Perioperative considerations of the patient with malaria
Considérations péricrétaires du patient atteint de paludisme

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Abstract

Purpose  Malaria is a life-threatening infectious disease caused by the Plasmodium parasite. Increased global travel has resulted in an escalation in the number of imported cases seen in developed countries. Patients with malaria may present for surgery in both endemic and non-endemic countries. This article reviews the perioperative considerations when managing patients with malaria.

Source  A literature review of anesthesia, perioperative care, and malaria-related articles was performed using the MEDLINE®, EMBASE™, and Web of Science databases to identify relevant articles published in English during 1945-2014. Of the 303 articles matching the search criteria, 265 were excluded based on title and abstract. Eleven of the remaining 38 articles were relevant to anesthesia/perioperative care, and 27 articles were identified as having direct relevance to critical care medicine.

Principal findings  The majority of imported malaria cases are caused by the falciparum species, which is associated with the greatest degree of morbidity and mortality. Various organ systems may be impacted as a consequence of changes in the structure and function of parasitized erythrocytes. Preoperative assessment should focus on establishing the species of malaria, the severity of disease, assessing the degree of end-organ impairment, and initiating treatment of malaria prior to surgery. Intravenous artesunate is the treatment of choice for severe falciparum malaria. Quinine is a second-line agent but has a narrow therapeutic index and particularly hazardous side effects. Intraoperatively, attention should focus on fluid management, dynamics of cerebral blood flow, and avoidance of hypoglycemia. Postoperative care of severe cases should ideally take place in a critical care unit as there may be ongoing requirements for multi-organ support, including renal replacement therapy, ventilation, and/or inotropic support. The safety of neuraxial anesthesia has not been well studied in the setting of malaria.

Conclusions  Malaria remains one of the most devastating infectious diseases worldwide. Multiple organ systems can be impacted as a consequence of changes in structure and function of parasitized erythrocytes. Safe perioperative management requires a sound knowledge of all these potential system effects.

Résumé

Objectif  Le paludisme est une maladie infectieuse possiblement fatale due au parasite Plasmodium. La multiplication des voyages à travers le monde a entraîné un accroissement du nombre de cas importés observés dans les pays développés. Les patients atteints de paludisme peuvent nécessiter une chirurgie, aussi bien dans les pays où la maladie est endémique que dans les autres. Cet article passe en revue les considérations péricrétaires lors de la prise en charge de patients atteints de paludisme.

Source  Une revue de la littérature à la recherche d’articles d’anesthésie, de soins péricrétaires et en
Malaria is a life-threatening infectious disease caused by the unicellular protozoan parasite, *Plasmodium*. In 2010, there were an estimated 216 million cases worldwide with 660,000 deaths reported. Increased global travel and immigration from malaria-endemic areas has resulted in an increase in the number of imported cases seen in developed countries. This has resulted in an increase in the number of patients presenting with either active or sub-acute malarial infection requiring acute surgical, anesthetic, and critical care management. Severe *falciparum* malaria can result in involvement of multiple organ systems, and deterioration can occur rapidly, resulting in seizures, multi-organ failure, and death. Many of the deleterious effects of severe malaria are a consequence of changes in the structure and function of parasitized erythrocytes with resulting occlusion of the microvasculature. This review aims to discuss the important perioperative considerations in managing patients with malaria. We focus specifically on *falciparum* malaria as this is the species responsible for > 95% of mortality attributable to malaria. Furthermore, we emphasize the importance of utilizing a systems-based approach.

### Methods

A literature review of articles covering the topic of “anesthesia and malaria” was performed using the MEDLINE®, EMBASE™, and Web of Science databases to identify relevant articles published in English during 1945-2014. Key words combining “anaesthesia”, “anesthesia”, “critical care”, “intensive care”, and “perioperative care” with “malaria” were matched to search criteria, 265 were excluded based on title and abstract. Eleven of the remaining 38 articles were relevant to anesthesia/perioperative care and malaria, and 27 articles were relevant to critical care/intensive care and malaria. Additional articles were identified from the references of the original 38 articles, and other articles were reviewed to expand on specific points.

### Epidemiology

Malaria is one of the most common infectious diseases worldwide. It is endemic to certain parts of the world with intense transmission rates in sub-Saharan Africa and South East Asia. The majority of imported cases are seen in travellers or migrants from malaria-endemic countries. In Canada, there are 300-1,000 cases reported annually; however, it is estimated that only 50% of cases imported into Canada are reported to Health Canada.

There are five species of *Plasmodium* known to cause malaria in humans: *falciparum, vivax, malariae, ovale,* and the extremely rare *knowlesi* (which is found only in areas of South East Asia). Worldwide, *falciparum* malaria is the most common species seen in imported cases. Cases of severe malaria are caused almost exclusively by the *falciparum* species, making it responsible for the greatest degree of morbidity and mortality. People living in high-endemic areas can acquire a degree of immunity due to repeated exposure to *Plasmodium falciparum*. These individuals rarely become critically ill when infected and can tolerate the...
parasite without symptoms developing. The exact mechanism of this immunity is unknown; however, it is rapidly lost if the individual moves away from the endemic area. The malaria-immune naive traveller or individuals who have previously lived in the area (and consider themselves immune) are particularly at risk of developing severe malaria.

