Chapter 13
Malaria

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Introduction

Plasmodium spp. are a protozoan parasite that causes malaria. It has been a companion to the human species since our inception, before we started our long journey out of Africa 60.000 years ago, and has shaped our population, genetics, and behaviors like no other organism [1, 2]. Malaria presentation ranges from a mild febrile illness to a life-threatening disease with multisystem organ failure. Severe malaria belongs in the intensive care unit due to the multitude of potential complications, remaining a major cause of mortality worldwide. In the context of a globalized community and changing climate, borders' relevance is ever decreasing. Critical care providers familiar with this disease will be equipped to deliver timely and appropriate care in the face of this changing epidemiology.

Epidemiology

Malaria is intrinsically linked to the *Anopheles* mosquito, and only a minority of its species are appropriate vectors [3]. Disease incidence is influenced by interactions between environmental factors affecting vector survival and certain characteristics

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of the vector itself, like resilience, population density, efficiency, and biting habits [3, 4]. As such, in conditions of natural disasters, war, and poverty, most of the potential anopheline vector species will triumph, but only a few of them could be responsible for ongoing endemic infections in certain regions, e.g., *Anopheles gambiae* complex in Africa.

Humans have attempted, and partially succeeded, at altering that balance. Although once prevalent throughout much of the inhabited world, after World War II, malaria was eradicated from the United States, Canada, Europe, and Russia. Nonetheless, it persisted in the tropics. During the ensuing decades, improvement in malaria control was few, and morbidity worsened in many areas due to resistance of mosquitoes to insecticides and resistance of the parasite itself to antimalarials [3, 4].

Only recently, a new large effort to control and eventually eradicate malaria has been initiated including renewed ways of delivering insecticides (e.g., impregnating nets or indoor residual spraying), prompt treatment, and prophylactic treatment of high-risk groups [5]. This has led to documented decrease in levels of morbidity and mortality in parts of Africa, Asia, and Oceania with relatively low levels of transmission intensity [6]. Despite these efforts, epidemiologic changes in the coming years are hard to predict given the unproven impact of the above measures on highly endemic regions and the potential implications of climate change [7].

Malaria in Endemic Countries

In 2017, 219 million cases and 435.000 deaths attributed to malaria were identified, remaining endemic in 91 countries [8]. This disease remains a disproportionate burden in tropical and subtropical regions of Africa, Asia, and Central and South America (Fig. 13.1). Children and pregnant women constitute the main high-risk groups. The first one accumulates most of the deaths, and the second one is susceptible to significant morbidity in their offspring when infected by *P. falciparum*, including many deaths secondary to low birth weight.

Malaria mortality is influenced by the complex interaction between immunity and specific *Plasmodium* spp. virulence. Wherever there is year-round transmission, *P. falciparum* is usually primarily involved, and, although adults are usually immune, children remain vulnerable and accumulate most of the mortality. This is the case in sub-Saharan Africa, where the World Health Organization reports 90% of malaria deaths occur [8]. In other regions of Asia and Central and South America, transmission is intense but concentrated over a few months out of the year. As such, people remain susceptible into their adulthood, but since both *P. falciparum* and *P. vivax* have similar incidence, mortality is lessened. These later regions are the most influenced by changing economic, social, or environmental landscapes [4].
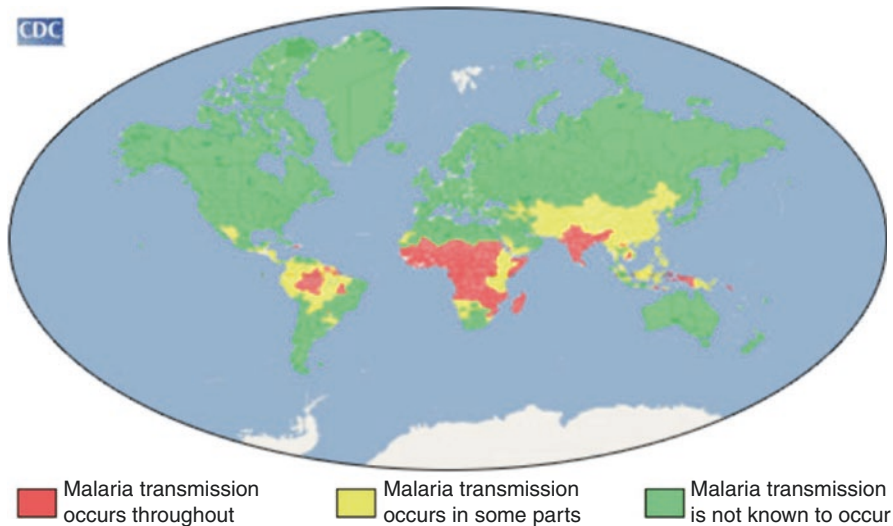
Fig. 13.1 Malaria distribution worldwide. (Source CDC)

In highly endemic countries, the effects of malaria are far-reaching. Beyond mortality, it exerts a major toll on child development and significant school and work absenteeism. In this way, millions of dollars are lost among the poorest citizens of the poorest countries of the world [8, 9]. Interestingly, a direct correlation has been made between malaria elimination and income growth, with recognized factors including increase in productivity, foreign investment, and economic networks within the country [9].

Malaria in Travelers

In recent decades, there has been a progressive increase in international travels, both for business and tourism. Consequently, there has been a progressive increase in tropical disease diagnosed in returning travelers [10, 11]. Among them, malaria is the most common documented cause of febrile illness in travelers returning from the tropics to developed countries, representing 5–29% of patients presenting to a specialist and 26–75% of the patients admitted to the hospital [10, 12–15].

