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Review

Diagnosis and management of malaria in the intensive care unit

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ABSTRACT

Malaria is responsible for approximately three-quarters of a million deaths in humans globally each year. Most of the morbidity and mortality reported are from Sub-Saharan Africa and Asia, where the disease is endemic. In non-endemic areas, malaria is the most common cause of imported infection and is associated with significant mortality despite recent advancements and investments in elimination programs. Severe malaria often requires intensive care unit admission and can be complicated by cerebral malaria, respiratory distress, acute kidney injury, bleeding complications, and co-infection. Intensive care management includes prompt diagnosis and early initiation of effective antimalarial therapy, recognition of complications, and appropriate supportive care. However, the lack of diagnostic capacities due to limited advances in equipment, personnel, and infrastructure presents a challenge to the effective diagnosis and management of malaria. This article reviews the clinical classification, diagnosis, and management of malaria as relevant to critical care clinicians, highlighting the role of diagnostic capacity, treatment options, and supportive care.

Introduction

Malaria is a curable but life-threatening parasitic disease often presenting as an acute febrile illness. The initial symptoms caused by members of the protozoan genus *Plasmodium* are fever, headache, chills, and weakness, which commonly appear 10–15 days after an infected mosquito bite and sometimes pose a diagnostic challenge; Figure 1 illustrates the life cycle of *Plasmodium* and how infection occurs.[1–4]

Five species of the genus *Plasmodium* can cause malaria in humans, namely, *Plasmodium falciparum, Plasmodium knowlesi, Plasmodium malariae, Plasmodium ovale*, and *Plasmodium vivax*.[4,5] If left untreated for 6–24 h, *P. falciparum* malaria can progress to severe illness or death. Severe malaria and malaria-related deaths caused by other species of the genus *Plasmodium* such as *P. malariae* and *P. vivax* have been reported, but the prevalence and mortality are low.[1,3,6–8] Managing severe forms of the disease often requires intensive care unit (ICU) admission and may be complicated by acute kidney injury (AKI), cerebral malaria, respiratory distress, bleeding complications, and co-infection with bacteria, fungi, or viruses.[9] As a complication, cerebral malaria has one of the highest mortality rates in severe malaria.[10–12]

Current evidence suggests that anti-parasite immune responses can efficiently control malaria infection at all parasite development stages and can prevent parasite infection under certain circumstances.[13] However, immune dysfunction is common among critically ill patients and an altered immune response may affect morbidity and mortality.[14,15] Vascular dysfunction is a reported feature of malaria pathogenesis and leads to impaired blood perfusion, vascular obstruction, and tissue hypoxia according to Georgiadou and Cunnington.[16] Other factors, such as the adhesion of infected red blood cells (RBCs) to the endothelium, endothelial activation, and reduced nitric oxide formation, have also been reported.[16,17] Emerging evidence suggests that endothelial glycocalyx (eGC) (which protects the vasculature by maintaining vessel integrity and regulating cellular adhesion and nitric oxide signaling pathways) can break down during *Plasmodium* infection, and that loss of eGC is associated with vascular dysfunction and malaria severity.[16,18]

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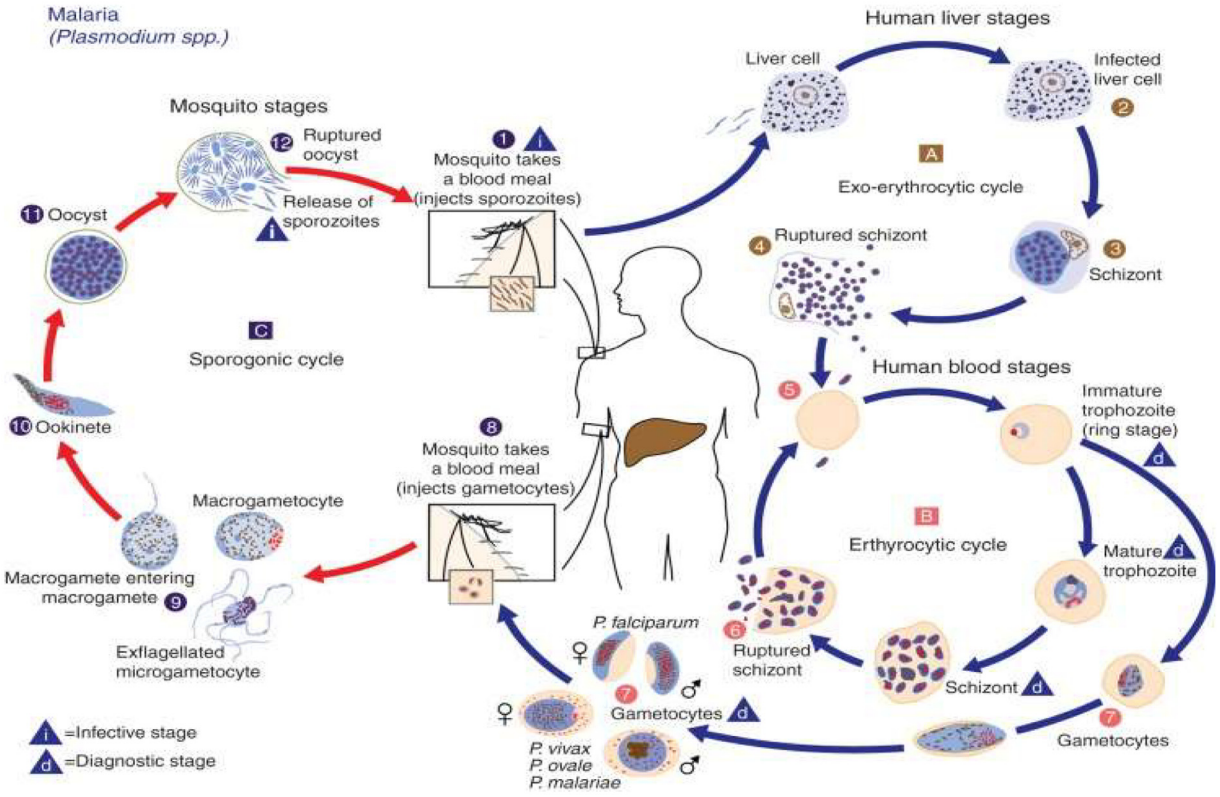

