Can J Anesth/J Can Anesth (2015) 62:304–318
DOI 10.1007/s12630-014-0286-7

REVIEW ARTICLE/BRIEF REVIEW

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

Daniel Soltanifar, MBBS · Brendan Carvalho, MBBCh · Pervez Sultan, MBChB

Received: 30 June 2014 / Accepted: 25 November 2014 / Published online: 4 December 2014

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 périopératoires 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 périopératoires et en*

Author contributions *Daniel Soltanifar*, *Brendan Carvalho,* and *Pervez Sultan* all made substantial contributions to the literature review, article appraisal and write-up of this review.

D. Soltanifar, MBBS (✉)
Royal Free Hospital, Pond Street, London NW3 2QG, UK
e-mail: dannysolts@hotmail.com

B. Carvalho, MBBCh
Department of Anesthesiology, Stanford University School of Medicine, Stanford, CA, USA

P. Sultan, MBChB
University College London Hospital, London, UK

rapport avec le paludisme a été menée dans les bases de données MEDLINE®, EMBASE™ et Web of Science pour identifier les articles pertinents publiés en anglais entre 1945 et 2014. Sur les 303 articles correspondant aux critères de recherche, 265 ont été exclus en se basant sur leur titre et leur résumé. Onze des 38 articles restants étaient pertinents pour l'anesthésie et/ou les soins périopératoires et 27 articles ont été identifiés comme directement pertinents pour la médecine en soins intensifs.

Constatations principales *La majorité des cas importés de paludisme est causée par l'espèce Pl. falciparum, associée au plus grand degré de morbidité et mortalité. Divers systèmes d'organes peuvent être concernés à la suite des modifications de structure et de fonction des érythrocytes parasités. L'évaluation préopératoire doit se concentrer sur la détermination de l'espèce responsable du paludisme, la sévérité de la maladie, l'évaluation du niveau d'atteinte des organes cibles et l'instauration d'un traitement antipaludéen avant la chirurgie. L'artésunate intraveineux constitue le traitement de choix du paludisme sévère à Pl. falciparum. La quinine reste l'agent thérapeutique de deuxième intention, mais elle a un index thérapeutique étroit et des effets secondaires particulièrement dangereux. En peropératoire, l'attention doit se concentrer sur la gestion des liquides, la dynamique de la circulation sanguine cérébrale et l'évitement de l'hypoglycémie. Les soins postopératoires des cas sévères doivent idéalement se dérouler dans une unité de soins intensifs, car un soutien multiorganes, incluant le traitement de remplacement rénal, un soutien ventilatoire, et/ou inotrope peuvent s'avérer nécessaires. L'innocuité de l'anesthésie neuraxiale n'a pas été bien étudiée dans le cadre du paludisme.*

Conclusions *Le paludisme reste l'une des maladies infectieuses les plus dévastatrices dans le monde. De nombreux systèmes d'organes peuvent être concernés par les changements de structure et de fonctions des érythrocytes parasités. Une gestion périopératoire sécuritaire requiert une bonne connaissance de tous ces effets systémiques potentiels.*

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.[1] Increased global travel and immigration from malaria-endemic areas has resulted in an increase in the number of imported cases seen in developed countries.[2,3] 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 reviewed by two authors (D.S. and P.S). 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 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.[4] 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.[5]

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.[1,6] 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