Plasmodium life cycle

Knowledge of the life cycle of the Plasmodium parasite helps explain some of the clinical manifestations and complications of the disease (Figure). Malaria parasites are spread by female Anopheles mosquitoes that bite and inoculate their saliva, containing sporozoites, into the bloodstream of humans. Within a few hours, the sporozoites move to the liver, enter hepatocytes, and begin to divide. The sporozoites eventually form mature tissue schizonts which contain daughter merozoites (known as exo-erythrocytic schizogony). After a period of incubation in the liver (5-15 days in falciparum malaria), schizonts rupture and release thousands of merozoites into the circulation which then enter erythrocytes. Asexual reproduction within erythrocytes (known as erythrocytic schizogony) eventually results in hemolysis of the red blood cells, releasing thousands more daughter merozoites into the bloodstream. This rupturing of erythrocytes and release of merozoites gives rise to clinical symptoms and promotes further erythrocyte infection, with each cycle of erythrocyte infection taking approximately 48 hr. Some merozoites differentiate into male and female gametocytes through a sexual erythrocytic stage, at which point, they become infectious to female Anopheles mosquitoes that bite the infected human. Sexual reproduction of these gametocytes in the mosquito (sporogenic cycle) eventually leads to production of new sporozoites that move to the mosquito salivary glands ready to be injected into a new human host with the next bite. Malaria can also be transmitted in utero through blood transfusion, intravenous drug use, needlestick injury, and organ transplantation.

Pathophysiology

Many of the effects of severe falciparum malaria on the various organ systems are a consequence of changes in the
Malaria usually presents as an acute febrile illness ten to fifteen days after inoculation with non-specific symptoms of fever, hyperdynamic circulation, and direct myocardial suppression. The very presence of the parasite in the erythrocyte reduces its cell membrane deformability and contributes to hemolysis by increasing the osmotic fragility of the red blood cell. The expression of certain membrane glycoproteins leads to adherence (i.e., increased “stickiness”) of erythrocytes to the vascular endothelium (i.e., cytoadherence). This process, known as sequestration, results in the microvascular obstruction of capillaries and small venules of vital organs and occurs in the pulmonary, cerebral, cardiac, renal, and hepatic circulations. The infected erythrocytes can also stick to uninfected circulating red blood cells in a process known as rosetting, which further contributes to microvascular obstruction. The pathogenic effects of malaria have also been attributed to parasitized erythrocytes promoting the release of pro-inflammatory cytokines. These cytokines, e.g., tumour necrosis factor and interleukin-1, have multiple effects, including systemic inflammatory response (SIRS), fever, hyperdynamic circulation, and direct myocardial suppression. Inducible nitric oxide (NO) synthase is also activated by the cytokines, leading to an increase in NO production as part of the SIRS response. Despite the increase in NO production, the sequestration and rosetting of red blood cells still results in microvascular occlusion. The cytokine hypothesis also suggests that release of these cytokines ultimately leads to death from severe malaria through direct mitochondrial dysfunction and impaired oxygen utilization. Thus, this process gives rise to functional cellular hypoxia rather than simply the effects of the vaso-occlusive phenomenon.

### Diagnosis

Malaria usually presents as an acute febrile illness ten to fifteen days after inoculation with non-specific symptoms of...
headache, myalgia, fatigue, chills, fever, and vomiting. In *falciparum* malaria, deterioration can occur rapidly and result in multiple organ failure and death. The non-specific nature of both the presenting symptoms and the basic laboratory investigations used in patients with this symptom constellation may result in a missed diagnosis. Usually a high index of clinical suspicion is required for prompt diagnosis. Specific tests designed to look for malaria should be requested in individuals who had a risk of exposure in the preceding year or in those with a history of previous malaria infection.16

Giemsa-stained thick and thin blood films are the reference standard for diagnosis of malaria, where the asexual form of the parasite can be viewed microscopically within the erythrocytes.17 Importantly, a single negative blood film does not exclude a diagnosis of malaria as there may be parasite sequestration deep within tissue capillaries which obscures visible parasitemia on the blood film.18 If there is a high clinical suspicion of malaria, blood microscopy should be repeated at intervals of eight to 12 hr for up to 48 hr.19 Characteristic morphological features of the erythrocyte and *Plasmodium* parasites viewed under microscopy help determine the malaria species.20 Rapid diagnostic tests based on dipstick immunoassays for specific malaria antigens or enzymes are useful diagnostic adjuncts, particularly with a negative blood film or in the absence of expert microscopy. Nevertheless, these rapid diagnostic tests do not quantify the level of parasitemia, which is necessary in guiding appropriate treatment and response.21

Once malaria is diagnosed, it is important to assess disease severity in order to initiate the appropriate treatment. This is generally based on species subtype, percentage of parasitized erythrocytes, and the degree of organ impairment. Empirical treatment should be initiated only if parasitological tests are inaccessible and there is a strong clinical suspicion of malaria infection.22 Table 1 summarizes the World Health Organization (WHO) diagnostic criteria for the diagnosis of severe *falciparum* malaria.23 It is important to exclude human immunodeficiency virus (HIV) in any patient diagnosed with malaria as co-infection is common. The immunosuppression caused by HIV co-infection increases the degree of parasitemia and the severity of malaria and also reduces the efficacy of treatment.24,25

Treatment and drugs

Treatment recommendations based on species subtype and severity of disease are provided by the WHO and are summarized in Table 2.23 Patients with a diagnosis of *falciparum* malaria should be admitted to hospital for at least 24 hr. Management in the critical care unit should be considered for those patients with clinical or laboratory features of severe malaria as deterioration can occur rapidly. Malaria caused by *vivax*, *ovale*, and *malariae* strains rarely cause life-threatening disease, and these cases are usually managed on an outpatient basis.22 The pharmacology of some of the principal antimalarial drugs and their important side effects are summarized in Table 3.