Figure 1. Life cycle of *Plasmodium*.[4,9] Image from the Centers for Disease Control and Prevention (www.cdc.gov) Public Health Library (PHL) and provided by CDC – DPDx/Alexander J. da Silva, Melanie Moser. Available via license: CC BY 4.0.

Early diagnosis followed by immediate treatment is an effective management strategy for malaria and fundamental to reducing ICU admissions and hospitalization, as well as preventing deaths and reducing transmission.[19–22] Standard practice requires all suspected cases of malaria to be confirmed using parasite-based diagnostic testing through microscopy or a rapid diagnostic test (RDT).[20,23] Primarily, treatment guarantees the complete elimination of *Plasmodium* parasites in a patient to prevent uncomplicated malaria from progressing to severe disease or death.[1,24] The existing treatment recommendations are artemisinin-based compounds as first-line agents in the clinical management of complicated and uncomplicated malaria.[20,25–28] However, treatment options are being threatened by the emergence of antimicrobial resistance.[19,29,30]

The World Health Organization (WHO) has recommended effective vector control and access to preventive antimalarial drugs as malaria prevention tools and strategies. These efforts align with the global targets of WHO set to be realized by 2030 and the United Nations Sustainable Development Goals (SDGs).[31–35] Although this initiative has impacted and reduced the global burden of the disease, malaria diagnosis, and management in the ICU remain a challenge amidst threats imposed by antimicrobial resistance.[19,36,37] This review provides valuable and critical information on the diagnosis and management of malaria in the ICU.

General Epidemiology

In 2021, there were an estimated 247 million cases of malaria and 619,000 malaria deaths worldwide.[1] According to WHO,[38] *P. falciparum* is the highest priority malaria species, causing 99% of malaria cases in Africa and 66% of cases in South-East Asia. Aside *P. falciparum, P. vivax* is more prevalent in South-East Asian countries and India and is responsible for most complications along with *P. falciparum*.[9,39,46,] The majority of severe malaria cases are caused by *P. falciparum*. Approximately 10% of imported *P. falciparum* malaria cases in the US report severe illness with a 1% case fatality rate.[40] Generally, case fatality varies between 5% and 50% depending on the severity of the complication presented, the availability of optimal antimalarial therapy (parenteral artesunate), and the initiation of appropriate supportive measures.[41,42] Further information is in Supplementary file 1.[43–61]

Clinical Manifestation

Positive outcomes in the clinical management and prognosis of malaria depend on early recognition, detailed clinical information, and timely effective treatment. The signs requiring ICU management include multiple organ dysfunction, coma, stupor, severe anemia, acute respiratory distress syndrome (ARDS), hypoglycemia, shock, metabolic acidosis, AKI, and cerebral malaria.[41,58,62–64]

Approximately 10–15 days after a bite by an infected mosquito, acute febrile disease symptoms like fever, headache, shivering, and vomiting appear.[22,65,66] These symptoms are non-specific. As a result, severe malaria must be distinguished from bacterial sepsis, meningitis, intoxications, non-infectious causes of coma, viral encephalitis, viral hemorrhagic fevers (such as dengue, severe influenza, leptospirosis, and typhoid

fever), and rickettsial disorders (such as typhus and viral hepatitis) for effective management.[41,42,67,68] A typical case scenario is that headaches in malaria may be severe but are not associated with the neck stiffness or photophobia that are common in bacterial meningitis.[42,69]

The main manifestations and complications are under the later section, management of severe malaria.

Clinical Classification

Malaria may be uncomplicated or severe based on a patient's clinical presentation (Table 1).[25,69] Severe malaria is a medical emergency, with cerebral malaria and acute respiratory distress being the most common reasons for admission to the ICU.[69] For imported cases of malaria, early and accurate assessment of disease severity using the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II scoring system, simplified acute physiology score (SAPS II), or Glasgow coma score (GCS) is essential for effective management.[26]

Diagnostic Testing and Investigations

Diagnostic methods are fundamental in the prompt management of malaria in the ICU. The methods range from conventional procedures such as microscopy (peripheral blood smear and routine quantitative buffy coat) and RDT to more advanced techniques like loop-mediated isothermal amplification, polymerase chain reaction (PCR), and molecular-based point-of-care test. All of these methods detect the presence of parasites within the patient's blood (Table 2).[70–72] A detailed description of the methods is provided in Supplementary file 2.[73–113]

Treatment and Management

Management of malaria in the ICU depends on various factors, including whether the disease is uncomplicated or severe, the patient's physiology, and the pharmacodynamics/pharmacokinetics of the available antimalarial(s).[28,114]

Table 1
Classification of malaria; constructed according to the WHO guidelines for the treatment of malaria[3,7,31]; available for use without permission.