In the United States, almost all the cases occur in patients that have recently traveled to regions with ongoing transmission. Nonetheless, malaria is also rarely transmitted when imported parasites are transmitted by local anopheline mosquitoes, by blood products or through congenital spread of infection [16]. As of 2015, the CDC reports an upgoing trend in cases of malaria reported in the United States, with the reduction seen between 2014 and 2015 attributable to changing traveling patterns in the face of the Ebola outbreak in West Africa (Fig. 13.2) [16].
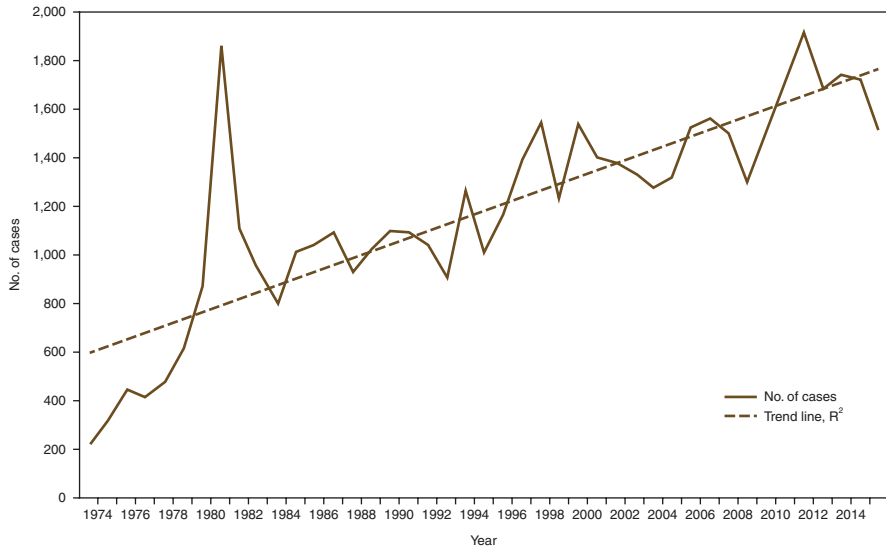
Fig. 13.2 Malaria cases in the United States. (Source CDC)

Plasmodium: A Closer Look

The genus *Plasmodium* encompasses over 200 species, of which only 5 are considered infectious to human beings. *P. falciparum* produces the highest levels of blood parasitemia and sequesters in key tissues, and it is the main cause of severe malaria. *P. vivax* usually produces milder disease, but it is increasingly recognized as a cause of severe malaria as well, especially in Asia and South America [3]. Two sympatric subspecies of *P. ovale* exist, *P.o. curtisi* and *P.o. wallikeri*, and tend to produce milder disease, as does *P. malariae* [17]. All these species are transmitted by the female *Anopheles* mosquito. *P. knowlesi* is believed to be mainly a zoonotic infection transmitted from macaques, and its importance is increasingly recognized, especially in Malaysia [18, 19]. Co-infections with different species can be seen in up to 10–30% of cases [20].

Parasite Life Cycle

Female mosquitoes carry sporozoites in their salivary glands, which may determine specific feeding habits including increased attraction for humans and more frequent and smaller feeds [21, 22]. These motile sporozoites are inoculated, circulate to the liver, and actively infect hepatocytes, causing asymptomatic liver infection (Fig. 13.3). Once they invade hepatocytes, they will mature over 7–10 days to produce schizonts. These schizonts rupture, releasing thousands of merozoites into the
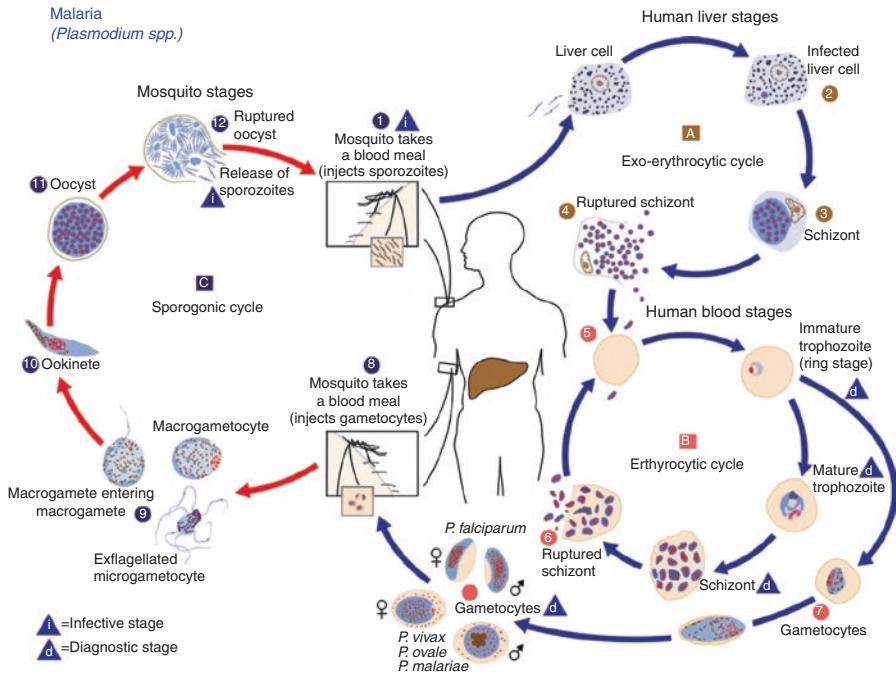
Fig. 13.3 Malaria life cycle. (Source CDC)

