Scientific Research Publishing

Open Journal of Emergency Medicine, 2023, 11, 162-173
https://www.scirp.org/journal/ojem
ISSN Online: 2332-1814
ISSN Print: 2332-1806

# Cerebral Malaria: Epidemiological, Clinical and Prognosis Aspects in the Anesthesia-Resuscitation Department CHU Ignace Deen

**Abdoulaye Touré[1*], Amadou Yalla Camara[2], Almamy Bangoura[1], M'mah Lamine Camara[3], Mohamed Soumah[1], Saramba Nabe[1]**

[1]Department of Anesthesia-Resuscitation, University Hospital of Ignace Deen of Conakry, Conakry, Guinea
[2]Department of Medical and Surgical Emergency, Donka University Hospital, Conakry, Guinea
[3]Department of Anesthesia-Resuscitation, Donka University Hospital, Conakry, Guinea
Email: *atfmamad@yahoo.fr

**How to cite this paper:** Touré, A., Camara, A.Y., Bangoura, A., Camara, M.L., Soumah, M. and Nabe, S. (2023) Cerebral Malaria: Epidemiological, Clinical and Prognosis Aspects in the Anesthesia-Resuscitation Department CHU Ignace Deen. *Open Journal of Emergency Medicine*, **11**, 162-173.
https://doi.org/10.4236/ojem.2023.114016

**Received:** August 15, 2023
**Accepted:** October 22, 2023
**Published:** October 25, 2023



## Abstract

**Objective:** To describe the epidemiological, clinical, paraclinical and prognostic aspects of cerebral malaria received in the anesthesia-resuscitation department. **Methodology:** This was a prospective descriptive type study carried out in the anesthesia-resuscitation department over a period of three (03) months (June 01 to August 31, 2022). All patients admitted for cerebral malaria were included. Sociodemographic, clinical and prognostic parameters were studied. **Results:** We collected 25 cases out of 105 admitted patients (23.8%). The average age was 27.6 ± 9.5 years with extremes of 11 and 50 years. The sex ratio was 0.7 (M/F). Students and housewives were in the majority, *i.e.* 52% and 24%. Neurological disorders were found on admission in all patients, dominated by impaired consciousness at 100% followed by convulsion (60%), prostration (44%), confusion (36%) associated with deep coma in (68%). Gross hemoglobinuria was present in (84%) of cases. On the blood count, anemia was present in (70%) of the patients followed by thrombocytopenia in more than half of the cases (60%) and transfusion was necessary in 19 cases. P Falciparum malaria was found in all patients (100%), the average parasite density was 60342.8 ± 30425.6 trophozoites/µl with extremes of 9000 to 100000 trophozoites/µl. All our patients were treated with intravenous injectable artesunate. Transfusion was performed in 76% of our patients. Eighty percent of the patients had benefited from dialysis. High oxygen therapy was performed in (92%) of cases. The average duration of hospitalization was 5.74 ± days with extremes of 1 to 17 days. Mortality was 48%. **Conclusion:** Cere-

bral malaria can take different clinical forms, the most important of which is cerebral involvement. Prompt initiation of appropriate resuscitation can reduce mortality.

## Keywords

Cerebral Malaria, Mortality, Resuscitation

## 1. Introduction

Malaria is the most common parasitosis in the world. This infection is responsible for one to two million deaths per year, the majority of which are children. Malaria is caused by a protozoan transmitted by a mosquito bite. Among the four species of Plasmodium (*P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*), *P. falciparum* is responsible for the most formidable infection and represents an emergency given the risk of rapid evolution towards a severe form, cerebral malaria [1]. Severe malaria can manifest immediately or following poor management of simple malaria and can cause death. It is defined according to the World Health Organization (WHO) by the detection of asexual forms of the parasite on a blood smear and the presence of at least one of the following criteria: clinically (prostration, impaired consciousness, respiratory distress, repeated convulsions, lung collapse, abnormal bleeding, jaundice, hemoglobinuria) and in the laboratory (severe anemia, hypoglycemia, acidosis, renal failure, hyperlactemia, hyperparasitaemia) [2].

These serious complications depend on age and transmission zone. In Africa, for example, most serious complications of malaria occur in children. It is cerebral malaria, severe anemia, and respiratory distress syndrome that develop separately or at the same time [3] while in areas with lower transmission, such as Asia, these complications affect both children and adults. In the latter, it is the kidneys, lungs and liver that are most often affected [4]. In a context where there is free care in all health centers in the country by the WHO stop malaria program. The extent of admissions to intensive care for cases of cerebral malaria motivated the realization of the present study, the objective of which was to describe the epidemiological, clinical, paraclinical and prognostic aspects of cerebral malaria received in the anesthesia-resuscitation department.