Class of malaria	Definition
Uncomplicated malaria	Patients who have symptoms of malaria with a positive result from microscopy or RDT but have no signs or symptoms of end-organ dysfunction.
Severe malaria[20,47]	Patients have >10% *P. falciparum* malaria parasitemia with signs of organ dysfunction. Patients have the following signs: prostration; multiple convulsions (>2 episodes in 24 h); GCS of <11 in adults or Blantyre Coma score of <3 in children; severe acidosis with serum lactate ≥5 mmol/L or serum bicarbonate of <15 mmol/L, which often manifests as respiratory distress; hypoglycemia, RBS <2.2 mmol/L; severe anemia, <5 g/dL in children or <7 g/dL in adults; renal dysfunction, serum creatinine >265 μmol/L; urea >20 mmol/L; coagulopathy; and shock.

GCS: Glasgow coma score; RBS: Random blood sugar; RDT: Rapid diagnostic test; WHO: World Health Organization.

Pharmacodynamic/pharmacokinetic characteristics

Artemisinin-based combination therapy (ACT)

Artesunate, artemether, and dihydroartemisinin (DHA) derivatives of artemisinin are the mainstays for the treatment of uncomplicated and complicated malaria (Tables 3 and 4) and multidrug-resistant *P. falciparum* malaria in Ghana.[27] Derived from sweet wormwood (*Artemisia annua*), these drugs have shown high tolerability and efficacy profiles in vulnerable groups such as infants, children, and pregnant women, although they have side effects, and have replaced chloroquine due to resistance.[115]

The antimalarial activity of the artemisinins is due to the endoperoxide trioxane moiety of this group of drugs. The endoperoxide bridges (deoxyartemisinin) are proven to be particularly important in artemisinins antimalarial activity. Upon a reaction with iron (Fe^{2+}), the endoperoxide bridges produce free oxygen radicals by a reductive process. These free radicals cause oxidative stress, which leads to the inhibition of protein and nucleic acid synthesis and decreased parasite survival.[116] Artesunate and DHA are active against the asexual stages of the parasite and gametocytes of species of the genus *Plasmodium*.[117] The derivatives of artemisinin are obtained from changes or substitutions in the tenth carbon position (C10) of the parent compound artemisinin.[118] These drugs exhibit high potency, rapid parasite clearance, and a wide therapeutic index. The artemisinin derivatives are converted rapidly to the active metabolite DHA once absorbed and changed into inactive metabolites by cytochrome P450 in hepatocytes.[116,119]

Artesunate is hydrolyzed rapidly to DHA, and the antimalarial activity of artesunate is predominantly mediated by DHA, which is approximately 90% bound to plasma proteins.[118–120] Artemether, on the contrary, is slowly converted to DHA. Critically ill patients with low serum albumin may experience intolerable effects of artemisinins because of decreased protein binding and high serum concentrations of DHA. Differences in responses to artemisinins may be due to variations resulting from auto-induction and inhibition of cytochrome P450 enzymes, particularly CYP2B6 and CYP3A4.[121]

The artemisinins have been formulated for oral, parenteral, and rectal administrations.[20,30] Orally administered artemisinin rapidly achieves ideal serum concentrations with good absolute bioavailability after a single oral dose of the drug for uncomplicated malaria.[122] However, physiological changes in patients that result in prolonged gastrointestinal time and reduced gastric motility, as seen in patients with ileus, may affect the bioavailability of orally administered artemisinin. The sodium salt of artesunate for intravenous (IV) administration is widely used in severe malaria.[122] Intramuscularly administered artemether exhibits variable bioavailability and absorption compared with the oral route.[123] Consequently, the parenteral route of administration is preferred for this agent. Furthermore, there may be a pharmacokinetic disadvantage when artemether is administered intramuscularly in patients with a reduced blood supply to the injection site, as observed in shock states.[124] There are indications that rapid but erratic absorption of rectally administered artesunate with peak serum DHA concentrations occurs within approximately 2 h, and this treatment may be useful for patients in whom oral administration is not possible.[125]

Table 2
Comparison among microscopy, RDT, and PCR for diagnosis of malaria[72]*

Parameter	Microscopy	RDT	PCR
Principle technique	Morphologic interpretation	Antigen and antibody binding	DNA amplification
Target diagnostic	All stages of the parasite (early trophozoite, mature trophozoite, schizont, and gametocyte)	*Pf*HRP2, *Pf*-pLDH, *Pv*-pLDH, pan-pLDH, aldolase, and *Pf*GAPDH	Small subunit rRNA/ssrRNA, *SICAvar* gene
Sensitivity	Up to 5 parasites/μL (the expert microscopist), 50–100 parasites/μL (the average microscopist)	50–250 parasites/μL	Below 5 parasites/μL
Specificity	High (unless for *P. knowlesi*), difficult to distinguish mixed and single infections	Moderate (limited to *P. falciparum* and *P. vivax*), cannot identify *P. ovale, P. malariae, and P. knowlesi*	High, can identify and differentiate among species
Time consumed	Up to 60 min	10–20 min	2–8 h
Interpretation	Quantitative	Qualitative	Quantitative and qualitative
Advantages	Low direct cost, can be stored for a long time	Simple, fast, more practical, and applicable method	Requires only a small sample
Disadvantages	Needs special equipment and well-trained technicians	Cannot be used for drug monitoring, more expensive	Supply costs, machinery fees, and training expenses

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PCR: Polymerase chain reaction; PfGAPDH: *P. falciparum* glyceraldehyde-3-phosphate dehydrogenase; PfHRP2: *P. falciparum* histidine-rich protein-2; Pf-pLDH: *P. falciparum* parasite lactate dehydrogenase; *Pv*-pLDH: *P. vivax* specific pLDH; pan-pLDH: Common human *Plasmodium* LDH; RDT: Rapid diagnostic test; rRNA: Ribosomal ribonucleic acid; *SICAvar*: Schizont-infected cell agglutination variant; ssrRNA: Single-stranded ribosomal ribonucleic acid.