bloodstream that quickly invade erythrocytes, beginning the asexual erythrocyte stage (Fig. 13.3). Merozoites develop into trophozoites that will become schizonts over a period of 48 h in the cases of *P. falciparum*, *P. vivax*, and *P. ovale*, 72 h in the cases of *P. malariae*, and 24 h in the case of *P. knowlesi*. Schizonts will then rupture, causing hemolysis and releasing many merozoites with every cycle causing clinical illness. Some erythrocytic parasites will develop into sexual gametocytes. When taken up by the mosquito, a female and a male gametocyte have the capability of fusing to produce a zygote. After multiple steps, sporozoites are generated in the anopheline salivary glands, completing the cycle. *P. vivax* and *P. ovale* generate hypnozoites in the liver that can lead to recurrent disease months or years after the initial infection (Fig. 13.3).

Pathogenicity

A key pathogenic characteristic of *P. falciparum* is its ability to mediate adherence of infected erythrocytes to endothelial cells. Erythrocytes that are infected with more mature stages of this parasite remain within small tissue vessels, including the brain. This process is termed cytoadherence, and it is thought to be caused by the expression of *Plasmodium falciparum* erythrocyte membrane protein 1 (Pfemp1) in

the erythrocyte membrane. Parasites avoid passing through the spleen where abnormal erythrocytes would be cleared while also being more likely to cause local tissue damage. This protein is member of the var family and continuously changes among more than 60 subtypes, impairing antigen recognition and host response [23, 24]. Moreover, subtypes of Pfemp1 may confer tissue specificity, as is the case with the affinity to endothelial protein C receptor and cerebral malaria [25]. The severity of disease is associated with both the increased parasitemia and a higher biomass of sequestered parasites [26].

Reinforcing a previously made point, *P. falciparum*'s life cycle requires a year-around transmission to survive, only possible in regions of the world with a high endemic rate. Given their capability to develop into hypnozoites, *P. vivax* and *P. ovale* can inhabit subtropical areas with marked seasonal patterns, remaining dormant until optimal conditions are met.

Immunity

Human immunity against malaria is still incompletely understood. Nonspecific host defense mechanisms control the infection initially [27]. After that, both humoral and cellular immunities are thought to contribute to protection.

In endemic countries where *P. falciparum* is prevalent, disease occurs primarily in children. The first few months of life are normally spared, likely due to protection conferred by maternal antibodies. Young children are infected frequently, experiencing repeated febrile malaria illness and being at high risk of severe disease. With repeated exposure, children develop partial immunity. Gradually, they gain protection against severe malaria and then increasingly to symptomatic illness and eventually strong protection against infection. Nonetheless, antimalarial immunity is incomplete, and malaria can occur in individuals of any age, and asymptomatic parasitemia is common in adults and older children living in areas with high transmission rates.

It is important to underline this only occurs in regions where there is constant exposure, year-round, but it is absent in areas where exposure is more seasonal or episodic. A corollary is adults that return to a highly endemic area after extended stay in a non-endemic area are at increased risk.

Genetics

No other disease has shaped human genetics as much as malaria [28]. Erythrocytes are the main host cell for *Plasmodium* species in our bodies, and certain changes may render them more or less susceptible to infection. Specific changes in hemoglobin generate environments that are more hostile to the parasite, e.g., decrease parasite growth at low oxygen tension or reduce cytoadherence [29].

Over the millennia, these changes have accumulated in certain regions, corresponding to the distribution of malaria prior to modern interventions [28]. Simultaneously, these changes have shaped the epidemiology of *Plasmodium*, probably the best example being *P. vivax*. As mentioned above, it is dependent on the presence of Duffy antigen in the erythrocyte membranes. As the population in Africa accumulated mutations rendering their erythrocytes Duffy-negative, *P. vivax* has all but disappeared from Africa, and it is now located in Asia and Central and South America [30, 31].

Clinical Presentation

Uncomplicated Malaria

Most cases of malaria, including when caused by *P. falciparum* malaria, present as a mild febrile illness. The incubation period is typically 12–14 days with *P. falciparum* and a little longer for the non-falciparum species. The incubation period may be longer in patients that have received certain antibiotics (tetracyclines, trimethoprim-sulfamethoxazole, quinolones, or macrolides) or inhabitants of endemic areas. Non-falciparum malaria is more likely to present with highly synchronous infections, leading if untreated to regular cycles of fever every 48 (*P. vivax* and *P. ovale*) or 72 (*P. malariae*) hours, often with minimal symptoms between episodes. Nonspecific symptoms are common like headache, malaise, myalgias, arthralgias, rigors, confusion, nausea, vomiting, diarrhea, abdominal pain, etc. Physical exam findings maybe include signs of anemia, jaundice, splenomegaly, and mild hepatomegaly, but may well be absent. Rash and lymphadenopathy are not typical in malaria and should trigger suspicion for alternative possibilities. Laboratory studies commonly show anemia, thrombocytopenia, and liver and renal function abnormalities.

Severe Falciparum Malaria

Severe malaria has a specific definition by the World Health Organization, applicable to both endemic and non-endemic cases (Table 13.1) [32]. It is mostly caused by *P. falciparum*, although *P. vivax* is increasingly recognized as a cause in certain regions.

Severe malaria is normally a rapidly progressing disease. One series of imported malaria reported a median of 9.5 days (IQR 3-14) between return from a malaria-endemic area and hospital admission [33]. Progression to severe disease is highly variable, but the best available evidence reported a mean duration of symptoms of 5.5 days before ICU admission [34].