## 2. Patients and Methods

This was a prospective descriptive type study carried out of multipurpose intensive care at the Ignace Deen University Hospital over a period of three (3) months from June 01 to August 31, 2022. They were included in the study of all patients admitted for cerebral malaria. Cerebral malaria was defined by the clinico-biological finding of a positive rapid malaria test, thick blood smear and positive parasite density for plasmodium falciparum and at least one of the severity criteria of the 2000 WHO (neurological disorders, prostration, Glasgow

score < 11, convulsion ≥ 2 in 24 hours, respiratory failure $SpO_2$ < 90% AA, respiratory rate > 22, circulatory failure (systolic blood pressure at 80 mm Hg), gross hemoglobinuria, renal failure (diuresis 400 ml/kg/24h or creatinine > 265 µmol/L), anemia < 7 g/dl or hematocrit < 20%, frank isolated jaundice, parasitaemia > 4% [1] The parameters studied were sociodemographic data (frequency, age, sex, profession, origin: urban or rural area), clinical data, these were clinical signs of seriousness found at the admission of patients or developed during hospitalization, paraclinical: these were biological and imaging assessments carried out in patients, therapeutic, progressive and prognostic.

## 3. Results

We collected 25 cases out of 105 patients received in the multipurpose intensive care unit from June 1 to August 31, 2022, *i.e.* a frequency of 23.8%. The average age of the patients was 27.6 ± 9.5 years with extremes of 11 and 50 years. The most represented age group is that of subjects aged 21 to 30 (52%). A female predominance was noted at 56% with a sex ratio of 0.7 (M/F). In our study, students and housewives were more numerous, 52% and 24% respectively. Patients came from urban areas in 68%. Table 1 shows the characteristics of the study population.

**Table 1.** Characteristics of the study population.

| | *Effective* | *Percentage* |
|---|---|---|
| **Age** | | |
| ≤20 | 4 | 16 |
| 21 - 30 | 13 | 52 |
| 31 - 40 | 6 | 26 |
| ≥41 | 2 | 8 |
| Total | **25** | **100** |
| **Sex** | | |
| Male | 11 | 44 |
| Feminine | 14 | 56 |
| **Occupation** | | |
| Student | 13 | 52 |
| Household | 6 | 24 |
| Trader | 2 | 8 |
| Worker | 2 | 8 |
| Unemployed | 1 | 4 |
| Farmer | 1 | 4 |
| ***Origin*** | | |
| Urban | 17 | 68 |
| rural | **8** | 32 |

In our study 100% patients had been admitted with loss of consciousness, 68% were in a deep coma, the average Glasgow score was 7.8 ± 2.8 with extremes of 4 and 14, 60% had a seizure, macroscopic hemoglobinuria and jaundice were present in 84% and 48% of patients. Respiratory failure was present in 92% with $SpO_2$ < 95% on room air. The average glycaemia was 1.3 ± 0.9 g/l with extremes of 0.6 and 5 g/l. Table 2 shows the distribution of patients according to the Glasgow score and clinical signs on admission.

Sixty-eight percent of the patients had a hemoglobin level of ≤9 g/dl, the mean hemoglobin level was 8.9 ± 2.5 g/dl with extremes of 6 and 14.9 g/dl. A platelet count less than or equal to $50 \times 10^3$ G/L (severe thrombocytopenia) was present in 16% of patients, 44% of patients had a platelet count between 50 and $100 \times 10^3$ G/L, 40% had a platelet count greater than or equal to $100 \times 10^3$ G/L. The mean platelet count was $102.9 \times 10^3 \pm 55.3 \times 10^3$ with extremes of $24 \times 10^3 \pm 220 \times 10^3$. All patients had a positive rapid malaria and thick film test, 64% of patients had a parasite density between 5001 and 100,000 trophozoids/μL. The average parasite density was 60342.8 ± 30425.6 trophozoids/μL with the extremes of 9000 and 100,000 trophozoids/μL. The glucose 6 phosphate dehydrogenase (G6PD) deficiency test was negative for 100% of patients, an electroencephalogram was performed in 28% of patients, brain scans were performed in 36% of patients, 20% of patients presented cerebral edema.