The treatment of choice for severe *falciparum* malaria is intravenous artesunate. Artesunate, an artemisinin derivative, is easier to administer and has a better side effect profile than quinine.26 Indeed, a large randomized controlled trial has shown a 35% reduction in case fatality rate when artesunate was compared with quinine, i.e., an absolute mortality of 15% with artesunate compared with 22% with quinine.27 Importantly, artemisinin derivatives should not be used as monotherapy as this may lead to resistance. Once the patient can tolerate oral drugs, oral artemisinin-based combination therapy (ACT) should then be administered. In Canada, oral ACTs are not available, so oral atovaquone-proguanil (Malarone™) is used instead as first-line oral therapy when this can be tolerated. The cinchona alkaloids, quinine or quinidine gluconate, should be used intravenously only if artesunate is unavailable or if there has been previous anaphylaxis with artesunate.17 Quinine has a narrow therapeutic index and side effects can be particularly hazardous. Perioperative considerations for patients on quinine therapy are summarized in Table 4.

Severe *falciparum* malaria has a high mortality if untreated and should be managed as a medical emergency. *Falciparum* malaria requires prompt treatment as deterioration can occur within hours. The Public Health Agency of Canada has supported the establishment of the Canadian Malaria Network to facilitate treatment of patients with severe malaria. This network allows intravenous artesunate and quinine to be obtained readily from sentinel hospital pharmacy sites across Canada by clinicians who need timely access to the drugs for the management of severe malaria.28 Indeed, the optimal management of malaria in a fully resourced country like Canada with such networks may differ widely from what is deliverable practically in poorer low-resource settings. Individuals living in poorer countries, particularly in rural areas, have higher death rates from *falciparum* malaria as a result of reduced access to diagnostic and treatment facilities and the availability of artesunate and ACTs. There is also reduced access to critical care facilities and availability of pathogen-free blood products in poorer countries.23

Practical conduct of perioperative management of patients with malaria

Operations on the spleen are the most common indication for surgery, with malaria similarly being the most common
| Drug          | Anti-malarial mechanism of action                                                                 | Formulations                                       | Pharmacokinetics                                                                 | Toxicity                                                                 | Interactions |
|---------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------|
| Artemisinin   | Potent blood schizonticide; kills all stages of the asexual parasite by inhibition of an essential calcium ATPase (PfATPase6) | Wide variety of formulations for oral, rectal, and parenteral use | Converted to inactive metabolites by CYP2B6                                      | Usually safe and well tolerated                                          | None known   |
|               | Extracted from the leaves of sweet wormwood, *Artemisia annua* (has given way to more potent derivatives: dihydroartemisinin, artemether, artemotil and artesunate) |                                                   | Potent inducer of its own metabolism                                              | Anaphylaxis in 1/3,000 cases                                             | None known   |
|               |                                                   |                                                   | Half-life (or t/2) = 1 hr                                                         | QT prolongation and bradycardia have been reported                         | None known   |
| Artesunate    | Same as for Artemisinin                                                                        | Tablets, ampoules for intramuscular, intravenous injection, and rectal capsules | Rapidly absorbed                                                               | As for Artemisinin                                                        | None known   |
| Sodium salt of the hemisuccinate ester of artemisinin    |                                                   |                                                   | Converted almost entirely to the active metabolite dihydroartemisinin           | Some reports of delayed hemolytic reactions and neutropenia               | None known   |
|               |                                                    |                                                   | t 1/2 = 45 min                                                                  |                                                                          |              |
| Chloroquine   | Interferes with parasite heme detoxification                                                    | Tablets and ampoules for intramuscular or intravenous injection                    | Rapid absorption when given orally, intramuscularly, or subcutaneously         | Low safety margin and very dangerous in overdose with multiple side-effects | Risk of arrhythmias with drugs that prolong the QT interval               |
| 4 aminoquinoline | Ineffective in *falciparum* malaria due to widespread resistance                                |                                                   | Eliminated very slowly by the kidneys                                           | Unpleasant taste                                                          | Risk of acute dystonic reactions with metronidazole                      |
|               |                                                   |                                                   | t 1/2 = 1-2 months                                                              | Rarely central nervous system toxicity, including convulsions and mental changes | Reduced bioavailability of ampicillin                                     |
|               |                                                   |                                                   |                                                                                  | Acute overdose can cause cardiac arrhythmias, hypotension, and hypokalemia  | Antagonist of antiepileptic effects of carbamazepine and sodium valproate |
| Primapicene   | Effective against intrahepatic forms of all types of malaria parasite                           | Tablets                                          | Well absorbed from gastrointestinal tract                                        | Hemolytic anemia in patients with Glucose-6-phosphate dehydrogenase deficiency | Concomitant drugs liable to induce hemolysis or bone marrow suppression should be avoided |
| 8 aminoquinoline | Exact mechanism of action unknown                                                                |                                                   | t 1/2 = 3-6 hr                                                                  | Abdominal pain                                                            |              |
|               |                                                   |                                                   |                                                                                  | Methemoglobinemia                                                         |              |
### Table 3 continued