Table 3
List of available ACTs used in the treatment of uncomplicated malaria and their dosages.[31]

Name of medication	Regime recommended	Dose according to body weight	
Artemether–lumefantrine (AL)	First-line recommended ACT for adults, children, pregnant women, and lactating mothers 3-day schedule; Patients ≥35 kg: 4 tablets (based on artemether 20 mg and lumefantrine 120 mg at 0 h and 8 h on day 1, every 12 hours on days 2 and 3)	Artemether + Lumefantrine Twice daily dosing regimen 5 kg to <15 kg 15 kg to <25 kg 25 kg to <35 kg ≥35 kg	 20 + 120 mg 40 + 240 mg 60 + 360 mg 80 + 480 mg
Artesunate–amodiaquine (AA)	Artesunate 4 mg/kg (range 2–10 mg/kg) and amodiaquine 10 mg/kg (range 7.5–15 mg/kg) once daily for 3 days	Artesunate + Amodiaquine Once daily dosing regimen 4.5 kg to <9 kg 9 kg to <18 kg 18 kg to <36 kg ≥36 kg	 25 + 67.5 mg 50 + 135 mg 100 + 270 mg 200 + 540 mg
Artesunate–mefloquine (ASMQ)	Artesunate 4 mg/kg Mefloquine 8 mg/kg once daily for 3 days	Artesunate + Mefloquine Once daily dosing regimen 5 kg to <9 kg 9 kg to <18 kg 18 kg to <30 kg ≥30 kg	 25 + 55 mg 50 + 110 mg 100 + 220 mg 200 + 440 mg
DHA–piperaquine	DHA 2 mg/kg and piperaquine 16 mg/kg once daily for 3 days	Dihydroartemisinin + Piperaquine Once daily dosing regimen 5 kg to <8 kg 8 kg to <11 kg 11 kg to <17 kg 17 kg to <25 kg 25 kg to <36 kg 36 kg to <60 kg 60 kg to <80 kg ≥80 kg	 20 + 160 mg 30 + 240 mg 40 + 320 mg 60 + 480 mg 80 + 640 mg 120 + 960 mg 160 + 1280 mg 200 + 1600 mg
Artesunate + sulfadoxine–pyrimethamine (AS + SP)	Artesunate 4 mg/kg given once daily for 3 days + single administration of 25/1.25 mg/kg sulfadoxine–pyrimethamine	Artesunate (Once daily for 3 days) + Sulfadoxine/Pyrimethamine (Single dose on day 1) 5 kg to <10 kg 10 kg to <25 kg 25 kg to <50 kg ≥50 kg	 25 + 250/12.5 mg 50 + 500/25 mg 100 + 1000/50 mg 200 + 1500/75 mg
Artesunate + pyronaridine (ASPY)		Artesunate + Pyronaridine Once daily dosing regimen ≥5 kg to <20 kg ≥20 kg 20 + 60 mg	 60 + 180 mg

Source: World Health Organization. (2010). WHO Guidelines for the treatment of malaria.
ACT: Artemisinin-based combination therapy; DHA: Dihydroartemisinin.

Table 4
Summary of treatment options for severe malaria.[31]

Medication	Loading dosing	Maintenance dosing	Recommended dosage	Special considerations
IV artesunate			Recommended first line for severe malaria in adults, children, and pregnant women: For patients <20 kg: 3 mg/kg per dose; For patients >20 kg: 2.4 mg/kg per dose Administer one dose at 0 h, 12 h, and 24 h. Complete treatment with 3 days of ACT once the patient can tolerate orals after 24 h.	Where ACTs are not available, options for follow-up treatment after completion of parenteral treatment include: Oral doxycycline: 100 mg twice daily for adults, 2.2 mg/kg (max dose 100 mg) for pediatrics Oral clindamycin: 20 mg/(kg·day) in 3 divided doses for adults and children
IM artemether	3.2 mg/kg	1.6 mg/kg	An initial dose of 3.2 mg/kg followed by a maintenance dose of 1.6 mg/kg daily. Administer a dose at 0 h, 8 h, and 24 h. Complete treatment with 3 days of ACT once the patient can tolerate orals after 24 h.	
IV/IM quinine Dose adjustments required for patients with renal impairment	20 mg/kg	10 mg/kg	Loading dose: 20 mg/kg followed by a maintenance dose of 10 mg/kg. Must be given as an infusion as administration as bolus may result in lethal hypotension.	

Source: World Health Organization. (2010). WHO Guidelines for the treatment of malaria.
ACT: Artemisinin-based combination therapy; IM: Intramuscular; IV: Intravenous.