Table 13.1 Criteria for severe malaria

Impaired consciousness: A Glasgow coma score <11 in adults or a Blantyre coma score <3 in children
Prostration: Generalized weakness so that the person is unable to sit, stand, or walk without assistance
Multiple convulsions: More than two episodes within 24 h
Acidosis: A base deficit of >8 mEq/L or, if not available, a plasma bicarbonate level of <15 mmol/L or venous plasma lactate ≥5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, labored breathing)
Hypoglycemia: Blood or plasma glucose <2.2 mmol/L (<40 mg/dL)
Severe malarial anemia: Hemoglobin concentration ≤5 g/dL or a hematocrit of ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) with a parasite count >10,000/μL
Renal impairment: Plasma or serum creatinine >265 μmol/L (3 mg/dL) or blood urea >20 mmol/L
Jaundice: Plasma or serum bilirubin >50 μmol/L (3 mg/dL) with a parasite count 100,000/μL
Pulmonary edema: Radiologically confirmed or oxygen saturation <92% on room air with a respiratory rate >30/min, often with chest indrawing and crepitations on auscultation
Significant bleeding: Including recurrent or prolonged bleeding from the nose, gums, or venepuncture sites; hematemesis or melena
Shock: Compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mmHg in children or <80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitemia: *P. falciparum* parasitemia >10%

Adapted from World Health Organization, Global Malaria Programme [32]

Diagnosis

Fever in a Returning Traveler: A Framework

Tropical disease accounts for up to 20–30% of critical care admissions in certain countries of Asia, Africa, and South America [35]. Critical care physicians in these areas of the world are familiar with the different presentations of different infectious agents, and their index of suspicion is high at baseline. People are traveling more than ever before and are being exposed to these pathogens, often presenting upon returning from traveling [11]. Modifying the base rate of disease based on certain epidemiological factors is one the hardest things we are required to do as diagnosticians [36]. Having a framework may reduce the change of experiencing biases. A thorough review is out of the scope of this chapter, but the astute clinician will be aware of the importance of understanding malaria's place within a diagnostic schema. We refer the interested reader to specific reviews on the topic, great examples being the recent articles by Fink et al. or Thwaites et al. or the critical care-focused by Karnad et al. [35, 37, 38].

In brief, the differential diagnosis of severe malaria is broad and varies depending on specific travel history. Consider both local and foreign causes of infectious disease, as well as non-infectious causes of fever. Prioritize highly contagious diseases, like hemorrhagic fevers, measles, Middle Eastern respiratory syndrome-

coronavirus virus (MERS-CoV), and others explored in this book. Obtain a detailed travel history with special emphasis on all the locations the patient might have visited (including layovers), activities that he/she engaged in, as well as exposures (e.g., mosquito bites, fresh water, or sexual commerce). The incubation period is crucially important in this presentation, as is the physical examination (e.g., conjunctival suffusion, skin rash, jaundice, or hepatosplenomegaly). Probably most relevant for critical care physicians, the pattern of organ involvement might also suggest specific etiologies [35].

Diagnosing Malaria

High index of suspicion is essential for diagnosing malaria, and any individual with a febrile illness and risk factors should be investigated. As mentioned above, it is the most common identifiable cause of fever in the returning traveler and in many areas of the world. Keeping an open mind to other possibilities will be key while attempting to perform a formal diagnosis and trying to identify the specific *Plasmodium* species (Fig. 13.4).

Thick and thin blood smears continue to be standard of care. In this procedure, one drop of blood is allowed to dry on a slide, erythrocytes are lysed, and parasites are then stained with Giemsa. Parasites are easily identified by trained personnel, and parasite density can be estimated on the basis of counts relative to those of leukocytes. However, thick blood smears do not allow identification of erythrocyte morphology, helpful in species diagnosis, and are difficult for those with limited training. Giemsa-stained thin blood smear offers an improved means of characterizing parasite morphology, but the process is much less efficient than for thick smears. As such, thick smear is standard of care in areas of high endemic burden, while thin are reserved for areas in which there is more trained personnel, with more time available to them. Finally, it is paramount to understand that a negative blood film does not exclude malaria and might very well be positive 8–12 h later [32, 39].

Antigen detection is a new way of diagnosing malaria. Multiple simple tests are now available that use calorimetric detection of one or two antigens in an assay that requires limited training and only a few minutes. The most used assays in Africa use histidine-rich protein-2, only able to detect *P. falciparum* [32]. Other assays are able to detect all human malarial species, as they detect lactate dehydrogenase and aldolase. Combination tests, that aim to detect both *P. falciparum* and *Plasmodium* spp., are now available. Issues are arising with standardization given the heterogeneity of manufacturers and tests available.

