection than thin films at low levels of parasitemia but microscopic examination of thick films requires greater skill for speciation. Consideration should be given to cases of *P. falciparum* where all the parasites can be sequestered out of the peripheral blood in late-stage forms. Errors in microscopy are possible; therefore, patients in whom repeated blood films are negative, despite a strong clinical suspicion of disease, should have a fine needle bone marrow aspirate performed for diagnosis. Other tests such as a histidine-rich protein 2 (HRP-2) based dipstick has shown a high sensitivity (92.7%) and specificity (99.2%) for *P. falciparum*. The acridine orange test was shown to be more sensitive (97.1%) in detecting *P. falciparum* in epidemiologic studies and has a specificity of 97.9%.

### Treatment of Malaria

Antimalarial chemotherapy should be commenced at the earliest possible opportunity. Strong clinical suspicion of severe malaria warrants chemotherapy even if the initial blood smear is negative. Oral therapy is used for uncomplicated disease and intravenous therapy for severe malarial infection. Parenteral quinine remains the mainstay of treatment in severe cases of *P. falciparum* malaria, particularly in chloroquine resistant areas. It is generally well tolerated. Commonly occurring side effects of quinine therapy include hypoglycemia, which can be attributed to enhanced stimulation of pancreatic insulin secretion, and cinchonism (tinnitus and slight deafness, visual disturbances, mental dullness, depression, confusion, headache, and nausea). Signs of severe quinine toxicity are rare and include myocardial conduction abnormalities, hypotension, blindness, deafness and coma. It is
generally considered unjustified to stop treatment even in the presence of persistent side effects since the hazards of uncontrolled *P. falciparum* malaria far outweigh the lesser hazards of therapy. The administered dosage may have to be modified.

If parenteral quinine is not available, then quinidine - the dextrorotatory optical isomer of quinine - is another choice. Quinidine is more readily available but is more toxic. Its efficacy has been well documented in Thailand where decreasing sensitivity to quinine has prompted a search for more potent agents. The major side effects of quinidine are cardiac conduction abnormalities, related to a prolongation of the QTc interval.

Chloroquine is the least expensive and most rapidly acting treatment. It provides fast symptomatic relief. Unfortunately, parasitic resistance to this agent is common. It may be used in conjunction with pyrimethamine-sulphadoxine (S-P), a convenient single dose treatment for uncomplicated malaria. Side effects include vomiting and skin rashes. Mefloquine is an expensive agent that is used to treat malaria resistant to chloroquine and S-P. Artemisinin (which includes the derivatives artesunate and artemether, and amodiaquine) is used for uncomplicated malaria that is resistant to other agents. Because of its simplicity and effectiveness, artemisinin-based combination therapy (artesunate-sulfamethoxypyrazine-pyrimethamine) is becoming more frequently used as a first line antimalarial therapy. It can be given as a fixed dose 1-day treatment (q12 hours for 24 hours) and thus may improve compliance. The 24 hour regimen was shown to be as effective as a 3 day treatment protocol. Dihydroartemisinin has also been used experimentally by intranasal administration and found effective (i.e., 93% effective for prophylaxis and 75% effective for treatment). It is important to consider that most treatments address the blood phase of the infection, and species that have dormant liver phases (*P. vivax and P. ovale*) may not be eradicated. Primaquine has been shown to be successful in removing hepatic residue.

The growing resistance to antimalarial drugs poses an ever-increasing threat to public health. Failures of prophylaxis or treatment with quinolines, hydroxynaphthoquinones, sesquiterpene lactones, antifolate drugs and sulfamides have greatly contributed to malaria-related morbidity and mortality. Resistance is associated with a decrease in accumulation of drugs in the vacuole, secondary to a reduced uptake of the drug and / or an increased efflux. The development of agents that interfere with the trans-membrane proteins involved in drug efflux or uptake have shown promise in isolating and attacking the source of resistance. Genes in *P. falciparum* may affect membrane transport leading to antimalarial drug resistance. Associations are seen in *P. falciparum* between the resistance to quinolines or artemisinin derivatives and codon changes in Pfmdr1 - a gene which encodes Pgh-1, an ortholog of the P-glycoproteins expressed in multi-drug resistant human cancer cells. Another gene being explored is Pfcrf, which encodes a PfCRT protein, resembling an anion channel. In drug-resistant isolates, codon changes found in the Pfcrf sequence facilitate the drug efflux through a putative channel. The reversal of quinoline resistance by verapamil may be due to hydrophobic binding to the mutated PfCRT protein.