Table 2. Distribution of patients according to the Glasgow score and neurological signs on admission.

| Settings | *Effective* | *Percentage* |
|---|---|---|
| **Glasgow score** | | |
| ≤8 | 17 | 68 |
| 9 - 12 | 6 | 24 |
| ≥13 | 2 | 8 |
| Total | **25** | **100** |
| **Clinical signs on admission** | | |
| altered consciousness | 25 | 100 |
| Seizure | 15 | 60 |
| Prostration | 11 | 44 |
| Confusion | 9 | 36 |
| **Gross hemoglobinuria** | | |
| clinical jaundice | 21 | 84 |
| Oligoanuria | 12 | 48 |
| Hypoglycemia | 14 | 56 |
| $SpO_2$* | 5 | 20 |
| <95 | 23 | 92 |
| ≥95 | 2 | 8 |

*peripheral oxygen saturation.

All patients were treated with 100% intravenous injectable artesunate, 76% had been transfused, 80% had required emergency dialysis. The average duration of hospitalization in intensive care was 5.74 ± days with extremes of 1 and 17 days. We recorded 48% of deaths. Among them 12% were aged < 20 years, 16% patients had a very high parasite density and 20% patients on dialysis.

## 4. Discussion

The frequency of cerebral malaria in our CHU Ignace Deen intensive care unit was 23.8%. This high frequency is found by several authors [5] who show that the incidence of malaria was very high in the tropical and subtropical zones which are also generally the least developed regions of the world. This relationship suggests that the intensity of malaria transmission is related to the economic arrangements of the region concerned [5]. In our study, students and housewives were the most represented, 52% and 24% respectively, patients came more from urban areas (68%). The objective urbanization in our study is similar to those reported by some authors named by Matthys *et al.* and Robert *et al.* showed in their study that the Poverty is often the cause of migration from rural to urban areas. Rapid and unplanned urban growth in tropical areas creates conditions conducive to malaria transmission, mainly on the outskirts of cities. People who migrate from rural areas usually settle in poorly constructed houses in densely populated and underdeveloped peri-urban areas and bring with them their traditional rural practices which can promote mosquito breeding [6] [7] [8]. Others [8] observed that Indeed, town planning through the lack of cement construction, access to drinking water, electricity, approved toilets and health care and the impossibility of acquiring mosquito nets are all elements that predispose to high transmission of malaria [8]. Added to these problems are the social determinants. According to Mejia *et al.* poverty often leads to a phenomenon of massive and intense rural exodus, the consequences of which are poor urbanization and high population density, especially on the outskirts of cities where transmission is increasing de facto [9]. Our study population is young with an average age of 27.6 ± 9.5 with the extremes of 11 and 50 years and a female predominance (sex-ratio M/F = 0.7). The most represented age group is that of 21 and 30 years (52%). The initial clinical examination noted that 100% of patients were unconscious, 68% of patients were in a deep coma with a Glasgow score less than or equal to 8, 28% had a Glasgow score between 9 and 12. The average Glasgow score was 7.8 ± 2.8 with extremes of 4 and 14. This result could be explained by the fact that coma is the frequent presentation of cerebral malaria. Seizures were present in only 60% of patients, while the literature [10] demonstrates that cerebral complications can occur quite quickly in children. In 80% of cases, they follow an epileptic seizure which may be the consequence of hypoglycaemia or, in the most frequent situation, be caused by an increase in intracranial pressure [10]. However, in adults, epileptic seizures are rarer and are only associated in 15% to 20% of cases with neurological damage, although epi-

sodes of convulsions are frequent [11]. Anemia was present in 68% of patients with an average hemoglobin level of 8.9 ± 2.5 g/dl with extremes of 6 and 14.9 g/dl. Sequestration is the most important process in establishing anemia in severe malaria with *P. falciparum*. Some authors have argued that sequestration was not the only factors involved in anemia, that other elements such as phagocytosis of parasitized and non-parasitized red blood cells and that severe infection indeed gives rise to a large increase in macrophage activity in the reticuloendothelial system [12]. This hyperactivity leads to intense phagocytosis not only of infected erythrocytes but also of uninfected ones. The latter are eliminated because both *P. falciparum and P. vivax*, upon infection, also cling to uninfected erythrocytes, a process called rosetting which triggers their phagocytosis by macrophages [13]. An old study from 1999 by Jakeman *et al.*, and a recent one from 2003 by collins *et al.* showed that *P. falciparum and P. vivax* phagocytose respectively 8 erythrocytes [14] and 34 erythrocytes [15] are eliminated for one parasitized cell. This could largely explain why the anemia persists for up to two weeks in some cases, after the infection has cleared.