Other diagnostic techniques available include serology and polymerase chain reaction (PCR). Serology utility is limited since the antibody response is slow and tends to persist for a long period of time. PCR is likely the most sensitive test available to date and useful for research purposes. Nonetheless, it is not scalable as it is time and resource intensive. Furthermore, patients might have a not clinically significant parasitemia that would still be detected.
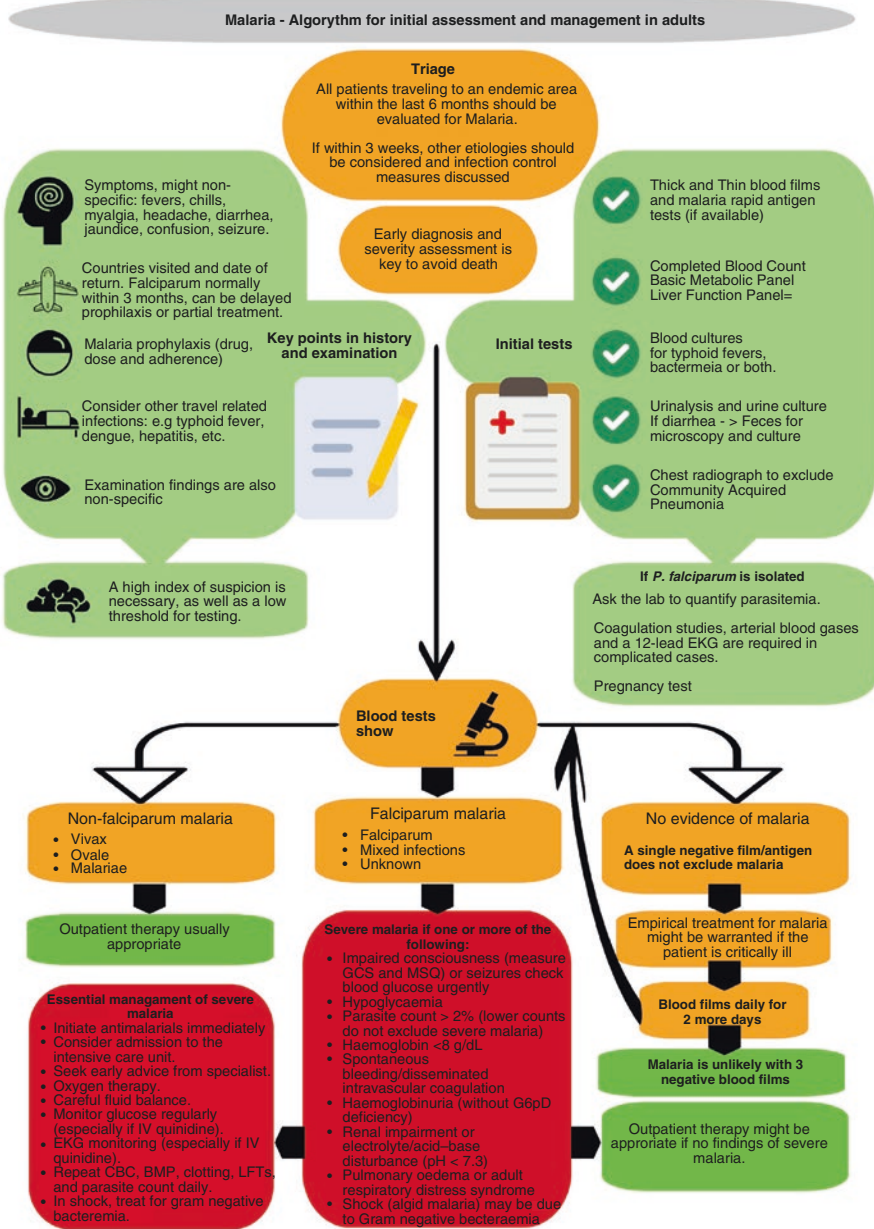
Malaria - Algorithm for initial assessment and management in adults

Triage
All patients traveling to an endemic area within the last 6 months should be evaluated for Malaria.

If within 3 weeks, other etiologies should be considered and infection control measures discussed

Early diagnosis and severity assessment is key to avoid death

Symptoms, might non-specific: fevers, chills, myalgia, headache, diarrhea, jaundice, confusion, seizure.

Countries visited and date of return. Falciparum normally within 3 months, can be delayed prophilaxis or partial treatment.

Malaria prophylaxis (drug, dose and adherence)

Consider other travel related infections: e.g typhoid fever, dengue, hepatitis, etc.

Examination findings are also non-specific

Key points in history and examination

A high index of suspicion is necessary, as well as a low threshold for testing.

Initial tests

Thick and Thin blood films and malaria rapid antigen tests (if available)

Completed Blood Count Basic Metabolic Panel Liver Function Panel=

Blood cultures for typhoid fevers, bactermeia or both.

Urinalysis and urine culture If diarrhea - > Feces for microscopy and culture

Chest radiograph to exclude Community Acquired Pneumonia

If *P. falciparum* is isolated

Ask the lab to quantify parasitemia.

Coagulation studies, arterial blood gases and a 12-lead EKG are required in complicated cases.

Pregnancy test

Blood tests show

Non-falciparum malaria
- Vivax
- Ovale
- Malariae

Falciparum malaria
- Falciparum
- Mixed infections
- Unknown

No evidence of malaria

A single negative film/antigen does not exclude malaria

Outpatient therapy usually appropriate

Severe malaria if one or more of the following:
- Impaired consciousness (measure GCS and MSQ) or seizures check blood glucose urgently
- Hypoglycaemia
- Parasite count > 2% (lower counts do not exclude severe malaria)
- Haemoglobin <8 g/dL
- Spontaneous bleeding/disseminated intravascular coagulation
- Haemoglobinuria (without G6pD deficiency)
- Renal impairment or electrolyte/acid–base disturbance (pH < 7.3)
- Pulmonary oedema or adult respiratory distress syndrome
- Shock (algid malaria) may be due to Gram negative becteraemia

Essential managment of severe malaria
- Initiate antimalarials immediately
- Consider admission to the intensive care unit.
- Seek early advice from specialist.
- Oxygen therapy.
- Careful fluid balance.
- Monitor glucose regularly (especially if IV quinidine).
- EKG monitoring (especially if IV quinidine).
- Repeat CBC, BMP, clotting, LFTs, and parasite count daily.
- In shock, treat for gram negative bacteremia.