Several compounds have shown some success in reversing antimalarial drug resistance in vitro in parasite isolates, animal models, and in human malaria. These compounds include pharmaceuticals such as calcium channel blockers, tricyclic antidepressants, antipsychotic calmodulin antagonists, histamine H1-receptor antagonists, analgesic and antipyretic drugs, and non-steroidal anti-inflammatory drugs; and chemicals such as synthetic surfactants, plant alkaloids, pyrrolidinoaminoalkanes and anthracenic derivatives.
The use of exchange transfusion for the treatment of cerebral malaria was described by Gyr in 1974, and has gained acceptance as an adjunct to conventional drug therapy in severe or complicated cases.\textsuperscript{15} Although all previous reports of exchange transfusion have been essentially favorable, there is still no randomized control trial data to conclusively support its use. Furthermore the indications for its use, mechanism of action and optimal method of exchange, remain unknown. Exchange transfusion offers a number of possible benefits when compared to conventional medical therapy. It facilitates a rapid reduction in parasite load over a short time without the accompanying hemolysis associated with medical treatment. A rapid reduction in parasitemia may halt the progression of deleterious pathophysiologic changes in the microcirculation with a concomitant improvement in rheology, hemodynamics and oxygen transport, and reduction in cytokine release.

Almost all patients with \textit{P. vivax}, \textit{P. ovale} or \textit{P. malariae} infection respond well to chloroquine and make an uneventful recovery. In patients with \textit{P. falciparum} infection, the best prognostic indicator is the quantitative parasite count. Patients with 5\% or greater parasitemia (>250,000 parasites per μl of blood) are at increased risk of severe complications. (The maximum parasite density achieved by \textit{P. falciparum} prior to death is 2 million parasites per μl or 40\% infected red blood cells). Patients with severe parasitemia should be considered for exchange transfusion if there is no response to quinine or other commonly used agents in 12-24 hours.

**Malaria prevention**

Risk assessment is based on review of a complete travel itinerary. Malaria is less common in short term travelers than in residents of endemic areas, and risk is further reduced for those who visit coastal areas only and stay in air conditioned hotels. About 95\% of cases occur within 30 days of return from travel. Updated information can be obtained from the Center for Disease Control and the World Health organization.

Measures to reduce transmission include use of a repellent containing DEET, and wearing of long sleeves, pants and full coverage footwear. \textit{P. falciparum} is resistant to chloroquine in most countries, remaining effective in Mexico, parts of Central America, the Caribbean, and East Asia. Recommended chemoprophylaxis for those traveling to Africa, South America, the Indian Subcontinent, Tajikistan, Asia, and the South Pacific includes atovaquone-proguanil, mefloquin or doxycycline.\textsuperscript{32} Most drugs do not prevent infection but act on parasites that infect erythrocytes once they have been released from initial maturation in the liver. Drugs must be continued for 4 weeks after the last exposure to mosquitoes. Drugs should be started the week before travel. Malaria in pregnancy is more severe and travel for pregnant women to endemic areas is not recommended. Should it be necessary, mefloquine is the drug of choice.

Tailored advice and treatment strategies have been developed for those who have compromised immune systems and those receiving transplants through medical tourism.\textsuperscript{16}

Research into the development of a vaccine has accelerated in the last 10 years. Some malaria antigens have been tested in endemic areas but no vaccine has shown sufficient and lasting efficacy to justify inclusion in a public health program.\textsuperscript{17}
Clinical Considerations

Malaria is a multifactorial disease that is partially explained by the magnitude and impact of the parasitemia. *P. falciparum* can invade red cells of any age and produce unrestricted parasitemias involving more than 20% of red cells. On the other hand, *P. virax* and *P. ovale* invade only young cells, limiting parasitemia to less than 25,000 per cubic millimeter. *P. malariae* attacks older red cells, invading less than 10,000 per cubic millimeter. Because of the repetitive nature of malaria, the immune response to infection becomes reduced and an inadequate host immune cycle develops.