| Drug                      | Anti-malarial mechanism of action                                                                 | Formulations                        | Pharmacokinetics                                                                 | Toxicity                                                                 | Interactions                                                                 |
|---------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Quinine                   | Proposed mechanism is inhibition of parasite heme detoxification in the food vacuole. Acts principally on the mature trophozoite stage of parasite development. | Tablets and ampoules for intravenous injections | Pharmacokinetic properties affected by the severity of malaria. Rapid absorption with wide volume of distribution. Metabolized by CYP3A4 in liver with polar metabolites excreted in urine. | Toxicity causes a complex of symptoms known as cinchonism, including tinnitus, impaired high-tone hearing, headache, nausea, dizziness, dysphoria, and disturbed vision. Hyperinsulinemic hypoglycemia in severe malaria which is particularly common in pregnancy. Hypotension and cardiac arrest may result from rapid intravenous injection, therefore should be given by infusion only. Prolonged QT interval and arrhythmias. | Quinine increases the plasma concentration of digoxin. Avoid other drugs that prolong the QT interval. |
| Atovaquone-Proguanil (Malarone™) | Combination of drugs work synergistically. Inhibits *Plasmodium* mitochondrial electron transport and collapses the mitochondrial membrane potential. | Tablets (containing 250 mg of Atovaquone and 100 mg of Proguanil) | Atovaquone is 99% protein bound t½ = 66-70 hr due to enterohepatic recycling. Excreted in feces as unchanged drug. Proguanil is 75% protein bound. 50% excreted in urine. | Side effects are mainly gastrointestinal including nausea vomiting, diarrhoea and abdominal pain. Can cause transient rise in amylase and transaminases. | Atovaquone can displace other highly protein-bound drugs from their protein binding sites. Proguanil potentiates the effects of warfarin. |

Adapted from WHO guidelines for the treatment of malaria.²²
Hypoglycemia (may be profound in children and pregnancy)  
Quinine is a potent stimulator of pancreatic insulin release  
Regular blood glucose monitoring is essential and should be performed with any decrease in level of consciousness or convulsions. Consider continuous intravenous dextrose infusion to prevent hypoglycemia. A baseline electrocardiogram and continuous cardiac monitoring to exclude lengthening of the QT interval is essential in patients receiving intravenous quinine therapy.

Cardiac arrhythmia (may be life-threatening in elderly or those with cardiovascular disease)  
Quinine blocks cardiac fast Na⁺ channels prolonging action potential duration and repolarization time  
A baseline electrocardiogram and continuous cardiac monitoring to exclude lengthening of the QT interval is essential in patients receiving intravenous quinine therapy.

Prolonged neuromuscular blockade  
Quinine affects neuromuscular transmission presynaptically by blocking voltage-gated Na⁺ channels and postsynaptically by potentiating depolarization. The overall effect is to reduce motor end-plate excitability. Monitor depth of neuromuscular blockade with nerve stimulator to ensure full reversal prior to extubation. Prolonged neuromuscular blockade may necessitate postoperative ventilation until full resolution of blockade.

cause of splenomegaly and splenic rupture worldwide. Surgical cases in patients with malaria have also been described in the context of cardiac surgery, liver and renal transplantation, and emergency Cesarean delivery. Preoperative consultation should focus on determining the species of malaria, the severity of the disease, and the degree of organ impairment. Non-urgent surgery should be postponed ideally until the malarial infection has been treated; however, for individuals requiring urgent surgery, it is essential to ensure treatment for malaria has been initiated prior to surgery. Recommended preoperative investigations and assessments are outlined in Table 5, and the main goals for intraoperative care are summarized in Table 6. The clinical course of malaria caused by Plasmodium vivax, malariae, and ovale tends to cause fewer complications, and these species are less likely to cause problems with perioperative management when compared with falciparum malaria. The stress of major surgery and anesthesia, however, may induce relapse of Plasmodium vivax and ovale malaria as these types can remain dormant in the liver for many years. Recurrence has also been described with falciparum malaria. In patients with a perioperative diagnosis of malaria infection, regular postoperative blood smears assessing for parasitemia should be performed every eight to 12 hr.

Pulmonary

Respiratory symptoms are common in malaria, with a dry cough experienced in up to 50% of uncomplicated vivax and falciparum malaria cases. Respiratory distress may

| Table 4 Perioperative considerations for patients on quinine therapy |
| Effect | Mechanism | Management strategy |
| --- | --- | --- |
| Hypoglycemia (may be profound in children and pregnancy) | Quinine is a potent stimulator of pancreatic insulin release | Regular blood glucose monitoring is essential and should be performed with any decrease in level of consciousness or convulsions. Consider continuous intravenous dextrose infusion to prevent hypoglycemia. |
| Cardiac arrhythmia (may be life-threatening in elderly or those with cardiovascular disease) | Quinine blocks cardiac fast Na⁺ channels prolonging action potential duration and repolarization time | A baseline electrocardiogram and continuous cardiac monitoring to exclude lengthening of the QT interval is essential in patients receiving intravenous quinine therapy. |
| Prolonged neuromuscular blockade | Quinine affects neuromuscular transmission presynaptically by blocking voltage-gated Na⁺ channels and postsynaptically by potentiating depolarization. The overall effect is to reduce motor end-plate excitability. | Monitor depth of neuromuscular blockade with nerve stimulator to ensure full reversal prior to extubation. Prolonged neuromuscular blockade may necessitate postoperative ventilation until full resolution of blockade. |