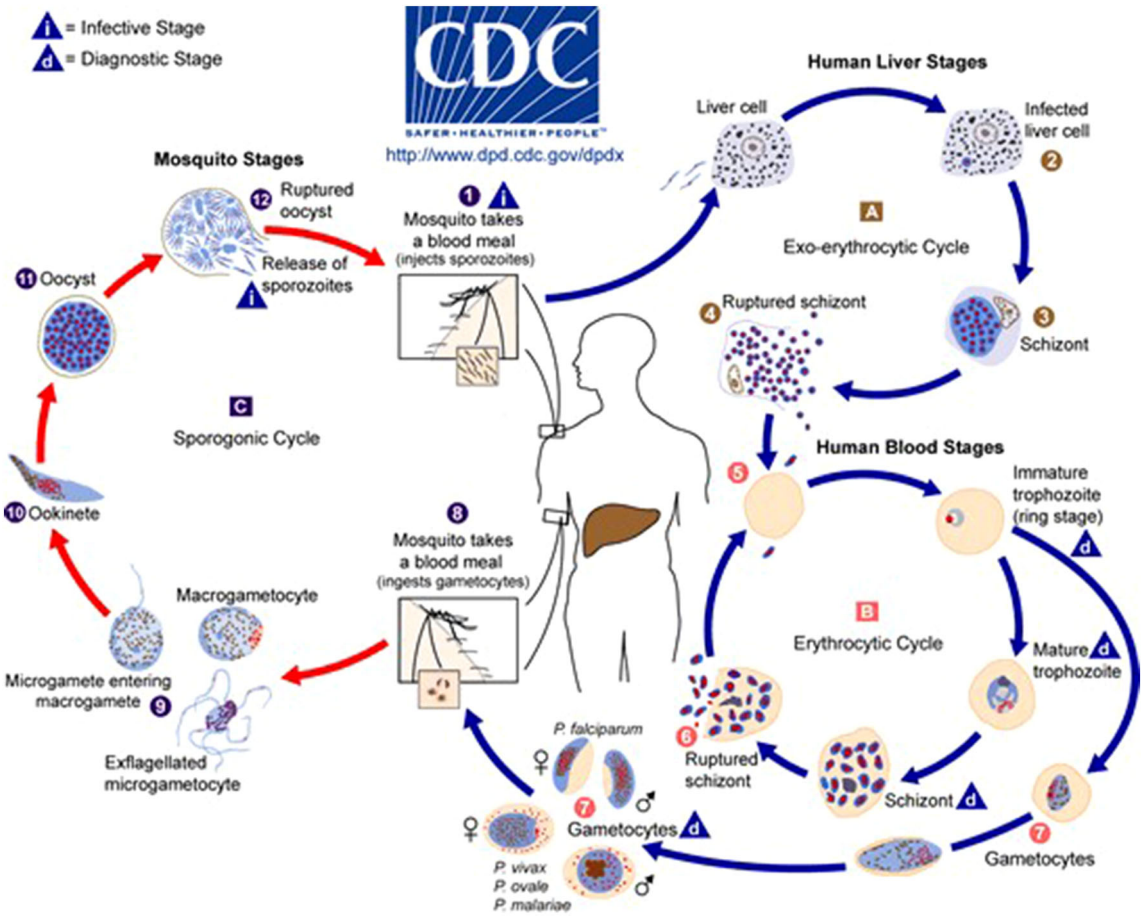

Figure Life cycle of the malaria parasite. Reproduced with permission from the Centers for Disease Control and Prevention

parasite without symptoms developing.[7] The exact mechanism of this immunity is unknown; however, it is rapidly lost if the individual moves away from the endemic area.[8] 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* mosquitos 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* mosquitos 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.[9-11]

Pathophysiology

Many of the effects of severe *falciparum* malaria on the various organ systems are a consequence of changes in the

Table 1 World Health Organization diagnostic criteria for severe *falciparum* malaria

Clinical Features	Laboratory Findings
Impaired consciousness or unrousable coma	Hypoglycemia (blood glucose < 2.2 mmol·L^{-1} or < 40 mg·dL^{-1})
Prostration, i.e., generalized weakness so the patient is unable to sit up or walk without assistance	Metabolic acidosis (plasma bicarbonate < 15 mmol·L^{-1})
Failure to feed	Severe normocytic anemia (Hb < 5 g·dL^{-1}, packed cell volume $< 15\%$)
Multiple convulsions	Hemoglobinuria
Deep breathing, respiratory distress	Hyperparasitemia $> 2\%$/100,000/μL in low intensity transmission area or $> 5\%$/100,000/μL in areas of high stable malaria transmission intensity
Circulatory collapse or shock; Systolic blood pressure < 70 mmHg in adults and < 50 mmHg in children	Hyperlactatemia (lactate > 5 mmol·L^{-1})
Clinical jaundice and evidence of other vital organ dysfunction	Renal impairment (serum creatinine > 265 μmol·L^{-1})
Hemoglobinuria	
Abnormal spontaneous bleeding	
Pulmonary edema (radiological)	

Hb = hemoglobin. The presence of one or more of the above clinical or laboratory features with confirmed *Plasmodium falciparum* parasitemia classifies the patient as suffering from severe malaria