Owing to their rapid parasiticidal activity, the artemisinins are extremely valuable considering the condition of most patients admitted to the ICU. However, the short half-life of the artemisinins means they are not reliable for prophylaxis. Furthermore, repeated dosing of these agents leads to increased drug clearance, potentially due to auto-induction of hepatic enzymes, although they achieve initial parasite clearance rates by a factor of 104 per 48 h during the asexual cycle of the parasite.[126] This limitation in the monotherapy use is offset with combination products such as DHA–piperaquine and artemether–lumefantrine for oral administration once the patient can tolerate feeding and in uncomplicated malaria. Piperaquine and lumefantrine have long plasma half-lives.[127,128]

Some pharmacokinetic changes such as reduced gastrointestinal motility, changes in total body water and fat content, and increased plasma volume in pregnancy may alter the absorption and distribution resulting in low serum concentrations of artesunate, artemether, and DHA in pregnant women.[129,130] However, artemisinin-based combination therapies (ACTs) are recommended as first-line antimalarials by WHO for managing uncomplicated malaria in the second and third trimesters of pregnancy.[131]

Artemether–lumefantrine is available as a dispersible tablet and can be administered easily via a nasogastric tube. This ACT has a short duration of action and a broad therapeutic index, reducing the incidence of drug accumulation and hence untoward effects.[132] QT prolongation may occur with the administration of DHA–piperaquine; thus, this ACT should be avoided in patients with clinically significant arrhythmias.[133,134]

As a potential partner drug for artesunate, pyronaridine was developed in China in the mid-1970s, using the nucleus of an earlier antimalarial compound (mepacrine) with an added amodiaquine side-chain.[135] Pyronaridine was used by clinicians extensively as monotherapy for *P. falciparum* and *P. vivax* infections in China.[136] However, concerns about observed resistance *in vitro* resulted in its recommendation to be used in combination with sulfadoxine and pyrimethamine, and primaquine.[135]

As a treatment option for uncomplicated malaria, Artesunate-pyronaridine is taken once daily for 3 days, provided as tablets for adults and children over 20 kg, or in granules for children and infants between 5 kg and 20 kg.[137]

The mode of action of pyronaridine is unclear, with several possible mechanisms reported in Croft et al.,[138] but it has shown potent activity *in vitro* against *P. falciparum*.[138,139] In addition, pyronaridine – as monotherapy or as a combination with artesunate – has shown potency against *P. falciparum* with resistance to other antimalarials, including chloroquine, cycloguanil, amodiaquine, and sulfadoxine–pyrimethamine.[140,141]

Quinine

Quinine, a cinchona alkaloid derived from the dried bark of the Cinchona tree, has long been used for the management of severe malaria, notably in pregnancy.[142] Quinidine, which is the enantiomer of quinine, is used as an antiarrhythmic agent.[143,144] Quinine was the mainstay for malaria treatment until the development of newer antimalarials such as artemisinins in recent years. However, quinine continues to play a key role in managing malaria amidst the challenge of chloroquine resistance, and oral quinine can be used as an alternative to first choice artemether–lumefantrine in managing malaria during treatment failure.[20]

Quinine acts by interfering with the detoxification processes and heme polymerization within the parasite's food vacuole and inhibits parasitic growth.[145] Quinine exhibits high schizonticidal activity against the asexual erythrocytic forms of *P. falciparum* and has activity against the gametocyte stages of *P. vivax* and *P. malariae*.[146]

Oral and parenteral forms of quinine as sulfate and dihydrochloride salts, respectively, are commonly used in clinical practice.[20] However, intramuscular (IM) administration of the drug leads to abscess formation, hence the IV route is often preferred.[146]

The pharmacokinetic parameters of quinine vary among different age groups and disease states.[147] Quinine displays a rapid absorption profile when administered orally and parenterally. Furthermore, quinine is widely distributed in plasma and predominantly protein bound, especially to alpha 1 acid glycoprotein, which is an acute phase reactant protein that is often elevated in patients with acute malaria.[148] High levels of alpha

1 acid glycoprotein in severe malaria reduce the levels of free quinine, hence toxicity to this drug may be uncommon. Quinine undergoes elimination through hepatic biotransformation by cytochrome P450 3A4 enzymes, with a small fraction excreted unchanged in the urine.[149] Children exhibit a low volume of distribution compared with adults, whose elimination is poor with reduced clearance. A low volume of distribution and clearance is also often observed in patients with severe malaria, probably due to increased levels of alpha 1 acid glycoprotein.[148]

Quinine has a narrow therapeutic index. Therefore, signs of toxicity may be apparent at therapeutic serum concentrations. In states of significant hepatic impairment, reduced biotransformation of the drug to nontoxic metabolites for excretion may lead to an increase in free drug levels and hence toxicity even when normal doses are administered.[149] There are no dosage adjustments for quinine in mild to moderate renal impairment making it generally not recommendable in cases of severe malaria.[30] The frequency of quinine administration is altered per estimated creatinine clearance (CrCL), that is, every 8–12 hours if CrCL is 10–50 mL/min and every 24 hours if CrCL <10 mL/min. No dosage adjustment is required in mild to moderate hepatic impairment (Child-Pugh Class A and B) and should be avoided in severe hepatic impairment.[150] Therapeutic doses are safe and recommended for use in the first trimester of pregnancy. However, quinine use is associated with hypoglycemia in pregnant women and periodic blood glucose monitoring may therefore be required.[151,152]

Common signs of quinine toxicity include nausea, vomiting, tinnitus, reversible hearing loss, headache and visual disturbances, and others. Neural, retinal, and auditory impairments are classic signs of cinchonism from drug toxicity.[74,153] Intolerance may be minimized when oral forms of quinine are administered with food. A rapid IV injection may lead to hypotension. Quinine-induced hypoglycemia may also occur.[154] Hemolytic anemia has been reported in patients treated with quinine, especially those with glucose-6-phosphate dehydrogenase deficiency.[155]