The pathology of severe malaria is that of a microvascular disease involving many organs, including the brain, lung and kidney. Several complications have major impact on perioperative care.

- **Central Nervous System**

  Coma as a result of cerebral malaria is the worst complication of *P. falciparum* infection. Causes combine microvascular obstruction, hypoglycemia and the effects of cytokines, especially TNF. Intracranial pressure may be very high and cerebral perfusion pressure greatly reduced. Cerebral autoregulatory mechanisms are frequently disturbed. Seizures may occur, especially in children. Adequate dilantin levels should be achieved. While general anesthesia and control of the airway are essential, the anesthetic technique should focus on agents that cause the least intracranial perturbations. Mannitol and furosemide should be available to quickly decrease intracranial pressure.

- **Cardiovascular System**

  Myocardial function is generally thought to be well preserved, although hemodynamic data to support this is limited. Early pathological studies have described blockage of the coronary vessels with parasites and pigments, fatty degeneration of the myocardium, and myocardial changes similar to those found in diphtheritic myocarditis. In view of these findings, clinicians should not expect universally good myocardial function in patients with severe malaria, particularly since TNF acts as a direct myocardial depressant. Monitoring with a pulmonary artery catheter may be indicated. Myocardial function may be supported with inotropes and balloon counterpulsation, if indicated.

- **Pulmonary System**

  Pulmonary edema is a common complication of severe malaria and is associated with a grim prognosis. Edema may result from fluid overload, increased plasma oncotic pressure, increased pulmonary capillary permeability, or a combination of these factors. While there have been several reports of pulmonary edema occurring in the presence of a normal or low pulmonary capillary wedge pressure, there is little doubt that iatrogenic fluid overload contributes substantially to the high mortality associated with this condition. An increase in the respiratory rate may be the first clinical indicator of edema and precedes the development of other ventilatory changes. Hemodynamic measurements indicate that the pulmonary edema is of a non-cardiogenic form. These findings, and the association with high TNF levels, suggest that the pathogenesis of pulmonary edema is similar to that of bacterial septicemia.
• **Renal Function**

Renal dysfunction in severe malaria is common and is usually due to acute tubular necrosis. Some patients may present with pre-renal failure, and renal function may be restored to normal with rehydration. Renal failure is typically oliguric and is strongly associated with hyperparasitemia, jaundice and hypovolemia. The mechanism by which renal dysfunction occurs remains uncertain. Sequestration of parasitized red cells occurs in the glomerular capillaries, although it is not as pronounced as in other organs such as the brain.\(^6\)

• **Hematologic System**

Anemia, an inevitable consequence of severe malaria, occurs due to destruction of red cells combined with marrow dysplasia. It correlates with the degree of parasitemia and total serum bilirubin levels.\(^2,4\) Tumor necrosis factor may play a direct role in depressing erythropoiesis. Thrombocytopenia occurs in both mild and severe *P. falciparum* malaria and is not usually associated with bleeding or other abnormalities of coagulation.\(^20,21\) Clinically significant coagulopathies occur in approximately 5% of adult patients with cerebral malaria, and mainly in individuals with no natural immunity.\(^2,22\) It is only this group that may require replacement of clotting factors. Blood transfusion should be considered for patients with a hematocrit below 25% (but caution should be taken as pulmonary edema may be precipitated).\(^2\) Hemodynamic monitoring with a pulmonary artery or central venous pressure cannula is advisable and will act as an invaluable guide to blood replacement and diuretic therapy.

• **Gastrointestinal Effects**

Diarrhea is especially common in children with *P. falciparum* infection. Postmortem studies have shown parasitized red cells in the microvasculature of the intestine.\(^23\) Dehydration, hypoglycemia, hypoproteinemia, electrolyte imbalance and anemia are common complications.