On admission, all the patients had a positive rapid malaria test, 64% of the patients had a thick film parasite density and parasite density between 5001 and 100,000 trophoides/μL. The average parasite density was 60342.8 ± 30425.6 trophozoids/μL with the extremes of 9000 and 100,000 trophozoids/μL. A recent study by Dondorp *et al.* had shown that the parasitic mass sequestered within the vascular network is difficult to quantify. Conversely, parasitaemia is an acceptable reflection of the circulating parasite mass. Finally, a recent study showed that the plasma level of histidine-rich protein2 (HRP2) was a good reflection of the total parasite mass (sequestered mass + circulating mass) [16]. In the end, the parasitized red blood cells sequestered in the deep capillaries, agglutinating healthy red blood cells (rosettes) and platelets, are well protected to progress in the parasitic cycle but also to interact with other cells and to stimulate coagulation.

In our study, the G6PD test was negative for all admitted patients. Several other studies [17] [18] confirmed the association between G6PD deficiency and severe malaria and its milder forms [19] [20]. This on the one hand, by the fact that in our series 84% of patients had macroscopic hemoglobinuria and clinical jaundice in 48% of patients, this test made it possible to eliminate acute or chronic hemolytic anemia and hyperbilirubinemia by destruction of red blood cells, on the other hand, we find this deficit very frequent in men of African origin living in tropical, subtropical and/or Afro-American zones.

In our study, the brain scan performed in 36% patients, 20% had shown cerebral edema. Currently, many studies tend to find that cerebral edema was more frequent and more marked in African children than in adults from Asia [21]. This same observation was made by Mohanty *et al.* [22] edema cerebral was found at most in 63% of cases. Another study by Seydel *et al.* in 168 African children with cerebral malaria found severe cerebral edema in 84% of deceased

children versus 27% of surviving children [23]. Laurent *et al.* have shown that during import cerebral malaria, abnormalities. Cerebral imaging would be quite frequent and varied: ischemic attacks, cerebral oedema, hemorrhages. These data argue for performing brain imaging, at best by MRI, in adult patients with severe imported malaria with the presence of neurological sign(s). In 2014, Maude *et al.* [21], in a prospective study including 43 adults, including 72% were in a coma and 28% died, revealed abnormalities on MRI in 79% cases, mostly minimal changes involving many anatomical areas, no difference between patients with cerebral malaria and those with severe malaria without cerebral malaria, and without difference between patients living and dead. The abnormalities found were in 51% of cases a cerebral oedema, moderate and diffuse, most often not vasogenic and without increase intracranial pressure. This could explain the performance of brain imaging and other complementary examinations depending on the context in search of another cause that could explain the cerebral edema during cerebral malaria.

Severe malaria is a diagnostic and therapeutic emergency. Anti-infective treatment must therefore be initiated immediately (at the latest within two hours). It is now based on intravenous artesunate in adults, pregnant women regardless of their term, and in children. French recommendations 2017 [24] aligned with WHO recommendations [25] [26] and recommend the use of artesunate for all forms of severe malaria and whatever the causative species [27]. Quinine is now a second line treatment, with very limited indications (artesunate allergy). The practical modalities for the use of artesunate and quinine are specified in **Table 3**.

All patients in our study were treated with intravenous injectable artesunate and the artesunate doses were 2.4 mg/kg the same in these dialysis patients. A randomized trial study of artesunate versus quinine for the treatment of severe Plasmodium falciparum malaria in 2005 by Dondorp *et al.* showed that since *Plasmodium falciparum* cerebral malaria is an emergency, treatment should be initiated immediately. It is now based on intravenous artesunate in adults, pregnant women and children [28] [29].