Adapted from WHO guidelines for the treatment of malaria[22]

Table 2 WHO recommendations for the treatment of malaria

Type of malaria infection	1st line treatment	2nd line treatments
Uncomplicated *falciparum* malaria	Artemisinin-based combination therapy* (ACT)**	1) Alternative ACT known to be effective in that region 2) Artesunate plus doxycycline or tetracycline or clindamycin 3) Quinine plus doxycycline or tetracycline or clindamycin
Severe *falciparum* malaria	Intravenous artesunate	Intravenous artemether or intravenous quinine if intravenous artesunate is not available
vivax malaria	Chloroquine plus primaquine*** for quinine-sensitive strains	ACT plus primaquine for quinine-resistant strains
ovale malaria	Chloroquine plus primaquine	
malariae malaria	Chloroquine	

ACTs recommended include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, and artesunate plus sulfadoxine-pyrimethamine

*For travellers returning to non-endemic countries atovaquone-proguanil, artemether-lumefantrine or quinine plus doxycycline or quinine plus clindamycin is recommended

**ACTs are unavailable in Canada and the CATMET recommended first-choice therapy for uncomplicated *falciparum* malaria is oral atovaquone-proguanil (Malarone^{TM})

***Primaquine required for clearance of liver-stage hypnozoites seen only in *vivax* and *ovale*

ACT = artemisinin-based combination therapy; CATMET = Committee to Advise on Tropical Medicine and Travel

Adapted from WHO guidelines for the treatment of malaria[22]

structure and function of parasitized erythrocytes. 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.[12] The pathogenic effects of malaria have also been attributed to parasitized erythrocytes promoting the release of pro-inflammatory cytokines.[13] 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.[13-15]

Diagnosis

Malaria usually presents as an acute febrile illness ten to 15 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^{TM}) 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

Table 3 Pharmacology of some of the main antimalarial drugs

Drug	Anti-malarial mechanism of action	Formulations	Pharmacokinetics	Toxicity	Interactions
Artemisinin Extracted from the leaves of sweet wormwood, *Artemisia annua* (has given way to more potent derivatives: dihydroartemisinin, artemether, artemotil and artesunate)	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 Potent inducer of its own metabolism Half-life (or t ½) = 1 hr	Usually safe and well tolerated Anaphylaxis in 1/3,000 cases QT prolongation and bradycardia have been reported	None known
Artesunate Sodium salt of the hemisuccinate ester of artemisinin *Artemisia annua*	Same as for Artemisinin	Tablets, ampoules for intramuscular, intravenous injection, and rectal capsules	Rapidly absorbed Converted almost entirely to the active metabolite dihydroartemisinin t ½ = 45 min No dose reduction with renal or hepatic impairment	As for Artemisinin Some reports of delayed hemolytic reactions and neutropenia	None known
Chloroquine 4 aminoquinoline	Interferes with parasite heme detoxification Ineffective in *falciparum* malaria due to widespread resistance	Tablets and ampoules for intramuscular or intravenous injection	Rapid absorption when given orally, intramuscularly, or subcutaneously Eliminated very slowly by the kidneys t ½ = 1-2 months	Low safety margin and very dangerous in overdose with multiple side-effects Unpleasant taste Rarely central nervous system toxicity, including convulsions and mental changes Acute overdose can cause cardiac arrhythmias, hypotension, and hypokalemia	Risk of arrhythmias with drugs that prolong the QT interval Risk of acute dystonic reactions with metronidazole Reduced bioavailability of ampicillin Antagonist of antiepileptic effects of carbamazepine and sodium valproate
Primaquine 8 aminoquinoline	Effective against intrahepatic forms of all types of malaria parasite Exact mechanism of action unknown	Tablets	Well absorbed from gastrointestinal tract t ½ = 3-6 hr Metabolized in the liver	Hemolytic anemia in patients with Glucose-6-phosphate dehydrogenase deficiency Abdominal pain Methemoglobinemia	Concomitant drugs liable to induce hemolysis or bone marrow suppression should be avoided