| Table 5 Recommended preoperative investigations and assessment in patients with malaria |
| --- | --- | --- |
| System | Investigation/ Assessment | Indication |
| Hematology | Complete blood count | Anemia / Thrombocytopenia |
| | Blood film | Degree of parasitemia |
| | Coagulation profile | Evidence of DIC |
| | Blood type and crossmatch | Need for blood transfusion more likely in the presence of anemia |
| Renal | Urea, creatinine, and urine output | Consider need for preoperative RRT |
| | Electrolytes, including Mg²⁺ and Ca²⁺ | Hyperkalemia and hyponatremia are the most common electrolyte disturbances |
| Hepatic | Liver function tests, albumin | Fluid overload will be more likely in the presence of hypoalbuminemia |
| Respiratory | CXR, ABG, Pulse Oximetry | Respiratory failure is common in severe falciparum malaria |
| | Myocardial dysfunction occurs in severe falciparum malaria |
| | Evidence of cerebral malaria or raised ICP in severe falciparum malaria |
| Cardiac | ECG | QT interval is prolonged in patients on quinine |
| | Echocardiogram | Myocardial dysfunction occurs in severe falciparum malaria |
| Neurological | GCS and Pupils | Evidence of cerebral malaria or raised ICP in severe falciparum malaria |
| Metabolic | Blood glucose | Hypoglycemia is common in severe falciparum malaria, especially during treatment with quinine |
| | Lactate | Acidosis is a predictor of disease severity |

DIC = disseminated intravascular coagulation; RRT = renal replacement therapy; CXR = chest radiograph; ABG = arterial blood gas; ECG = electrocardiogram; GCS = Glasgow Coma scale; ICP = intracranial pressure
In up to 20% of adults with severe *falciparum* malaria, respiratory compromise is usually a multifactorial process arising from a combination of severe anemia, non-cardiogenic pulmonary edema, co-existing pneumonia, and the respiratory compensation resulting from the metabolic acidosis. Respiratory failure can progress to acute lung injury (ALI) or adult respiratory distress syndrome (ARDS) and the need for mechanical ventilation. The exact pathophysiology of developing ALI/ARDS in malaria is not fully understood. It is thought to involve a combination of factors, including parasite sequestration in pulmonary capillaries and host immune responses, both of which can initiate direct lung damage and lead to thickening of alveolar septa, intra-alveolar hemorrhage, and pulmonary edema. A post-treatment inflammatory response can also persist and lead to an ALI/ARDS picture even when the parasite count is declining.

Preoperative assessment of respiratory function should include noninvasive pulse oximetry, arterial blood gas analysis, chest radiograph, and an assessment of the need for supplemental oxygen and postoperative critical care management. Mechanical ventilation can be challenging due to ventilation/perfusion mismatching and reduced lung compliance that occurs in the context of ALI/ARDS. As ALI/ARDS treatment trials are lacking in patients with malaria, recommendations for ventilation follow non-malaria ARDS treatment guidelines. A lung protective ventilation strategy is advised with the application of positive end-expiratory pressure (PEEP), limiting tidal volumes to 6 mL·kg⁻¹ and plateau pressures to <30 cm H₂O. In patients with concomitant cerebral malaria, achieving normocapnia is essential to prevent further rises in intracranial pressure (ICP) that could precipitate cerebral herniation. Lung protective strategies may have to be sacrificed to achieve normocapnia in the presence of raised ICP. The use of extracorporeal carbon dioxide removal devices may be beneficial in this scenario. Positioning the patient in a head-up position may help with both ventilation and reducing ICP.

### Cardiac

Cardiac function is usually well preserved in malarial infection; however, it can become impaired in severe *falciparum* malaria infection. Post-mortem examination has shown evidence of microvascular obstruction in coronary capillaries caused by parasitized erythrocytes, leading to ischemic cardiomyopathy in some patients.

| Table 6 | Intraoperative anesthetic goals in patients with malaria |
|---------|----------------------------------------------------------|
| Anesthesia | Goals | Suggested management strategies |
| **Induction** | Hemodynamically stable induction without increased CBF | Propofol |
| | Avoid surges in ICP and hypercapnia | Avoid Ketamine |
| | | Ensure full neuromuscular blockade prior to intubation |
| | | Obtund the autonomic response to intubation |
| | | Start ventilation as soon as intubation is confirmed |
| **Maintenance** | Avoid cerebral vasodilation /raised ICP | Sevoflurane/Propofol (less CBF increase with Propofol) |
| | | Maintain normocapnia |
| | | 15° head-up position |
| | | Avoid endotracheal tube ties |
| | | Regular assessment of pupils |
| **Lung protective ventilation strategy** | TV 6 mL·kg⁻¹ | Application of PEEP |
| | | Limit plateau pressures <30 cm H₂O |
| **Avoid fluid overload** | TEE/CVP guided fluid therapy | Early use of inotropes preferential to excessive fluid boluses |
| **Avoid hypoglycemia** | 10% Dextrose as maintenance infusion | Measure blood glucose twice hourly |
| **Appropriate transfusion of blood products** | Blood transfusion if hemoglobin <7 g·dL⁻¹ or hematocrit <20% | Platelet transfusion for surgery if platelets <50 × 10⁹·L⁻¹ |
| | | Ensure resolution of neuromuscular blockade |
| | | Prolonged blockade in the presence of quinine may require postoperative ventilation |
| | | Minimize increases in ICP on extubation |
| | | Avoid excessive use of sedative drugs |
| | | Short-acting opioids preferred |
| Extubation | Safe and appropriate extubation | |