This medicine is better tolerated, has fewer adverse effects than quinine, and can still be used in the event of hepatic or renal insufficiency, without dose adjustment. Intravenous artesunate is therefore now recommended everywhere as first-line therapy in severe malaria. The recommended dosage is 2.4 mg/kg. H0, H12, H24 then every 24 hours are for a maximum of 7 days. Intravenous treatment should be continued for at least the first 3 doses, or until the severity criteria(s) are amended. In our study, 56% of patients were clinically oligo-anuric on admission, 84% had macroscopic hemoglobinuria. Other studies attest that 60% to 70% of renal complications are of an oliguric nature, that is to say that the result is a rarefaction of urine in the individual [30], and 80% of patients had required a emergency dialysis. This result agrees with those found in the study by Phu *et al.*, which show that acute renal complications are more frequent in adults. Their mechanism is not properly dissected, but obstruction by sequestered cells,

**Table 3.** Therapeutic modalities and main characteristics of the curative treatment of severe malaria by intravenous artesunate or quinine.

| | Artesunate (Malacef®) | Quinine (Quinimax®) |
|---|---|---|
| Loading dose | 2.4 mg·kg$^{-1}$ intravenously at H0, H12 and H24<br>Gently dilute 60 mg of artesunate in 1 ml of sodium bicarbonate provided, then dilute again in 5 ml of 5% glucose, to obtain 6 ml of a 10 mg solution ml$^{-1}$<br>Injection rate: 3 ml·min$^{-1}$ | 16 to 20 mg·kg$^{-1}$ over 4 hours intravenously in G10%, without exceeding 1800 mg (if obese patient)<br>Contraindications to the loading dose:<br>- QT prolongation > 25%<br>- Previous treatment with quinine, halofantrine or mefloquine Dysfunction hepatic: reduction of one third of the loading dose |
| Maintenance dose | 2.4 mg·kg$^{-1}$ 24 h$^{-1}$ for a maximum of 7 days then systematic relay with a complete 3-day treatment with ACT (oral route or SNG)<br>After a minimum of 3 to 4 intravenous doses, if the patient is conscious, without criteria persistent in severity, with functional transit: oral relay with a complete 3-day treatment with ACT (Eurartesim® or Riamet®) | To start 4 hours after the end of the loading dose:<br>- Either 24 to 30 mg·kg$^{-1}$·d$^{-1}$ continuously intravenously<br>- Or 8 to 10 mg·kg$^{-1}$ over 4 hours every 8 hours, without exceeding 3000 mg·d$^{-1}$ (obese)<br>Relay per os at the same dosage to be considered after 72 hours if functional digestive tract Total duration: 7 days |
| Specific monitoring | Clinical and blood examination on D3, D7, D14, D21 and D28: particularly NFS, reticulocyte level, haptoglobin (PADH) level Smear/thick drop on D3, D7, D28 If onset of anemia delayed until D28 (PADH): complete diagnostic work-up for anemia Daily ECG | Hourly blood glucose during the loading dose then every 4 hours. Increased risk of hypoglycaemia in pregnant women<br>Quininemia at the end of the loading dose then daily, especially if renal or hepatic insufficiency<br>Expected concentration between 10 and 15 mg·l$^{-1}$ after loading dose, then between 10 and 12 mg·l$^{-1}$. Check-up recommended at the 72nd hour<br>Daily ECG with QTc Smear/thick film check-up on D3, D7, D28 |
| Side effects | Digestive disorders<br>Neutropenia (1%), reticulocytopenia (<1%)<br>Alteration in liver function angioedema (1/3000) Theoretical risk of neurological damage, but not found clinically Risk of transient deafness Possible risk of convulsion and vertigo Delayed hemolytic anemia (PADH) | Sometimes very profound hypoglycaemia with coma<br>Prolongation of QTc followed by arrhythmias and conduction disorders Cinchonism (damage to the VIIIth cranial nerve: digestive disorders, headaches, tinnitus, reversible deafness). This phenomenon reflects the therapeutic impregnation, it should not lead to a reduction in dosage, and disappears when stopped |
| Pharmacokinetics (PK)/ Pharmacodynamics (PD) | Prodrug hydrolysed in the systemic circulation to dihydroartemisinin (DHA)<br>Cmax reached in 1 hour Bioavailability: 80%<br>Protein binding: 75% Hepatic elimination<br>Elimination half-life: 15 to 45 min<br>In the event of severe renal impairment: no dosage modifications | Cmax reached in 1 to 3 hours<br>Bioavailability: 76% Binding to plasma proteins in a concentration-dependent manner<br>Hepatic elimination Elimination half-life: 12 hours<br>In the event of severe renal impairment: decrease in dosage after the first 48 hours by adapting to quinine levels |

Legend: ACT: Artemisinin-based Combination Therapy; NGS: Nasogastric tube; ECG: Electrocardiogram; PADH: Post-Artesunate Deferred Hemolysis.