• **Liver Function**

Jaundice and abnormal liver function tests are extremely common findings in patients with moderate and severe malaria.\(^2,24\) Generally no specific treatment is required. Jaundice is usually non-obstructive and occurs as a consequence of intravascular hemolysis. Levels of both total and indirect bilirubin are elevated.\(^2\) When levels of bilirubin are very high, hepatocyte dysfunction occurs and levels of conjugated bilirubin rise.\(^25,26\) Decreased blood flow in the hepatoporal system has been demonstrated during severe malaria and is likely the result of erythrocyte sequestration.\(^4\)

• **Hypoalbuminemia**

Hypoalbuminemia is nearly universal in patients with severe malaria.\(^2\) Hypoalbuminemia may be a dilutional effect reflecting an increased circulating plasma volume.\(^27\)

• **Hypoglycemia**

Hypoglycemia occurs frequently in severe malaria. Pregnant women and patients hospitalized for more than 48 hours are at highest risk for hypoglycemia.\(^2\) Quinine is one of the most potent in vitro stimulants to pancreatic insulin secretion. Glucose consumption may be increased due to
fever and infection. Other contributory factors include impaired gluconeogenesis due to lactic acidosis, reduced hepatic blood flow, or endotoxemia.

**Perioperative Patient Assessment**

Perioperative patient assessment should be directed toward determining the severity of the disease state. The type of parasite and percentage of parasitemia are the most useful indicators of severity and determinants of prognosis. Non-immune patients, such as those normally living in non-endemic areas and those traveling without appropriate chemoprophylaxis (as in the case presented) are at particular risk.

The following laboratory tests are appropriate:

- complete blood count
- urea and creatinine levels
- electrolytes
- glucose
- coagulation profile
- albumin
- liver function tests
- type and cross match for blood and blood products

For infected patients, baseline liver function tests are invariably abnormal. Obtaining baseline levels is essential for monitoring disease progression. Arterial blood gas analyses, electrocardiography and chest radiograph should also be performed.

Thrombocytopenia is nearly always present with severe infection, and platelet transfusion is often required. Each unit of platelets increases the serum count by 5,000 to 10,000/mm³. Because of the risk of bleeding, surgery is contraindicated when the platelet count is below the range of 50,000 - 100,000/mm³. Other types of coagulation replacement factors are rarely necessary.

The patient’s baseline level of consciousness should be carefully assessed and recorded utilizing the Glasgow coma scale. Patients with impaired neurological function preoperatively are likely to deteriorate postoperatively. Exchange transfusions (for treatment of severe *P. falciparum* infection) can result in an improved level of consciousness and should be conducted prior to administration of general anesthesia.

Premedication and administration of sedative drugs are not recommended for patients presenting with drowsiness prior to securing the airway. Respiratory depression increases arterial carbon dioxide levels leading to cerebral vasodilation and increasing the risk of herniation in the presence of elevated intracranial pressure.
Considerations for the Anesthetic Plan

Abnormalities of hepatic function preclude the use of halothane. Inhalation agents with minimal degradation such as desflurane are acceptable. Atracurium or cis-atracurium are the recommended relaxants for cases where there is pre-existing renal dysfunction. Regional anesthetic techniques are contraindicated in the presence of thrombocytopenia unless adequate platelet transfusion has been given and there is no other alternative (i.e., general anesthesia cannot be administered).

Monitoring of fluid balance and central venous pressure are imperative for any procedure where fluid shifts are anticipated. Central venous pressure should not be allowed to rise above 5 cmH₂O. Malarial patients are especially prone to fatal pulmonary edema. Replacement with whole blood is recommended to reduce the circulating parasite count and reduce levels of TNF.

Hypoglycemia associated with *P. falciparum* malaria is often refractory to treatment, and an infusion of 10% dextrose together with regular assessment of blood glucose levels is advisable. To ensure adequate access to timely sampling, an arterial cannula should be inserted.

Temperature monitoring is particularly important for infected patients who often present with preoperative temperatures in excess of 40°C. The onset of malignant hyperpyrexia may thus be obviated.

Parallels exist between the coma associated with cerebral malaria and general anaesthesia. They both produce reversible loss of consciousness, and patients may recover without sequelae. One study described auditory evoked response (AER) in 6 patients with cerebral malaria. In this group, the early complex of the AER (waves Pa, Nb, and Pb) was clearly represented and was similar to the AER observed at light planes of general anesthesia. When comatose patients emerged from malarial coma or were stimulated by talking loudly to them, they showed changes in the Pa/Nb/Pb complex similar to those seen on awakening from anesthesia.