Table 3 continued

Drug	Anti-malarial mechanism of action	Formulations	Pharmacokinetics	Toxicity	Interactions
Quinine Alkaloid derived from bark of the Cinchona tree L-stereoisomer of quinidine	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 Accumulates in renal failure	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^{TM})	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 t ½ = 66-70 hr due to enterohepatic recycling Excreted in feces as unchanged drug Proguanil is 75% protein bound. 50% excreted in urine Accumulates in renal failure with dose reduction needed	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]

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)[80]	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[81]	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[63]
	Blood film	Degree of parasitemia[17]
	Coagulation profile	Evidence of DIC[67]
	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[55]
	Electrolytes, including Mg^{2+} and Ca^{2+}	Hyperkalemia and hyponatremia are the most common electrolyte disturbances[52]
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[37] Anticipate need for postoperative ventilation
Cardiac	ECG	QT interval is prolonged in patients on quinine[43]
	Echocardiogram	Myocardial dysfunction occurs in severe *falciparum* malaria[41]
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[70]

DIC = disseminated intravascular coagulation; RRT = renal replacement therapy; CXR = chest radiograph; ABG = arterial blood gas; ECG = electrocardiogram; GCS = Glasgow Coma scale; ICP = intracranial pressure

cause of splenomegaly and splenic rupture worldwide.[29] Surgical cases in patients with malaria have also been described in the context of cardiac surgery, liver and renal transplantation, and emergency Cesarean delivery.[30-32]

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.[33] Recurrence has also been described with *falciparum* malaria.[34] 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.[35] Respiratory distress may

Table 6 Intraoperative anesthetic goals in patients with malaria

Anesthesia	Goals	Suggested management strategies
Induction	Hemodynamically stable induction without increased CBF	Propofol
		Avoid Ketamine
	Avoid surges in ICP and hypercapnia	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 $mL \cdot kg^{-1}$
		Application of PEEP
		Limit plateau pressures < 30 cm H_2O[38]
	Avoid fluid overload	TEE/CVP guided fluid therapy
		Early use of inotropes preferential to excessive fluid boluses[18]
	Avoid hypoglycemia	10% Dextrose as maintenance infusion
		Measure blood glucose twice hourly[21]
	Appropriate transfusion of blood products	Blood transfusion if hemoglobin < 7 $g \cdot dL^{-1}$ or hematocrit $< 20\%$
		Platelet transfusion for surgery if platelets $< 50 \times 10^9 \cdot L^{-1}$
Extubation	Safe and appropriate extubation	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

CBF = cerebral blood flow; ICP = intracranial pressure; TV = tidal volume; PEEP = positive end expiratory pressure; TEE = transesophageal echocardiography; CVP = central venous pressure

occur in up to 20% of adults with severe *falciparum* malaria, though less frequently with *vivax* and *ovale* malaria.[36,37] 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.[38]

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.[38] A lung protective ventilation strategy is advised with the application of positive end-expiratory pressure (PEEP), limiting tidal volumes to 6 $mL \cdot kg^{-1}$ and plateau pressures to < 30 cm H_2O.[39] 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.[40] 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.[41]

Severe malaria infection may also be associated with direct myocardial dysfunction.[42] 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.[43] Parasite toxins, host immune mediators, metabolic acidosis, and decreased NO levels have all been implicated as causative for direct myocardial dysfunction. Conduction defects and non-specific electrocardiogram abnormalities can occur, particularly in patients on quinine therapy.[44] 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 under-filled, which may worsen perfusion and acidosis, and over-filled, which may precipitate pulmonary edema. In the absence of volume depletion or hypotension, patients with severe malaria should receive fluids conservatively.[19] 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.[18] 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.[45] 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.[46]

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.[47] Cerebral symptoms are thought to be caused by obstruction of the cerebral microcirculation by parasitized erythrocytes.[48] 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.[49] Nevertheless, cerebral edema is not considered to be responsible for coma.[50] Cerebral autoregulation becomes disrupted in those with intracranial hypertension.[49]

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 $PaCO_2$ prior to induction as part of compensation for a metabolic acidosis. This low $PaCO_2$ maintains cerebral vasoconstriction. 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.[51]

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.[52] 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.[53] 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.[54] 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.[53] 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.[55] 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.[56] 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.[57] 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.[58] 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.[59] 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.[29] The spleen contributes to the anemia of malaria by increased destruction and retention of the less deformable parasitized red blood cells. The severe complications of non-*falciparum* malaria usually involve the spleen.[60] 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.[61] 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.[62] 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.[63] 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.[64] 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}.[23] 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.[65] 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 $< 10 \times 10^9$·L^{-1}. If surgery is required, it is reasonable to treat platelet counts $< 50 \times 10^9$·L^{-1} with platelet infusions.[66]