as in the case of acidosis, seems to play an important role [31]. A study by Kute *et al.* reported that the use of artesunate during hemodialysis in an Indian study involving 45 patients infected with *P. falciparum*, and the doses used were unsuitable (2.4 mg/kg/d) [32]. The conclusion of this study notes a recovery of renal function was noted in 81% of cases with an overall mortality of patients in this study of 12%. The average duration of hospitalization was: 5.7 ± 4 days with extremes of 1 and 17 days. Thus 68% of patients had a Glasgow score of ≤8, only seven patients or 28% benefited from orotracheal intubation with sedation and mechanical ventilation. This is explained by the fact that the service has only three resuscitation respirators on the one hand, and on the other hand, the absence of medical care cover does not allow patients to take care of themselves. The literature [28] recommends early orotracheal intubation in the management of coma, the prevention of cerebral edema and secondary cerebral lesions of systemic origin by implementing the usual neuroprotective measures. We recorded a death rate of 48%. Among them 12% were aged < 20 years, 16% patients had a very high parasite density and 20% patients on dialysis. This relatively high mortality rate would be mainly linked to the delay in admission, the severity of cerebral malaria with a very low Glasgow score on admission, high parasitaemia and multiple multi-organ failures. In 2010, the WHO adopted the threshold of 2% in the non-immune subject and that of 5% in the semi-immune, and it is true that fatal cases have been described with low parasitaemia on admission [33]. But in 2014-2015, the WHO retained the 10% threshold, taking into account the most recent studies carried out in endemic areas [25] [26]. A study of 65 patients who died of severe malaria in Thailand and Vietnam showed that death linked to cerebral malaria was directly associated with the massive sequestration of parasitized erythrocytes in the cerebral micro-vessels. The number of sequestered erythrocytes was correlated with pre-mortem coma. This can be explained by the fact that cerebral malaria is most often associated with significant cytoadherence of parasitized erythrocytes at the level of brain micro-vessels [34]. In a French study reporting 400 cases of severe malaria in adults treated in intensive care, the factors collected on admission and independently associated with mortality in intensive care were: age, depth of neurological damage and parasitaemia [35]. Regarding parasitaemia, the risk was increased by 1.4 times for each 5% increase, and the most relevant threshold for predicting mortality was 15% [35].

Our study has limitations insofar as it was not carried out over a long period and its monocentric nature.

## 5. Conclusion

Cerebral malaria is a diagnostic and therapeutic emergency. Cerebral malaria is mainly caused by *P. falciparum* and can take different clinical forms, the most important of which is cerebral involvement. Mortality in our study remains high in our context, despite the existence of a free treatment program for malaria with injectable artesunate. Awareness of the populations on the health problem and

the distribution of mosquito nets associated with the improvement of infrastructures and medical equipment sufficient to allow the management of all patients in deep coma would greatly reduce mortality.

## Conflicts of Interest

No conflicts of interest on the part of the authors to report.

## References

[1] World Health Organization (2000) Communicable Diseases Cluster. Severe Falciparum Malaria. *Transactions of The Royal Society of Tropical Medicine and Hygiene*, **94**, 1-90. https://doi.org/10.1016/S0035-9203(00)90300-6

[2] WHO: World Health Organization (2016) World Malaria Report 2016. Genoa.

[3] Marsh, K. and Snow, R.W. (1999) Malaria Transmission and Morbidity. *Parassitologia*, **41**, 241-246.

[4] Cowman, A.F., Healer, J., Marapana, D. and Marsh, K. (2016) Malaria: Biology and Disease. *Cell*, **167**, 610-624. https://doi.org/10.1016/j.cell.2016.07.055

[5] Sachs, J. and Malaney, P. (2002) The Economic and Social Burden of Malaria. *Nature*, **415**, 680-685. https://doi.org/10.1038/415680a

[6] Matthys, B., Vounatsou, P., Raso, G., Tschannen, A.B., Becket, E.G., Gosoniu, L., *et al.* (2006) Urban Agriculture and Risk Factors for Malaria in a Medium-Sized City in Cote d'Ivoire. *The American Journal of Tropical Medicine and Hygiene*, **75**, 1223-1231. https://doi.org/10.4269/ajtmh.2006.75.1223