Patients may be discharged postoperatively when they have regained or exceeded their preoperative level of consciousness. Prolonged sedation may occur in patients with reduced circulating albumin. The decreased protein binding of drugs such as sodium thiopental creates greater availability of pharmacologically active agents in the bloodstream.

Dapsone is used to treat several systemic inflammatory diseases such as leprosy, lupus erythematosus, and pemphigus and has sometimes been used in treatment regimens for malaria and AIDS. Chlorproguanil-dapsone is a new combination of existing drugs and being marketed for treating malaria. Trials to date show some evidence of benefit in cure rates 14 days after the treatment is started, but there is no obvious advantage demonstrated over sulfadoxine-pyrimethamine. In addition, there is some evidence of more frequent serious adverse effects with chlorproguanil-dapsone. Induction of general anesthesia may be complicated by methemoglobinemia, a potential side effect of dapsone, that is typically treated with intravenous methylene blue.
Management of the Case Presented

Examination of a peripheral blood film revealed infection with *Plasmodium falciparum* with a parasitemia of 50%. Antimalarial therapy was started immediately with quinine, sulphadoxine and pyrimethamine. Because of the low hemoglobin and platelet counts, the patient was transfused with whole blood and platelets prior to surgery. MRI of the head indicated markedly raised intracranial pressure. Following intubation and sedation, an intracranial pressure (ICP) monitor was inserted. ICP was measured at 22mmHg. A Foley catheter was inserted and the patient was given mannitol and furosemide. Anesthesia was continued with low dose isoflurane and fentanyl infusion. No muscle relaxants were required. The fracture was reduced according to surgical protocol. Postoperatively, the patient was monitored in the intensive care unit. ICP returned to normal within 24 hours and the trachea was extubated successfully. The patient made an uneventful recovery.

Summary

The presence of malaria should be suspected whenever a patient presents with otherwise unexplained fever, malaise and history of recent travel in a country where malaria is endemic. The disease exerts multisystem pathologic effects. Careful preanesthetic evaluation is necessary, and baseline preoperative laboratory findings and abnormalities should be documented. General anesthetic techniques are usually preferable to regional anesthesia.
References:


32. Freedman DO. Malaria Prevention in Short Term Travelers. NEJM 2008; 359: 603-12

POST-TEST

1. Which of the following has NOT contributed to the increased incidence of malaria?
   a. improved methods of diagnosis
   b. break down of health care units in the aftermath of war
   c. DDT resistance among vectors
   d. increased prevalence of HIV infection

2. The genus *Plasmodium*:
   a. has 6 main species
   b. comprises protozoa that are extracellular parasites
   c. has, as its most virulent protozoa for man, *P. falciparum*
   d. contains viruses that cause malaria

3. In making a definitive diagnosis of malaria:
   a. HRP-2 dipstick may be useful for detecting *P. vivax*
   b. thin blood films have better detection but require greater skill
   c. detection of parasites in the peripheral blood is required
   d. all of the above

4. The cycle of infection of malaria requires:
   a. a non-infective sporozoite phase
   b. bite of an infected male Anophelus mosquito
   c. development of gametocytes in the liver tissue
   d. rupture of a schizont to release merozoites into circulation

5. Chloroquine:
   a. is usually be combined with other agents as resistance is common
   b. is expensive and thus rarely used
   c. acts very slowly
   d. has no side effects
6. Release of tumor necrosis factor in patients with cerebral malaria causes:
   a. cancer
   b. hypertension and cardiac arrhythmia
   c. increased pulmonary microvascular permeability
   d. spread of schizonts

7. The clinical features of uncomplicated malaria are:
   a. often non existent
   b. non-specific including malaise, weakness, headache
   c. characterized by very high temperatures and mild cough
   d. associated with splenomegaly in 75% patients

8. Antimalarial chemotherapy:
   a. should only be started if protozoa are detected in the blood smear
   b. should be discontinued if persistent side effects occur
   c. must be stopped if visual disturbances develop
   d. usually includes parenteral quinine

9. The best prognostic indicator of *P. falciparum* infection is:
   a. temperature trending
   b. quantitative parasite count
   c. level of consciousness
   d. serum glucose level

10. The most severe complications of malaria are caused by invasion of the:
    a. brain
    b. skin
    c. kidney glomeruli
    d. intestinal mucosa