Empirical treatment for malaria might be warranted if the patient is critically ill

Blood films daily for 2 more days

Malaria is unlikely with 3 negative blood films

Outpatient therapy might be approriate if no findings of severe malaria.

Fig. 13.4 Algorithm for initial diagnosis and management of suspected Malaria in the returning traveler. (Source http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1240212774627)

Treatment

Antimalarials: Overview and Resistance Emergence

Early in the twentieth century, there was a pressure to find a substitute for quinine as a treatment for malaria. This led to the discovery of primaquine and quinacrine and finally chloroquine in 1934 [40]. The United States later generalized its use, making it the drug of choice by the end of World War II [41]. Chloroquine quickly became one of the most important drugs ever developed against an infectious agent [40]. It is key to understand this in the context of the discovery of DDT and other vector control measures. Optimism was such that WHO launched an eradication campaign in 1955. Although we fell short and it had to be cancelled on 1969, the extraordinary impact that chloroquine had in vulnerable areas like the sub-Saharan Africa is undeniable [40, 41].

Its widespread use was not without consequence. *P. falciparum* initially found to develop resistance in the 1950s–1960s in foci in Colombia and Southeast Asia [42]. Resistance steadily spread during the 1960s, finally getting to Africa in the 1980s [42]. *P. vivax* was found to develop resistance to chloroquine first in Papua New Guinea in 1989 but is now found in Asia and South America [40].

Quinine, in the 1970s, would take back its place as the drug of choice [4, 39, 40]. The most common dose dependent is cinchonism (nausea, vomiting, blurred vision, reversible hearing loss, and headache). Despite this and other side effects like hypoglycemia, it would remain the treatment of choice until 2005, when the first trials comparing it with artemisinin(s) derivatives were published.

Artemisins, derived from the Chinese herb *qinghausu* or wormwood, have been used by Chinese traditional healers for millennia but have been adopted in the Western world only recent years. One of its derivatives, artesunate, was recently found in two large randomized control trials to be superior to quinine. SEAQUAMAT randomized patients in South and Southeast Asia, almost all adults, and found a reduction in mortality in patients treated with artesunate compared with quinine (15% vs. 22%) [43]. The subsequent AQUAMAT focused on children in 11 countries in sub-Saharan Africa and demonstrated a similar reduction in mortality (8.5% vs. 10.9%) [44].

In the acute setting, while treating severe malaria, intravenous quinine therapy requires close monitoring of QTc interval as well as capillary blood glucose, while artesunate is safe in both of those regards. Nonetheless, the latter cannot be used as a single agent due to its short biological half-life, as it leads to prompt recrudescence. Availability of artesunate is limited to specialized centers, and access to it might prove challenging. It is important to recognize that treatment with quinine should not be delayed while attempting to obtain artesunate.

For outpatient or consolidation treatment, artemisin combination treatments (ACTs) are now the standard of care for *P. falciparum* and recommended by the WHO in 3-day regimens [32]. This treatment combines artesunate with other active antimalarial agents, some of them are once daily (e.g., artesunate-mefloquine), while others require twice-daily dosing (e.g., artemether-lumefantrine). These therapies should be used in every patient confirmed to have *P. falciparum*, or in which

the species involved is in doubt, after an initial administration of parenteral artesunate.

Chloroquine remains the treatment of choice for non-falciparum malaria and the few areas that have not registered any resistance (primarily Central America and the Caribbean). For *P. vivax* and *P. ovale*, it should always be given to eradicate hepatic hypnozoites. Also, chloroquine-related compounds are found on ACTs active against *P. falciparum*.

The development of resistance to quinine has been relatively slow [45]. It had been in use for over two centuries by the time the first resistance was first described. As a comparison, for chloroquine and proguanil, it only took 12 and 1 year, respectively [46]. Quinine resistance has been extensively documented in Asia and South America, but it seems relatively uncommon in Africa [47–51]. Quinine normally retains some efficacy, although its activity might be delayed or diminished. A recent meta-analysis of multiple randomized clinical trials demonstrates that the recrudescence rates after quinine treatment have been relatively stable for over 30 years [52]. With all the side effects and drawbacks pointed before, quinine seems to remain a viable treatment option.

Artesunate resistance was first reported in western Cambodia, and it was further confirmed by randomized control trials [53]. This was characterized by decreased clearance of parasites in vivo but hardly any sign on susceptibilities in vitro. Of note, the rapid parasite elimination is one of the main advantages of artemisin therapies and accounts for a significant part of its rapidity of therapeutic response and could drastically affect outcomes. Sadly, this has continued to be reported in other areas of the Southeast Asian subcontinent [49, 53, 54]. Worrisome laboratory data points the possibility of extreme artemisin resistance and, under the appropriate in vitro conditions, was accompanied with more complex patterns of multiple drug resistance [55]. As of now, contentment of resistant strains and judicious use of current available therapies and multiple agent regimens in the face of clinical failures are the only measures available.

Treatment of Severe Malaria

As any septic patient, treatment should immediately follow or be concurrent with treatment. Stabilizing the patient and isolating and treating the causative agent, here with parenteral antimalarials, is imperative. Although both *P. vivax* and *P. knowlesi* are increasingly recognized as causes of severe malaria, *P. falciparum* should be assumed to be the causative agent until proven otherwise.

Initial Stabilization

Aggressive fluid resuscitation is considered an intrinsic part of initial sepsis management, but evidence is mounting it might be detrimental in patients with malaria due to difference in pathogenesis and increased vascular permeability [56, 57].