CBF = cerebral blood flow; ICP = intracranial pressure; TV = tidal volume; PEEP = positive end expiratory pressure; TEE = transesophageal echocardiography; CVP = central venous pressure.
Severe malaria infection may also be associated with direct myocardial dysfunction. Levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a sensitive marker of left ventricular dysfunction, have been shown to be elevated in patients presenting with severe malaria. Parasite toxins, host immune mediators, metabolic acidosis, and decreased NO levels have all been implicated as causative for direct myocardial dysfunction. Conduction defects and nonspecific electrocardiogram abnormalities can occur, particularly in patients on quinine therapy. Preoperative cardiac evaluations should include an electrocardiogram, transthoracic echocardiography, and laboratory biomarkers of cardiac dysfunction. When available, intraoperative transesophageal echocardiography and cardiac output monitoring should be considered to help guide appropriate inotropic and fluid therapy for the hypotensive patient and to distinguish between cardiogenic and distributive shock. There remains a degree of uncertainty about the optimal fluid management strategy in patients with severe malaria. Patients with malaria are particularly vulnerable to developing pulmonary edema from fluid overload, and there is a fine balance between keeping the patients underfilled, which may worsen perfusion and acidosis, and overfilled, which may precipitate pulmonary edema. In the absence of volume depletion or hypotension, patients with severe malaria should receive fluids conservatively. It is generally advisable to keep the intravascular volume at the lowest level while still allowing adequate systemic perfusion; early inotropic support is preferable to excessive intravascular filling. Nevertheless, the point at which inotropic agents should be commenced in patients with severe malaria is yet unknown. Since malaria can be associated with profound acidosis, if inotropic support is instituted, it may be preferable to avoid or limit the dose of epinephrine as this agent can increase lactate production and exacerbate acidosis. Dopamine, dobutamine, or norepinephrine have been used in the treatment of severe malaria and are suitable alternatives. Fluid balance may be particularly difficult to manage during surgery if there is acute blood loss. Central venous pressure, pulmonary artery catheters, and/or echocardiography should be considered to help guide treatment in this context; however, neither central venous nor pulmonary artery occlusion pressure has been shown to correlate well with markers of end-organ perfusion in severe malaria.

Neurological

Cerebral malaria is the most common neurological complication of falciparum malaria and is invariably fatal if left untreated. It is diagnosed by confirmation of peripheral malaria parasitemia coupled with altered consciousness, in the absence of other causes of coma. Cerebral symptoms are thought to be caused by obstruction of the cerebral microcirculation by parasitized erythrocytes. Parasitic sequestration leads to a static blood flow, localized tissue hypoxia, acidosis, and inflammation, which results in venous congestion, raised ICP, altered consciousness, and convulsions. Nevertheless, cerebral edema is not considered to be responsible for coma. Cerebral autoregulation becomes disrupted in those with intracranial hypertension.

Seizures must be treated promptly with a benzodiazepine (e.g., midazolam or lorazepam), though prophylactic therapy is not recommended. Hypoglycemia must be excluded as a cause of the coma or altered mental status. Lumbar puncture is often undertaken to rule out meningitis; however, raised ICP and coagulopathy must be excluded before this is performed.

Airway protection and prevention of aspiration is essential in patients with altered mental status or seizures. A hemodynamically stable induction technique is required that maintains cerebral perfusion pressure and cerebral blood flow, prevents increases in ICP, and avoids hypercapnia. Propofol is a suitable induction agent as it does not raise cerebral blood flow, while ketamine should be avoided as it increases cerebral blood flow and ICP. Techniques to help minimize surges in ICP during induction of anesthesia include obtunding the pressor response to laryngoscopy and intubation, ensuring adequate neuromuscular blockade to avoid coughing, and maintaining a head-up position. Avoidance of endotracheal tube ties to reduce cerebral venous congestion, a 15° head-up position, and adequate oxygenation are essential. Patients will often have a low PaCO\textsubscript{2} prior to induction as part of compensation for a metabolic acidosis. This low PaCO\textsubscript{2} maintains cerebral vasodilation. Transient hypercapnia, which can be common around the time of intubation, must be avoided as the resultant cerebral vasodilation could precipitate a catastrophic rise in ICP.

All volatile anesthetic agents result in a dose-related increase in cerebral blood flow and a reduction in the cerebral metabolic rate of oxygen consumption, with isoflurane, sevoflurane, and desflurane having very similar effects. The quick offset and recovery from sevoflurane and desflurane may make them more suitable agents for maintenance of anesthesia if the patient’s trachea is to be extubated immediately following surgery for rapid neurological assessment. The usefulness of mannitol for treatment of raised ICP in cerebral malaria has been questioned and should be used only as a salvage therapy in the event of impending cerebral herniation. Sedative agents and opioids must be used with caution if extubation is planned postoperatively, and assessments of the patient’s Glasgow Coma score and pupil size and function should be performed regularly in recovery.
Renal