Clindamycin

Clindamycin, which is a lincosamide antibiotic with gram-positive and anaerobic microbial coverage, is an effective treatment for uncomplicated malaria caused by *P. falciparum*.[156,157] It is often used in combination with quinine, and the efficacy of this combination has been reported to be comparable to ACT.[20,158,159] Clindamycin inhibits protein synthesis by binding to the 50S ribosomal subunit and suppressing the initiation of peptide chain synthesis.[160] Clindamycin is available in oral formulations (clindamycin hydrochloride and clindamycin palmitate) and IV preparations (clindamycin phosphate). Oral forms of the drug are well absorbed from the gastrointestinal tract. However, absorption may be reduced in patients with gastrointestinal mucosal edema, as is reported in cases of heart failure.[161]

Clindamycin undergoes hepatic metabolism into active metabolites and is subsequently excreted into the bile, with only a small fraction excreted by the kidneys. The half-life of the medication is not altered in patients with kidney impairment, but hepatic impairment may decrease elimination and prolong the half-life.[161] No dosage adjustments are recommended for patients with mild to moderate hepatic impairment. Consequently, the drug is used with caution in severe cases of hepatic impairment with periodic monitoring of liver enzymes during therapy.[162] Co-administration with drugs that are cytochrome P450 enzyme inducers, such as rifampicin, may reduce the serum concentration of clindamycin and may affect the minimum effective concentration and minimum inhibitory concentration.[157]

Metabolites of clindamycin are effective against *P. falciparum*, although the drug slowly accumulates in the parasite and produces a delayed effect. [159]Evidence is available according to Saito et al.[159] for the safe use of clindamycin in pregnancy, and a quinine combination with clindamycin has demonstrated safety with acceptable cure rates in pregnant mothers. However, gastrointestinal disturbances are common side effects reported with clindamycin use as with *Clostridioides difficile* diarrhea.[163–165]

Management of severe malaria

Treatment for severe malaria encompasses specific antimalarial treatment and supportive care provided to address physiologic dysfunction resulting from the presence of malaria parasites. The provision of supportive care is instrumental in disease management due to the organ dysfunction that is usually present in such patients. If not addressed promptly, this organ dysfunction may result in poor outcomes such as severe morbidity with residual long-term effects or mortality, particularly in patients with cerebral malaria. The mortality rate in cerebral malaria is 15%–20%, even when treated, and rises to >30% in patients with multiple organ dysfunction who are managed in the ICU. In this review, supportive care will be grouped into general and specific measures to address the complications.[166]

General measures

Fluid therapy

The findings from the Fluid Expansion as Supportive Therapy (FEAST) trial[167] created a paradigm shift in the fluid management of critically ill patients, with a movement from liberal fluid therapy to conservative fluid therapy. The current recommendation is individualized conservative fluid management for patients with severe malaria.[168] Key factors that affect fluid administration include peripheral perfusion, venous filling, blood pressure, skin turgor, and urine output, and these parameters require continuous monitoring in all patients. Patients in the ICU of well-resourced settings benefit from the use of more sophisticated invasive and non-invasive techniques to estimate intravascular volume and aid decision-making on fluid management. These techniques include invasive procedures such as global end-diastolic volume index and pulmonary artery occlusion pressure, and non-invasive procedures such as echocardiograms to estimate stroke volume and ultrasound of the inferior vena cava diameter and collapsibility.[168]

Nutrition

Feeding should commence as soon as the patient can eat or drink. For patients who present with reduced consciousness, feeding should be initiated through a nasogastric tube with variable meal preparations dependent on geographical location. There is a risk of pneumonia caused by aspiration of gastric contents, particularly in patients with reduced consciousness.

Therefore, once feeding is initiated, IV fluids are reduced gradually until completely discontinued when the patient's maintenance requirement is provided by the feeds given.[169,170]

Hyperpyrexia

High temperatures are common in patients with severe malaria and demonstrate the host response to the endogenous pyrogens released when schizonts rupture.[169] Adopting stringent measures to ensure temperature control is crucial, especially considering the association between high temperatures and convulsions in children. Temperature control may also help reduce long-term neurologic outcomes in children with cerebral malaria. Management of hyperpyrexia includes administration of paracetamol 15 mg/kg body weight every 6 hours (maximum dose 1000 mg/day) in pediatrics and 1 g every 6 hours for adults. The route of administration can be oral or rectal (suppository), depending on the patient's ability to swallow. In cases where fever persists, ibuprofen 10 mg/kg every 6 hours for pediatrics, and 400 mg every 8 hours for adults can be administered alternatively with paracetamol. However, non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen are associated with renal dysfunction and often low platelet counts and should be used with caution.[169,170]

Specific measures

Severe malaria requires prompt parenteral antimalarial treatment once a diagnosis has been made. Parenteral artemisinins – artesunate, artemether, and other antimalarials such as quinine – are all suitable for treating severe malaria.[20,148,171,172] In western Cambodia, studies on artemisinin alone have reported a parasite clearance time (PCT) of 84 h. However, this time was related to artemisinin resistance.[173,174] In African patients, the PCT observed is much lower (32 h) than that reported in western Cambodia. A delayed PCT of 72 h is reported as an *in vivo* predictor of treatment failure and an indicator of choice for suspected artemisinin resistance in *P. falciparum*.[175,176] The estimated PCT is 48 h for both artesunate + amodiaquine and artemether + lumefantrine. Parasitemia can be measured daily or only on days 0, 2, and 3 in accordance with WHO guidelines; however, this process does require frequent sampling.[177]