In adults with malaria, the base deficit is the strongest predictor of mortality, and the degree of acute kidney injury (AKI) is an additional risk factor [58, 59]. Hypovolemia is present in severe malaria and can exacerbate both conditions [60, 61]. Nonetheless, the microvascular pathology of malaria is unique since impaired tissue perfusion is mostly caused by sequestration of infected erythrocytes [56]. The degree of acidosis and AKI is intrinsically related to sequestration, especially in the kidney and liver [56, 62, 63]. We have increasing evidence that fluid resuscitation cannot reverse this pathological process.

The recent FEAST trial suggested that among sub-Saharan African children with a particular definition of shock, saline and albumin bolus resuscitation appeared to increase mortality when compared to no-bolus strategy. Malaria was the reason for the admission in 57% in these children [64]. It is hard to translate these results directly to resource-rich countries, as it might be safe to assume the time of presentation to the hospital might be prolonged, as well the potential effect of the absence of tools like mechanical ventilators. Moreover, children with severe malaria rarely develop AKI, as opposed to 45% of adult patients.

More evidence is mounting fluid resuscitation might be detrimental, even with close monitoring. In a completely different study, they evaluated liberal vs. conservative fluid strategy while monitoring extracellular water with a well-validated tool, PiCCO™ [65]. Even though only hypovolemic patients were recruited, the acid-base status deteriorated after a reasonable amount of fluids (mean 5450 mL over the first 24 h). Pulmonary edema—secondary to increased pulmonary vascular permeability—was common, unpredictable, and exacerbated by fluid loading. Lactate, the strongest mortality predictor, was correlated with the degree of visualized microvascular sequestration of parasitized erythrocytes (i.e., decreased flow velocity by orthogonal polarized spectroscopy) and not impacted by fluid resuscitation [66]. In fact, 70% of patients' acid-base status deteriorated after fluid resuscitation [65].

Multiple studies have associated fluid resuscitation with worse outcomes in malaria [64, 65, 67]. Beyond early initiation of antimalarials, we recommend against overzealous liberal fluid resuscitation and for a rapid escalation to vasopressor therapy for hemodynamic management. Clinicians should be vigilant of the various complications associated with increased vascular permeability seen in this disease.

Antimalarials

Standard therapy for severe malaria is parenteral quinine, under continuous cardiac monitoring. As mentioned above, evidence is mounting that artesunate is superior, in terms of efficacy and safety profile, but availability is still a major issue. In the United States, IV quinine is not available in all hospitals, and IV artesunate should be requested on a name patient basis to the Center for Disease Control. As such, treatment should be started with whatever agent may be administered first (Table 13.2). After the three initial doses, patients that tolerate the oral route should receive oral medications, including the regimen mentioned above [32].

Table 13.2 Complicated falciparum malaria or unable to tolerate oral medications

IV artesunate	2.4 mg/kg every 12 h on day 1 and then daily for 2 additional days
Or	
IV quinidine gluconate	10 mg/kg over 1–2 h and then 0.02 mg/kg/min or 15 mg/kg over 4 h and then 7.5 mg/kg over 4 h every 8 h
Or	
IV quinidine dihydrochloride	20 mg/kg over 4 h and then 10 mg/kg every 8 h
Or	
IM artemether	3.2 mg/kg IM and then 1.6 mg/kg/day

Adjunctive Measures

Adjunctive measures as exchange transfusion have been proposed in the treatment of severe falciparum malaria. Although it seems to address the issue at its core, the evidence to support its use is still lacking. There are several case reports documenting successful use, but the only retrospective review available showed no improve in parasite clearance or outcomes [68–70].

Complications

Cerebral Malaria

Cerebral malaria is more common in children from Africa. Patients may present with stupor, coma, seizures, decerebrated posturing, and raised intracranial pressure. More strictly, cerebral malaria is defined by coma (GCS < 9) in a patient with malaria in which all other causes have been ruled out. More broadly, any patient with altered mental status should be presumed to have cerebral malaria after ruling out common causes like hypoglycemia. Cerebral malaria is associated with worse outcomes [71].

Patients with cerebral malaria have subclinical seizures [72]. Although prophylactic anticonvulsants reduce seizure incidence, a meta-analysis showed they may in fact worsen outcomes [73]. The main criticism is that the trials reported thus far were mainly done with phenobarbital, so the increase in mortality was attributed to respiratory depression. Whether the use of other antiepileptics is of any use remains to be determined. Regardless, current evidence discourages routine electroencephalogram monitoring and use of prophylactic phenobarbital. Clinical seizures should be treated appropriately.

Cerebral edema is a well-recognized complication of severe malaria. Multiple interventions have been tested in randomized clinical trials without success, including steroids and mannitol [74–76]. As such, no adjunctive therapies are currently recommended for cerebral malaria at the moment.

Severe Anemia and Coagulopathy

Anemia in patients with malaria is more than just a hemolytic process. It also involves dyserythropoiesis and removal of infected erythrocytes from the circulation by the spleen. Uninfected erythrocytes can be indirectly affected by antigens, antibody activation, and minor alterations in red cell membranes. WHO defines severe anemia as a Hgb of <5 mg/dL [32]. However, this degree of anemia is mainly seen in endemic areas and is likely to be multifactorial [77, 78]. It is exceptionally rare on imported cases [33, 34, 66]. Transfusion thresholds are currently the same as with any other critically ill patient.

Coagulopathy is seen in 5% to >20% of patients with severe malaria [33, 34]. Severe thrombocytopenia is common in severe and non-severe malaria secondary to increased platelet destruction, sequestration within the spleen, or both. Disseminated intravascular coagulation occurs in 5–10% of patients and should be treated with supportive transfusions [33, 34, 66].