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.[67] Disseminated intravascular coagulation can occur but is seen in only 1% of cases.[68]

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.[69,70] 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.[22]

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.[71] Microvascular obstruction with resultant tissue hypoxia and anerobic glycolysis are the main drivers of lactic acidosis. 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.[72,73]

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.[74] The rise in CO_2 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.[75] 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.[76] 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.[77] 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.[60] 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.[78] 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.[79] Spinal anesthesia has previously been used without complication in a parturient with babesiosis, a disease also characterized by intraerythrocytic parasites similar to malaria.[80] 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.[1,6] 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.

References

1. *World Health Organization.* World Malaria Report 2011. Available from URL: http://www.who.int/malaria/world_malaria_report_2011/en/ (accessed May 2014).
2. *Agarwal A*, *McMorrow M*, *Arguin PM*. The increase of imported malaria acquired in Haiti among US travelers in 2010. American Journal of Tropical Medicine and Hygeine 2012; 86: 9-10.
3. *Kain KC*, *Keystone JS*. Malaria in travelers. Epidemiology, disease, and prevention. Infectious Disease Clinics of North America 1998; 12: 267-84.
4. *Centre for Disease Control and Prevention*. Morbidity and Mortality Weekly Report. Available from URL: http://www.cdc.gov/malaria/references_resources/mmwr.html#surveillance (accessed October 2014).
5. *Public Health Agency of Canada*. Canadian Recommendations for the Prevention and Treatment of Malaria 2014. An Advisory Committee Statement (ACS) Committee to Advise on Tropical Medicine and Travel (CATMAT). Available from URL: http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-102-2014-eng.pdf (acessed October 2014).
6. *MacLean JD*, *Demers AM*, *Ndao M*, *Kokoskin E*, *Ward BJ*, *Gyorkos TW*. Malaria epidemics and surveillance systems in Canada. Emerging Infectious Diseases 2004; 10: 1195-201.
7. *Artavanis-Tsakonas K*, *Tongren JE*, *Riley EM*. The war between the malaria parasite and the immune system: immunity, immunoregulation and immunopathology. Clinical and Experimental Immunology 2003; 133: 145-52.
8. *Keenihan SH*, *Gramzinksi R*, *Ratiwayanto S*, *et al*. Plasmodium falciparum. Mechanisms of innate and acquired protection against Plasmodium falciparum in Javanese transmigrant adults and children newly resident in malaria-endemic Northwest Papua. Advances in Experimental Medicine and Biology 2003; 531: 83-102.
9. *Rodriguez M*, *Tome S*, *Vizcaino L*, *et al*. Malaria infection through multiorgan donation: an update from Spain. Liver Transplantation 2007; 13: 1302-4.
10. *Brouwer EE*, *van Hellemond JJ*, *van Genderen PJ*, *et al*. A case report of transfusion-transmitted Plasmodium malariae from an asymptomatic non-immune traveller. Malar J 2013; 12: 439.
11. *Menendez C*, *Mayor A*. Congenital malaria: the least known consequence of malaria in pregnancy. Semin Fetal Neonatal Med 2007; 12: 207-13.
12. *David PH*, *Hommel M*, *Miller LH*, *Udeinya IJ*, *Oligino LD*. Parasite sequestration in Plasmodium falciparum malaria: spleen and antibody modulation of cytoadherence of infected erythrocytes. Proc Natl Acad Sci U S A 1983; 80: 5075-9.
13. *Clark IA*, *Budd AC*, *Alleva LM*, *Cowden WB*. Human malarial disease: a consequence of inflammatory cytokine release. Malar J 2006; 5: 85.
14. *Prato M*, *Giribaldi G*, *Polimeni M*, *Gallo V*, *Arese P*. Phagocytosis of hemozoin enhances matrix metalloproteinase-9 activity and TNF-alpha production in human monocytes: role of matrix metalloproteinases in the pathogenesis of falciparum malaria. J Immunol 2005; 175: 6436-42.
15. *Newbold C*, *Craig A*, *Kyes S*, *Rowe A*, *Fernandez-Reyes D*, *Fagan T*. Cytoadherence, pathogenesis and the infected red cell surface in Plasmodium falciparum. International Journal for Parasitology 1999; 29: 927-37.
16. *Taylor SM*, *Molyneux ME*, *Simel DL*, *Meshnick SR*, *Juliano JJ*. Does this patient have malaria? JAMA 2010; 304: 2048-56.
17. *Askling HH*, *Bruneel F*, *Burchard G*, *et al*. Management of imported malaria in Europe. Malar J 2012; 11: 328.
18. *Trampuz A*, *Jereb M*, *Muzlovic I*, *Prabhu RM*. Clinical review: severe malaria. Critical Care 2003; 7: 315-23.