Acute renal failure complicates up to 30% of imported cases of malaria. Renal failure is usually multifactorial, arising from a combination of hypovolemia, hyperparasitemia, sepsis, pyrexia, rhabdomyolysis, and hemolysis. These factors combined lead to acute tubular necrosis and usually oliguric renal failure. Renal failure in turn contributes to the acidosis that is seen commonly in severe malaria. Preoperative evaluation of renal function should include urea, creatinine and electrolytes, arterial blood gas, and an assessment of urine output. The most common electrolyte disturbances are hyponatremia and hyperkalemia. Hyperkalemia can be profound, particularly if there has been severe hemolysis. Calcium and magnesium can also be reduced in severe malaria, leading to a prolonged QT interval on electrocardiogram. Fluid balance must be monitored carefully and preoperative dialysis should be considered if there is evidence of fluid overload. Fluid overload in the presence of renal failure and severe anemia can precipitate cardiogenic pulmonary edema, and early institution of renal replacement therapy may limit pulmonary complications. Loop diuretics help reduce the risk of volume overload in the setting of renal failure and should be available in the operating room. Renal failure can affect the handling of many anesthetic drugs. Drugs which are cleared independently of the kidneys are preferred if renal function is compromised. Preserving renal blood flow and perfusion pressure through fluids and vasoactive drugs may help prevent further deterioration in renal function. The antimalarial drug, quinine, is renally excreted, and dose adjustments must be made to avoid side effects in patients with renal failure. No dose adjustments are required with artesunate. Nephrotoxic drugs, including nonsteroidal anti-inflammatories and aminoglycosides, should be avoided. Esterase-metabolized remifentanil is a good choice of intraoperative opioid, and short-acting opioids, such as sufentanil and fentanyl, are preferable to longer-acting opioids, such as morphine, for postoperative pain relief in the patient with established renal failure. Succinylcholine is considered a safe neuromuscular blocking agent in the presence of a normal serum potassium level, and atracurium and cisatracurium are the most suitable non-depolarizing muscle relaxants. It is essential to establish full reversal of neuromuscular blockade prior to extubation. The interaction of neuromuscular blocking drugs with quinine can lead to prolonged neuromuscular blockade.

Gastrointestinal and hepatic

Hepatic dysfunction is found in over 60% of patients presenting with severe falciparum malaria, and if present, confers a poor prognosis. Hyperbilirubinemia and jaundice arise from both hemolysis and direct hepatic parenchymal injury. Hepatic dysfunction leads to acidosis, hypoglycemia, coagulopathy, and altered drug handling. Malaria also induces a catabolic state causing hypoalbuminemia. The presence of hypoalbuminemia warrants careful attention as iatrogenic fluid overload resulting in pulmonary edema is more likely when it is present. The interaction of malaria with the spleen is complex. During the erythrocytic stages of the malaria infection, the spleen is the main organ involved in the immune response and in the removal of parasitized erythrocytes. The spleen plays an important role in the destruction of the malaria parasites and expression of parasite antigens on the surface of infected erythrocytes. Malaria infection, however, can result in remodelling of the splenic architecture that eventually results in impairment of the immune response. Splenomegaly can arise in patients with chronic malarial infection and can be massive. Indeed, this hyperreactive malarial splenomegaly is the main cause of massive splenomegaly in Africa. In addition to a profound anemia, the massive splenomegaly can complicate intraoperative management by causing cardiovascular instability through aortocaval compression by the spleen when the patient is supine. Wedging or tilting the patient can help limit hypotension related to aortocaval compression. Splenic complications, including hematoma, rupture, and infarction can complicate malarial infection, may be fatal, and are more common with vivax malaria. These complications should be suspected in patients complaining of abdominal pain in the left upper quadrant or lower left-sided pleuritic pain. Malaria is the most common cause of spontaneous splenic rupture in the tropics. Splenic rupture occurs most commonly during an acute infection, and lack of pre-existing immunity is a major risk factor. Although splenomegaly was traditionally treated surgically by splenectomy, conservative splenic conserving strategies are now advocated, particularly in patients with a high likelihood of future exposure to malaria infection. In patients with a history of malaria infection, it is important to find out if they have undergone a splenectomy as specific antibiotic prophylaxis may be required with future surgery.

Hematological

Depending on the severity of the disease, there may be varying degrees of anemia, thrombocytopenia, and coagulopathy. Anemia often develops rapidly and occurs secondary to hemolysis, splenic sequestration of non-deformable erythrocytes, and cytokine-induced dyserythropoiesis. In rare cases, rapid intravascular hemolysis can result in severe
anemia and hemoglobinuria (i.e., “blackwater fever”). There are few studies on the optimum level at which to transfuse patients with malarial anemia. In areas where the disease is endemic, pathogen-free fresh blood and blood products are often in short supply, and there is the additional risk of transmissible infections, such as HIV, with blood transfusion. The WHO has taken a pragmatic approach to treatment guidelines based mainly on expert opinion. In areas where malaria is endemic, transfusion is recommended if the hematocrit falls below 15% or the hemoglobin is < 5 g·dL⁻¹. In low transmission areas, blood transfusion is advisable if the hematocrit falls below 20% or the hemoglobin is < 7 g·dL⁻¹. Transfusion warrants careful attention to fluid balance as patients with severe malaria are prone to fluid overload and pulmonary edema. Additional diuretic therapy may be required to prevent this during transfusion.

Thrombocytopenia is a very common finding in malaria, though disease severity does not correlate with level of thrombocytopenia. Thrombocytopenia arises secondary to splenic sequestration and immune-mediated lysis of platelets. Spontaneous bleeding secondary to thrombocytopenia is rare, and treatment guidelines recommend that, in the absence of spontaneous bleeding, transfusion of platelets should occur only at counts < 10 × 10⁹·L⁻¹. If surgery is required, it is reasonable to treat platelet counts < 50 × 10⁹·L⁻¹ with platelet infusions.

Malaria is also associated with activation of the coagulation and fibrinolytic pathways, with tissue factor activation suggested as the unifying mechanism in the pathology of severe malaria. Disseminated intravascular coagulation can occur but is seen in only 1% of cases.