Metabolic Changes

Lactic acidosis is a marker of poor prognosis [4, 58, 65]. It has been attributed mainly to microvascular obstruction secondary to parasite cytoadherence and leading to hypoperfusion. Other factors contributing are thought to be direct production of lactate by the parasite and decreased clearance in the setting of liver dysfunction [58]. As we have pointed out before, this differs from other Type A lactic acidosis, and treating it as we would any other might result in deleterious effects [65, 79].

Hypoglycemia defined by a blood sugar <40 mg/dL (<2.2 mmol/L) is common in severe malaria, and it is associated with worse outcomes specially in children [32, 80, 81]. This seems to be applicable to imported cases of malaria, where although the prevalence is smaller, it is correlated with worse outcomes [33, 66]. The pathogenesis is incompletely understood but likely involves direct glucose consumption by the parasite as well as impaired gluconeogenesis in the liver, paired with hyperinsulinemia [82]. It has also been shown to be more frequent when patients are treated with quinine as compared to artesunate (combined HR < 0.55) [83].

Clinical features include decreased level of consciousness and seizures. Blood glucose should be regularly assessed specially in patient treated with quinine. Early enteral feeding is recommended for any critically ill patient but could be particularly beneficial in patients with malaria [84, 85].

Pulmonary Complications

The WHO includes as pulmonary manifestations for malaria deep breathing, respiratory distress, and pulmonary edema [32]. Tachypnea might be caused by fever, anemia, and metabolic acidosis but also primary lung pathology like pulmonary edema and acute respiratory distress syndrome (ARDS). The reported incidence of

ARDS varies, in part due to the use of different definitions, but ranges from 3% to 30% [33, 34, 66, 86]. It is more common in adults as compared to children [57, 86]. It portends a worse prognosis [34, 87, 88].

Pulmonary complications of malaria are attributed to direct toxicity by the cytoadherence of *P. falciparum* paired with a hyperactive host response [86, 89]. Concurrent bacteria pneumonia and pulmonary edema are other important causes of respiratory distress in this population.

Acute Kidney Injury

Acute kidney injury (AKI) is mainly associated with *P. falciparum* although it has been described with other species [90]. The WHO uses a different criterion (>265 mmol/L or ≥ 3 mg/dL) to qualify severe malaria than what is currently used in any other disease [32]. Interestingly, acute kidney injury is more frequent in patients with primoinfection [90–92]. As such, AKI is much more frequent in patients with imported malaria (ranging from 23% to >50%) as compared to endemic cases (1–5%) [33, 34, 66, 91].

The pathophysiology is likely multifactorial with cytoadherence in glomerular and tubular vasculature likely playing a major role, but with contribution from hypovolemia, hemolysis, immune-complex deposition, and cytokine release [62, 90].

All patients should be screened for AKI, which may be absent initially [90]. Once discovered, the treatment is mainly supportive with avoidance of further nephrotoxic agents, maintenance fluids, and controlling electrolytes and acid-base disturbances, including renal replacement therapy when indicated. Improving perfusion with dopamine and epinephrine has been tested and failed to improve renal outcomes [93]. The prognosis is usually good, with complete resolution in most cases upon infection control [33].

Jaundice

Hyperbilirubinemia can be multifactorial. It may occur in the setting of hemolysis, cholestasis, and hepatocyte dysfunction. Bilirubin can be significantly elevated, but transaminases are normally less affected. In a cohort of critically ill patients, Krishnan et al. found that hyperbilirubinemia to more than 6 mg/dL was seen in 26% of patients and a transaminase level more than three times the upper limit of normal was seen in less than half. The patients with elevated transaminases had a higher incidence of hypoglycemia and worse mortality [94].

Interactions with Other Infections

In endemic areas, concurrent gram-negative infection, especially non-typhoidal *Salmonella* has been shown in up 10% of children [93, 95, 96]. Some community studies point to up to two thirds of community bacteremia to be related to

co-infection with malaria. When this happens, it is associated with a worse prognosis [95, 96].

Rates of community-acquired bacterial infection have been reported to be between 5% and 10% in patients admitted to intensive care units with imported cases of malaria [33, 34]. Community-acquired pneumonia is the commonest.

The use of prophylactic antibiotics remains controversial. Bacterial co-infection should be suspected in patients with significant neutrophilia or focal signs of infection. In these cases, blood cultures should be drawn and therapy de-escalated or tailored based on culture results. As with any other critically ill patient, physicians should remain vigilant for nosocomial infections, including ventilator-associated pneumonia or catheter-related sepsis, with common stewardship practices (i.e., monitor for extubating readiness or limiting use of urinary catheters) applying in a similar manner.

Prognosis

Patients with *P. falciparum* malaria tend to respond well if treatment is started promptly. The mortality rate in those with uncomplicated *P. falciparum* is about 0.1%. Nonetheless in the critical care population, high-level parasitemia or clinical features might determine worse outcomes. However, with aggressive support, even individuals with severe disease can often experience complete recoveries. As an example, Marks et al. report a mortality of only 4% and Antinori et al. a mortality of 0% [33, 97]. Moreover, *non-falciparum* malaria usually responds well to treatment and makes an uneventful recovery.

Resistance emergence and changing epidemiology might be the greatest challenge we will face in the future. A judicious use of existing therapies, careful monitoring, and attention to other co-occurring complications will help us navigate the changing landscape of the treatment of malaria in our critical care units.

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