Artesunate – IV or IM – is recommended as the first-choice treatment for severe malaria, to be administered for a minimum of 24 h, following its demonstrated superiority in reducing mortality as well as its safety profile when compared to alternatives such as quinine. The current dosing regimen is 3 mg/kg for children weighing <20 kg, and 2.4 mg/kg for patients >20 kg given every 12 hours for at least 24 h. Upon completion of the parenteral treatment, once a patient can tolerate orals, the recommendation is to continue and complete treatment with a full course of oral ACTs. In the absence of IV artesunate, alternative initial parenteral medications that can be used are included in Table 4.[20]

Quinine can be administered intravenously in a continuous infusion or given intramuscularly.[20,171] The recommended dosage of quinine is a loading dose of 20 mg/kg followed by a maintenance dose of 10 mg/kg every 8 hours. In settings where the ACTs are not readily available, parenteral treatment can be continued with clindamycin or doxycycline for 7 days following the last parenteral dose (Table 4).[20,94,147]

It is estimated that 6% of children hospitalized with severe *P. falciparum* malaria in Africa may present with associated bacteremia.[178] WHO recommends that all children with severe malaria should receive empirical antibacterial therapy in addition to parenteral artesunate, especially in places where definitive therapy cannot be established through bedside examination or simple laboratory tests. For adults, antibacterial therapy is only suggested when a clinical syndrome is compatible with a serious bacterial infection, particularly in critically ill patients.[179]

Specific Complications

Cerebral malaria

Cerebral malaria is a medical emergency requiring an urgent clinical assessment and treatment. Signs of this complication include altered consciousness, convulsions, ataxia, hemiparesis, and other neurologic and psychiatric impairments. The recommendation is that all patients with positive diagnostic tests for *P. falciparum* malaria with neurologic manifestations of any degree should be treated as cases of cerebral malaria.[41,180]

Diagnosis of cerebral malaria requires the presence of asexual *P. falciparum* in a peripheral blood smear, in thick and thin blood smear films. Sequestration of parasitized RBCs may cause the absence of parasites in some patients even though they may have cerebral malaria. The recommendations are to obtain at least three smears 6 h apart for examination; all three smears should be negative before excluding cerebral malaria. Other useful tests include RDT (antigen detection test) and PCR, although examinations using cerebrospinal fluid (CSF) are necessary to exclude other causes.[41,181,182]

According to Misra et al.,[182] the CSF in cerebral malaria is generally normal but cases with mild pleocytosis (10–50 cells/mm^3) and protein up to 200 mg/dL must be attended to. The review further indicates that computed tomography and magnetic resonance imaging usually are normal or show edema and cortical or subcortical infarcts in the watershed zone in 15%–20% of patients. Other findings include electroencephalography results showing a diffuse slowing, spike-wave discharges, and burst suppression pattern.

Treatment of cerebral malaria must be prompt while awaiting confirmation of the diagnosis. Treatment options include parenteral artemisinin derivatives or quinine. In a randomized control trial involving adult participants, artesunate reduced mortality by 34.7% compared to quinine, and reduced the occurrence of convulsion, coma, and hypoglycemia. In older patients and patients with cardiac disease, recommendations are that the corrected QT (QTc) interval should be monitored and quinine discontinued if the QTc interval exceeds 25% of the basal value. A prompt oral switch should be completed as soon as the patient is capable.[182,183]

Convulsions

Convulsions may be seen in patients diagnosed with cerebral malaria as well as in those without a cerebral malaria diagnosis. In children under 5 years, convulsions may be due to untreated hyperpyrexia (febrile convulsion). Management principles require a clinician to ensure a patent airway, check blood

glucose and ensure normoglycemia, and abort the convulsion. Anticonvulsants that may be used include IV or rectal diazepam, lorazepam, midazolam, or IM paraldehyde.[20,29,41]

With increasing insight into the pathogenesis of cerebral malaria, several adjunctive treatments have been proposed including heparin, prostacyclin, desferrioxamine, pentoxifylline, low-molecular-mass dextran, urea, aspirin anti-tumor necrosis factor (TNF) antibody, cyclosporine A, dichloroacetate, adrenaline, hyperimmune serum, *N*-acetylcysteine, and bolus administration of albumin. However, all these treatments have been ineffective and are not recommended. Steroids have been proposed as a strategy to combat cerebral edema noted in patients with cerebral malaria; however, there is evidence of no benefits and an increased risk of gastrointestinal bleeding and seizures. This makes steroids an inappropriate choice for managing edema in patients with cerebral malaria.[20,29]

Hematologic complications

Severe anemia

WHO defines severe malaria as a hemoglobin (Hb) concentration of ≤5 g/dL or hematocrit (Hct) of ≤15% in children less than 12 years of age, or Hb <7 g/dL with Hct <20% in adults with a parasite count >100,000/μL. The pathogenesis of anemia in severe malaria is multifactorial. Hemolysis of parasitized cells, increased clearance of abnormal erythrocytes (erythrocytes with antibody coating or with reduced deformability) by the spleen and dyserythropoiesis have been outlined as major contributors to severe malarial anemia.[184] Artesunate-induced hemolysis, also referred to as post-artemisinin delayed hemolysis (PADH), has recently been reported as a possible contributor to anemia in patients with severe malaria. The mechanism, although not fully understood, is speculated to be a result of the breakdown of RBCs following the destruction of the parasites after artesunate administration. This has been reported to occur within days to 4 weeks post-artesunate administration.[47] Transfusion of fresh cross-matched blood is recommended in patients with severe malaria; however, given the variations in pathophysiology and clinical presentation, the decision to transfuse must be taken on a patient-to-patient basis.[20,184,185] The practice of exchange transfusions has been reported anecdotally, but there are currently no recommendations for its use as there is no consensus on the indications and procedure, advantages, and risks involved.[20]