[7] Robert, V., Macintyre, K., Keating, J., Trapé, J.F., Duchemin, J.B., Warren, M., *et al.* (2003) Transmission of Malaria in Urban Sub-Saharan Africa. *The American Journal of Tropical Medicine and Hygiene*, **68**, 169-176. https://doi.org/10.4269/ajtmh.2003.68.169

[8] Ayele, D.G., Zewotir, T.T. and Mwambi, H.G. (2012) Prevalence and Risk Factors of Malaria in Ethiopia. *Malaria Journal*, **11**, Article No. 195. https://doi.org/10.1186/1475-2875-11-195

[9] Mejia, A.T.A.P. (2008) Malaria and Poverty. *Annals of the New York Academy of Sciences*, **1136**, 32-37. https://doi.org/10.1196/annals.1425.037

[10] Crawley, J. (2001) Electroencephalographic and Clinical Features of Cerebral Malaria. *Archives of Disease in Childhood*, **84**, 247-253. https://doi.org/10.1136/adc.84.3.247

[11] Gay, F., Zougbede, S., N'Dilimabaka, N., Rebollo, A., Mazier, D. and Moreno, A. (2012) Cerebral Malaria: What Is Known and What Is on Research. *Neurological Review*, **168**, 239-256. https://doi.org/10.1016/j.neurol.2012.01.582

[12] Menendez, C., Fleming, A.F. and Alonso, P.L. (2000) Malaria-Related Anaemia. *Parasitology Today*, **16**, 469-476. https://doi.org/10.1016/S0169-4758(00)01774-9

[13] Douglas, N.M., Anstey, N.M., Buffet, P.A., Poespoprodjo, J.R., Yeo, T.W., White, N.J. and Price, R.N. (2012) The Anemia of *Plasmodium vivax* Malaria. *Malaria Journal*, **11**, Article No. 135. https://doi.org/10.1186/1475-2875-11-135

[14] Jakeman, G.N., Saul, A., Hogarth, W.L. and Collins, W.E. (1999) Anaemia of Acute Malaria Infections in Non-Immune Patients Primarily Results from Destruction of Uninfected Erythrocytes. *Parasitology*, **119**, 127-133. https://doi.org/10.1017/S0031182099004564

[15] Collins, W.E., Roberts, J.M. and Jeffery, G.M. (2003) A Retrospective Examination of Anemia during Infection of Humans with *Plasmodium vivax*. *The American Journal of Tropical Medicine and Hygiene*, **68**, 410-412. https://doi.org/10.4269/ajtmh.2003.68.410

[16] Dondorp, A.M., Desakorn, V., Pongtavornpinyo, W., Sahassananda, D., Silamut, K., Chotivanich, K., *et al.* (2005) Estimation of the Total Parasite Biomass in Acute Falciparum Malaria from Plasma PfHRP2. *PLOS Medicine*, **2**, e204. https://doi.org/10.1371/journal.pmed.0020204

[17] Lopera-Mesa, T.M., Doumbia, S., Konaté, D., Anderson, J.M., Doumbouya, M., Keita, A.S., Fairhurst, R.M., *et al.* (2015) Effect of Red Blood Cell Variants on Childhood Malaria in Mali: A Prospective Cohort Study. *The Lancet Haematology*, **2**, E140-E149. https://doi.org/10.1016/S2352-3026(15)00043-5

[18] Ndila, C.M., Uyoga, S., Macharia, A., Nyutu, G., Peshu, N., Ojal, J., Yamoah, L., *et al.* (2018) Human Candidate Gene Polymorphisms and Risk of Severe Malaria in Children in Kilifi, Kenya: A Case-Control Association Study. *The Lancet Haematology*, **5**, E333-E345. https://doi.org/10.1016/S2352-3026(18)30107-8

[19] Ouattara, A.K., Bisseye, C., Télesphore Elvira Bazie, B.V.J., Diarra, B., Compaore, T.R., Djigma, F., Simpore, J., *et al.* (2014) Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency Is Associated with Asymptomatic Malaria in a Rural Community in Burkina Faso. *Asian Pacific Journal of Tropical Biomedicine*, **4**, 655-658. https://doi.org/10.12980/APJTB.4.2014APJTB-2014-0100

[20] Mombo, L.E., Krishnamoorthy, R., Bisseye, C., Ntoumi, F., Lu, C.Y., Nagel, R.L. and Ossari, S. (2003) Human Genetic Polymorphisms and Asymptomatic Plasmodium Falciparum Malaria in Gabonese Schoolchildren. *The American Journal of Tropical Medicine and Hygiene*, **68**, 186-190. https://doi.org/10.4269/ajtmh.2003.68.186