19. *Cheng MP*, *Yansouni CP*. Management of severe malaria in the intensive care unit. Critical Care Clinics 2013; 29: 865-85.
20. *Centers for Disease Control and Prevention*. Laboratory Identification of Parasitic Diseases of Public Health Concern: Malaria. Available from URL; http://www.cdc.gov/dpdx/malaria/dx.html#table (accessed November 2014).
21. *Maltha J*, *Gillet P*, *Jacobs J*. Malaria rapid diagnostic tests in travel medicine. Clinical Microbiology & Infection 2013; 19: 408-15.
22. *Lalloo DG*, *Shingadia D*, *Pasvol G*, *et al*. UK malaria treatment guidelines. J Infect 2007; 54: 111-21.
23. *World Health Organization*. Guidelines for the Treatment of Malaria - Second Edition. Geneva (Switzerland): 2010: 1-194. Available from URL: http://www.who.int/malaria/publications/atoz/9789241547925/en/ (accessed November 2014).
24. *Van Geertruyden JP*. Interactions between malaria and human immunodeficiency virus anno 2014. Clinical Microbiology & Infection 2014; 20: 278-85.
25. *Reithinger R*, *Kamya MR*, *Whitty CJ*, *Dorsey G*, *Vermund SH*. Interaction of malaria and HIV in Africa. BMJ 2009; 338: b2141.
26. *Sinclair D*, *Donegan S*, *Isba R*, *Lalloo DG*. Artesunate versus quinine for treating severe malaria. Cochrane Database Systematic Review 2012; 6: CD005967.
27. *Dondorp A*, *Nosten F*, *Stepniewska K*, *Day N*, *White N*, *South East Asian Quinine Artesunate Malaria Trial (SEAQAMAT) Group*. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005; 366: 717-25.
28. *Canadian Malaria Network*. Streamlined Medical Access to Artesunate or Quinine for Severe Malaria Treatment. Available from URL; http://thinkottawamedicine.ca/clinical-care/canadian-malaria-network/ (accessed November 2014).
29. *Del Portillo HA*, *Ferrer M*, *Brugat T*, *Martin-Jaular L*, *Langhorne J*, *Lacerda MV*. The role of the spleen in malaria. Cellular Microbiology 2012; 14: 343-55.
30. *Balkanay M*, *Mansuroglu D*, *Kirali K*, *Omeroglu SN*, *Yakut C*. Coronary bypass surgery in patient with malaria. Asian Cardiovasc Thorac Ann 2002; 10: 160-1.
31. *Kute VB*, *Vanikar AV*, *Shah PR*, *et al*. Postrenal transplant Plasmodium vivax malaria: neglected and not benign. Parasitology Research 2013; 112: 1791-3.
32. *Mathew DC*, *Loveridge R*, *Solomon AW*. Anaesthetic management of caesarean delivery in a parturient with malaria. Int J Obstet Anesth 2011; 20: 341-4.
33. *Gibney EJ*. Surgical aspects of malaria. British Journal of Surgery 1990; 77: 964-7.
34. *Eykyn SJ*, *Braimbridge MV*. Open heart surgery complicated by postoperative malaria. Lancet 1977; 2: 411-2.
35. *Anstey NM*, *Jacups SP*, *Cain T*, *et al*. Pulmonary manifestations of uncomplicated Falciparum and vivax malaria: cough, small airways obstruction, impaired gas transfer, and increased pulmonary phagocytic activity. Journal of Infectious Diseases 2002; 185: 1326-34.
36. *Agarwal R*, *Nath A*, *Gupta D*. Noninvasive ventilation in Plasmodium vivax related ALI/ARDS. Internal Medicine 2007; 46: 2007-11.
37. *Lee EY*, *Maguire JH*. Acute pulmonary edema complicating ovale malaria. Clinical Infectious Diseases 1999; 29: 697-8.
38. *Taylor WR*, *Hanson J*, *Turner GD*, *White NJ*, *Dondorp AM*. Respiratory manifestations of malaria. Chest 2012; 142: 492-505.
39. *Putensen C*, *Theuerkauf N*, *Zinserling J*, *Wrigge H*, *Pelosi P*. Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Annals of Internal Medicine 2009; 151: 566-76.