Coagulopathy

The loss of eGC in severe malaria is associated with vascular dysfunction, endothelial activation, and reduced availability of nitric oxide.[18] Microvascular obstruction by fibrin and thrombi occurs due to endothelial damage and dysregulated activation of the coagulation pathway. Thrombocytopenia is also common as a result of this process. However, clinically evident disseminated intravascular coagulation in severe malaria is less than 5%.[166] Treatment of disseminated intravascular coagulation (DIC) involves transfusion with blood products – fresh whole blood, fresh frozen plasma, and platelets, if available. Also, an injection of vitamin K should be administered if available.[20]

Renal complications

AKI defined by the "Kidney Disease: Improving Global Outcomes" (KDIGO) as either an increase in serum creatinine by at least 0.3 mg/dL within 48 h, an increase in serum creatinine to at least 1.5 times the baseline level within the previous 7 days, or a decrease in urine output to less than 0.5 mL/(kg·h) for 6 h.[186] Extensive intravascular hemolysis, hemodynamic instabilities, parasite sequestration, microvascular dysfunction, and endothelial activation act in synergy in patients with severe malaria and result in kidney injury. Histopathological features of malaria-related AKI include acute tubular necrosis and sometimes interstitial nephritis and glomerulonephritis.[186–188] The prevalence of AKI was recently reported to range from 20% to 40% among adults and children with severe malaria, with some studies reporting an AKI incidence of 59% in children.[187] Therefore, it is necessary to ensure that all patients diagnosed with severe malaria are screened for AKI. Management is largely supportive and involves maintaining optimal fluid and electrolyte balance (for patients with pre-renal causes) and renal replacement therapy – hemodialysis or peritoneal dialysis – where indicated.[20] The prognosis for malaria-related AKI is good as it resolves in days to weeks, although 5% of patients with severe malaria develop chronic kidney disease.[187]

Respiratory complications

Respiratory distress is a common description for children who have obvious abnormal breathing and use more effort than usual.[41] Up to 25% of adults and 40% of children with severe *P. falciparum* malaria develop respiratory distress.[189] In patients with severe malaria, the respiratory distress may be a result of pulmonary edema, an associated lower respiratory tract infection, or ARDS.[169]

Metabolic acidosis is due to the accumulation of lactate and other organic acids produced by the gastrointestinal tract. Clinically, metabolic acidosis presents as abnormal breathing patterns and/or coma, with a poor prognosis except when the condition results from severe anemia.[29,42,188,190] Factors such as severe anemia, hypovolemia, impaired hepatic gluconeogenesis, and reduced clearance due to AKI worsen the disorder.[41,186]

Effective management of respiratory complications in severe malaria must target the underlying cause. For a well-resourced setting, it is recommended that blood gasses and arterial pH are measured, in addition to continued monitoring of oxygenation by oximetry. Generally, the management recommendations are to[20,41,169]: (1) Correct any reversible cause of acidosis like dehydration and severe anemia with an IV infusion at the most accessible peripheral site or an intraosseous infusion if the former is impossible. Caution should be taken not to give excessive fluid as this may precipitate pulmonary edema. (2) Give screened whole blood (10 mL/kg) over 30 min and a further 10 mL/kg over 1–2 h without diuretics if Hct <18% or Hb <6 g/dL in a child with signs of metabolic acidosis. Monitor the respiratory rate and pulse rate every 15 minutes and if either of these parameters shows any increase, then transfuse more slowly to avoid precipitating pulmonary edema. (3) Continue clinical observations to monitor the response by repeated measurement of acid–base status, Hct or Hb concentration, and glucose, urea, and electrolyte levels.

Hypoglycemia

Defined as blood glucose <2.2 mmol/L in adults and <3 mmol/L in young children. Although widely used as a definition in the setting of malaria, a blood glucose level of 3.9 mmol/L is more adequate in diagnosing hypoglycemia in adults.[20,191] The pathogenesis of hypoglycemia in patients with malaria is not completely understood but is postulated to occur due to parasite glucose consumption and/or impaired gluconeogenesis.[176] Therefore, the maintenance fluid administered must contain dextrose (commonly, 5% dextrose is used or 10% in patients with recurrent hypoglycemia) to maintain normoglycemia.[175] It is also important to note that the administration of quinine or quinidine can result in iatrogenic hypoglycemia.[41] Consequently, blood glucose monitoring is crucial in patients with severe malaria.

Conclusions

Malaria remains a significant cause of morbidity and mortality worldwide. Clinicians must have a high index of suspicion when patients present with symptoms and complications, especially with the current challenges imposed by antimicrobial resistance. Diagnosis of malaria is by an RDT and/or microscopy, and once diagnosed, appropriate treatment must be prompt using ACTs or parenteral artesunate. Furthermore, patients in the ICU must be monitored closely and managed for complications when they arise.

Future Research Directives

Understanding the mechanisms underlying eGC breakdown in malaria remains a critical aspect of disease management in the ICU. Specific areas of future research are listed in Supplementary File 3.

Author Contributions

All authors contributed equally to the original draft and review of the manuscript. George Akafity reviewed, edited, and finalized the manuscript.

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Ethics Statement

No ethical approval or informed consent was required for this review.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI Disclosure Statement

No artificial intelligence program was used in writing and reviewing the manuscript.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2023.09.002.

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