[21] Maude, R.J., Barkhof, F., Hassan, M.U., *et al.* (2014) Magnetic Resonance Imaging of the Brain in Adults with Severe Falciparum Malaria. *Malaria Journal*, **13**, Article No. 177 https://doi.org/10.1186/1475-2875-13-177

[22] Mohanty, S., Mishra, S.K., Patnaik, R., *et al.* (2011) Brain Swelling and Mannitol Therapy in Adult Cerebral Malaria: A Randomized Trial. *Clinical Infectious Diseases*, **53**, 349-355. https://doi.org/10.1093/cid/cir405

[23] Seydel, K.B., Kampondeni, S.D., Valim, C., *et al.* (2015) Brain Swelling and Death in Children with Cerebral Malaria. *The New England Journal of Medicine*, **372**, 1126-1137. https://doi.org/10.1056/NEJMoa1400116

[24] Bouchaud, O., Bruneel, F., Caumes, E., Houzé, S., Imbert, P., Pradines, B., *et al.* (2020) Management and Prevention of Imported Malaria. 2018 Update of the 2007 French Clinical Guidelines. *Médecine et Maladies Infectieuses*, **50**, 161-193. https://doi.org/10.1016/j.medmal.2019.10.009

[25] World Health Organization (2014) Severe Malaria. *Tropical Medicine & International Health*, **19**, 7-131. https://doi.org/10.1111/tmi.12313_2

[26] World Health Organization (2018) World Malaria Report 2018. Geneva.

[27] Bruneel, F., Raffetin, A., Corne, P., Llitjos, J.F., Mourvillier, B., Argaud, L., *et al.* (2020) Management of Severe Imported Malaria in Adults. *Médecine et Maladies Infectieuses*, **50**, 213-225. https://doi.org/10.1016/j.medmal.2018.08.003

[28] Dondorp, A., Nosten, F., Stepniewska, K., *et al.* (2005) Artesunate versus Quinine for Treatment of Severe Falciparum Malaria: A Randomized Trial. *The Lancet*, **366**, 717-725. https://doi.org/10.1016/S0140-6736(05)67176-0

[29] Dondorp, A.M., Fanello, C.I., Hendriksen, I.C., *et al.* (2010) Artesunate versus Quinine in the Treatment of Severe Falciparum Malaria in African Children (AQUAMAT): An

Open-Label, Randomized Trial. *The Lancet*, **376**, 1647-1657. https://doi.org/10.1016/S0140-6736(10)61924-1

[30] White, N.J., Turner, G.D.H., Day, N.P.J. and Dondorp, A.M. (2013) Lethal Malaria: Marchiafava and Bignami Were Right. *Journal of Infectious Diseases*, **208**, 192-198. https://doi.org/10.1093/infdis/jit116

[31] Phu, N.H., Hien, T.T., Mai, N.T.H., Chau, T.T.H., Chuong, L.V., Loc, P.P. and Day, N. (2002) Hemofiltration and Peritoneal Dialysis in Infection-Associated Acute Renal Failure in Vietnam. *New England Journal of Medicine*, **347**, 895-902. https://doi.org/10.1056/NEJMoa020074

[32] Kute, V.B., Shah, P.R., Munjappa, B.C., Gumber, M.R., Patel, H.V., Jain, S.H., *et al.* (2012) Outcome and Prognostic Factors of Malaria-Associated Acute Kidney Injury Requiring Hemodialysis: A Single Center Experience. *Indian Journal of Nephrology*, **22**, 33-38. https://doi.org/10.4103/0971-4065.83737

[33] World Health Organization (2010) World Health Organization Guidelines for the Treatment of Malaria. Geneva.

[34] Pongponratn, E., Turner, G.D., Day, N.P., Phu, N.H., Simpson, J.A., *et al.* (2003) An Ultrastructural Study of the Brain in Fatal *Plasmodium falciparum* Malaria. *The American Journal of Tropical Medicine and Hygiene*, **69**, 345-359. https://doi.org/10.4269/ajtmh.2003.69.345

[35] Bruneel, F., Tubach, F., Corne, P., Megarbane, B., Mira, J.P., Peytel, E., *et al.* (2010) Severe Imported Falciparum Malaria: A Cohort Study in 400 Critically Ill Adults. *PLOS ONE*, **5**, e13236. https://doi.org/10.1371/journal.pone.0013236