40. *Cove ME*, *Maclaren G*, *Federspiel WJ*, *Kellum JA*. Bench to bedside review: Extracorporeal carbon dioxide removal, past present and future. Critical Care 2012; 16: 232.
41. *Mohsen AH*, *Green ST*, *West JN*, *McKendrick MW*. Myocarditis associated with Plasmodium falciparum malaria: a case report and a review of the literature. J Travel Med 2001; 8: 219-20.
42. *Mishra SK*, *Behera PK*, *Satpathi S*. Cardiac involvement in malaria: an overlooked important complication. J Vector Borne Dis 2013; 50: 232-5.
43. *Ehrhardt S*, *Wichmann D*, *Hemmer CJ*, *Burchard GD*, *Brattig NW*. Circulating concentrations of cardiac proteins in complicated and uncomplicated Plasmodium falciparum malaria. Trop Med Int Health 2004; 9: 1099-103.
44. *Franzen D*, *Curtius JM*, *Heitz W*, *Hopp HW*, *Diehl V*, *Hilger HH*. Cardiac involvement during and after malaria. Clin Invest 1992; 70: 670-3.
45. *Day NP*, *Phu NH*, *Bethell DP*, *et al*. The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. Lancet 1996; 348: 219-23.
46. *Nguyen HP*, *Hanson J*, *Bethell D*, *et al*. A retrospective analysis of the haemodynamic and metabolic effects of fluid resuscitation in Vietnamese adults with severe falciparum malaria. PLoS ONE 2011; 6: e25523.
47. *Anonymous*. Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster. Trans R Soc Trop Med Hyg 2000; 94(Suppl 1): S1-90.
48. *Ponsford MJ*, *Medana IM*, *Prapansilp P*, *et al*. Sequestration and microvascular congestion are associated with coma in human cerebral malaria. Journal of Infectious Diseases 2012; 205: 663-71.
49. *Idro R*, *Marsh K*, *John CC*, *Newton CR*. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. Pediatric Research 2010; 68: 267-74.
50. *Medana IM*, *Day NP*, *Sachanonta N*, *et al*. Coma in fatal adult human malaria is not caused by cerebral oedema. Malar J 2011; 10: 267.
51. *White NJ*. The management of severe falciparum malaria. American Journal of Respiratory and Critical Care Medicine 2003; 167: 673-4.
52. *Mohanty S*, *Mishra SK*, *Patnaik R*, *et al*. Brain swelling and mannitol therapy in adult cerebral malaria: a randomized trial. Clinical Infectious Diseases 2011; 53: 349-55.
53. *Barsoum RS*. Malarial acute renal failure. Journal of the American Society of Nephrology 2000; 11: 2147-54.
54. *Sitprija V*. Nephropathy in falciparum malaria. Kidney International 1988; 34: 867-77.
55. *Pasvol G*. The treatment of complicated and severe malaria. British Medical Bulletin 2005; 75-76: 29-47.
56. *Wilairatana P*, *Westerlund EK*, *Aursudkij B*, *et al*. Treatment of malarial acute renal failure by hemodialysis. American Journal of Tropical Medicine and Hygeine 1999; 60: 233-7.
57. *Das BS*. Renal failure in malaria. J Vector Borne Dis 2008; 45: 83-97.
58. *Dean M*. Opioids in renal failure and dialysis patients. Journal of Pain and Symptom Management 2004; 28: 497-504.
59. *Das SN*, *Mohapatra B*, *Mohanty R*, *Dash PC*, *Kar K*, *Dash PK*. Malarial hepatitis as a component of multiorgan failure—a bad prognostic sign. Journal of the Indian Medical Association 2007; 105: 247-50.
60. *Zingman BS*, *Viner BL*. Splenic complications in malaria: case report and review. Clinical Infectious Diseases 1993; 16: 223-32.
61. *Yagmur Y*, *Kara IH*, *Aldemir M*, *Buyukbayram H*, *Tacyildiz IH*, *Keles C*. Spontaneous rupture of malarial spleen: two case reports and review of literature. Critical Care 2000; 4: 309-13.