Metabolic

Hypoglycemia often complicates malaria. The etiology of malaria-associated hypoglycemia is multifactorial and includes massive glucose consumption by the parasites, hyperpyrexia, anorexia, cytokine-induced impairment of hepatic gluconeogenesis, and anerobic glycolysis. Iatrogenic hypoglycemia is also seen with quinine therapy, which is a potent stimulator of insulin release. Hypoglycemia can be profound in children and pregnancy.

Symptoms of hypoglycemia include autonomic activation, sweating, anxiety, tachypnea, and tachycardia, but these may be masked under general anesthesia. Prolonged hypoglycemia can cause irreversible neurological damage, and fastidious attention should be paid to blood glucose levels under general anesthesia. Performing surgery under regional blockade, if not contraindicated, may be advantageous in detecting hypoglycemia as patients are more likely to be symptomatic when awake. Patients with hypoglycemia should be treated with a 1 mL·kg⁻¹ bolus of 50% dextrose followed by an infusion of 10% dextrose. Maintenance fluids in the operating room should include 5-10% dextrose infusions. Serial blood glucose measurements should be taken every two hours on patients who are receiving intravenous quinine.

Metabolic acidosis is frequently seen in patients with malaria. The origin of acidosis is multifactorial, arising from a combination of tissue hypoxia, liver dysfunction, and impaired renal handling of bicarbonate. The presence and degree of acidosis is an important predictor of mortality and should alert the clinician to the severity of the disease. Caution should be taken against an overly aggressive fluid resuscitation strategy, which is often an initial treatment response for severe lactic acidosis. Volume depletion is usually not the main problem, and there is the risk of precipitating pulmonary and cerebral edema. Fever is a common clinical feature of malaria. The temperature, particularly in non-immune individuals, may rise above 40°C and can be associated with significant tachycardia, tachypnea, and sweating. Under general anesthesia, fever and the hypermetabolic state caused by malaria may result in an increased end-tidal carbon dioxide reading, which may be mistaken for malignant hyperpyrexia. The rise in CO₂ may also have effects on cerebral blood flow and cause increases in ICP. Active external cooling blankets and acetaminophen should be used to treat pyrexia. Postoperative fever in patients with a history of malaria should prompt investigation to exclude reactivation of malarial infection.

Pregnancy

Approximately 25% of women in sub-Saharan Africa have malaria during pregnancy. Pregnancy increases susceptibility to severe infection and complications; in particular, anemia, hypoglycemia, and pulmonary edema are more likely. Death rates from severe malaria in the pregnant population are two to ten times higher than in the non-pregnant population. Increased susceptibility to severe infection in pregnancy arises due to alterations in the acquired immune responses that occur in pregnancy and the tendency of the *falciparum* species to become sequestered in the placenta. Hypoglycemia is a prominent feature of *falciparum* malaria in pregnancy and can be exacerbated by quinine therapy. Blood glucose should be checked if there are any signs of fetal distress, as this can be precipitated by maternal hypoglycemia. Malaria has multiple effects on birth outcome, including intrauterine growth retardation, preterm delivery, still birth, and neonatal death. There is potential for vertical transmission of malaria parasites across the placenta throughout pregnancy and during delivery at the time of placental separation.
There is limited literature on the use of regional and neuraxial anesthesia in parturients with malaria. In the absence of significant thrombocytopenia, coagulopathy, secondary bacterial sepsis, or cerebral malaria with raised ICP, neuraxial anesthesia may be a viable alternative to general anesthesia in women requiring Cesarean delivery or non-obstetric surgery during pregnancy. There are theoretical concerns of parasite transfer into the cerebrospinal fluid (CSF) and precipitation of cerebral malaria through spinal anesthesia, though this has not been reported. Importantly, *Plasmodium* species are obligate intracellular parasites which are unable to replicate in CSF in the absence of available erythrocytes to invade. Cerebral malaria is a consequence of sequestration of malaria parasites within cerebral capillaries; the parasites are confined to the intravascular space with no direct contact with parasites within neuronal tissue. Spinal anesthesia has previously been used without complication in a parturient with babesiosis, a disease also characterized by intraerythrocytic parasites similar to malaria. It is also likely that many neuraxial blocks have been performed in pregnant patients with malaria worldwide with no published reports of harm. Nevertheless, there are few published data on this topic and further work is required specifically to investigate the safety of neuraxial anesthesia in this setting.

**Summary**

Malaria remains one of the most devastating infectious diseases worldwide. Increased global travel has resulted in an increase in the number of imported cases seen in developed countries. The majority of imported cases are caused by the *falciparum* species which is associated with the greatest degree of morbidity and mortality. Multiple organ systems can be impacted as a consequence of changes in structure and function of parasitized erythrocytes. Safe perioperative management requires knowledge of all these potential system effects. Preoperative investigation and assessment should assess the type of malaria, the severity of disease, and the degree of end-organ impairment. Treatment of malaria should be initiated prior to surgery. Neuraxial, regional, and general anesthesia are appropriate anesthetic techniques. Intraoperatively, close attention must be paid to fluid management, cerebral blood flow dynamics, and avoidance of hypoglycemia. Postoperatively, blood films should be repeated every eight to 12 hours until they are negative. Postoperative care of patients with severe malaria should take place in the critical care unit as there may be ongoing requirements for renal replacement therapy, ventilation, or inotropic support.

**Conflicts of interest**  None declared.

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