62. *Jimenez BC*, *Navarro M*, *Huerga H*, *Lopez-Velez R*. Spontaneous splenic rupture due to Plasmodium vivax in a traveler: case report and review. J Travel Med 2007; 14: 188-91.
63. *Hamel CT*, *Blum J*, *Harder F*, *Kocher T*. Nonoperative treatment of splenic rupture in malaria tropica: review of literature and case report. Acta Tropica 2002; 82: 1-5.
64. *Haldar K, Mohandas N*. Malaria, erythrocytic infection, and anemia. Hematology Am Soc Hematol Educ Program 2009: 87-93.
65. *Jadhav UM*, *Patkar VS*, *Kadam NN*. Thrombocytopenia in malaria—correlation with type and severity of malaria. Journal of the Association of Physicians of India 2004; 52: 615-8.
66. *Rebulla P*. Revisitation of the clinical indications for the transfusion of platelet concentrates. Rev Clin Exp Hematol 2001; 5: 288-310; discussion 311-2.
67. *Francischetti IM*. Does activation of the blood coagulation cascade have a role in malaria pathogenesis? Trends in Parasitology 2008; 24: 258-63.
68. *Francischetti IM*, *Seydel KB*, *Monteiro RQ*. Blood coagulation, inflammation, and malaria. Microcirculation 2008; 15: 81-107.
69. *White NJ*, *Warrell DA*, *Chanthavanich P*, *et al*. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. New England Journal of Medicine 1983; 309: 61-6.
70. *Thien HV*, *Kager PA*, *Sauerwein HP*. Hypoglycemia in falciparum malaria: is fasting an unrecognized and insufficiently emphasized risk factor? Trends in Parasitology 2006; 22: 410-5.
71. *Day NP*, *Phu NH*, *Mai NT*, *et al*. The pathophysiologic and prognostic significance of acidosis in severe adult malaria. Critical Care Medicine 2000; 28: 1833-40.
72. *Planche T*, *Onanga M*, *Schwenk A*, *et al*. Assessment of volume depletion in children with malaria. PLoS Med 2004; 1: e18.
73. *Losert H*, *Schmid K*, *Wilfing A*, *et al*. Experiences with severe P. falciparum malaria in the intensive care unit. Intensive Care Medicine 2000; 26: 195-201.
74. *Delas Alas V*, *Geddes LA*, *Voorhees WD*, *Bourland JD*, *Schoenlein WE*. End-tidal CO2, CO2 production, and O2 consumption as early indicators of approaching hyperthermia. Biomedical Instrumentation and Technology 1990; 24: 440-4.
75. *Desai M*, *ter Kuile FO*, *Nosten F*, *et al*. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis 2007; 7: 93-104.
76. *Brabin BJ*. An analysis of malaria in pregnancy in Africa. Bulletin of the World Health Organization 1983; 61: 1005-16.
77. *Fried M*, *Duffy PE*. Adherence of Plasmodium falciparum to chondroitin sulfate A in the human placenta. Science 1996; 272: 1502-4.
78. *SaaChai T*, *Lin J*. Anesthetic aspect of malaria disease: a brief review. Middle East J Anaesthesiol 2012; 21: 457-62.
79. *Armah HB*, *Wilson NO*, *Sarfo BY*, *et al*. Cerebrospinal fluid and serum biomarkers of cerebral malaria mortality in Ghanaian children. Malar J 2007; 6: 147.
80. *Sultan P*, *Green C*, *Riley E*, *Carvalho B*. Spinal anaesthesia for caesarean delivery in a parturient with babesiosis and Lyme disease. Anaesthesia 2012; 67: 180-3.
81. *Padmaja UK*, *Adhikari P*, *Periera P*. Experience with quinine in falciparum malaria. Indian Journal of Medical Sciences 1999; 53: 153-7.