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Review

# Pulmonary complications of malaria: An update☆

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ABSTRACT

Malaria is the most important parasitic disease worldwide, being a public health challenge in more than 90 countries. The incidence of pulmonary manifestations has increased in recent years. Acute respiratory distress syndrome is the most severe form within the pulmonary complications of malaria, with high mortality despite proper management. This syndrome manifests with sudden dyspnoea, cough and refractory hypoxaemia. Patients should be admitted to intensive care units and treated with parenteral antimalarial drug treatment and ventilatory and haemodynamic support without delay. Therefore, dyspnoea in patients with malaria should alert clinicians, as the development of respiratory distress is a poor prognostic factor.



## Actualización de las complicaciones pulmonares de la malaria

*Palabras clave:*
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*Plasmodium falciparum*
Mortalidad

RESUMEN

La malaria es, globalmente, la enfermedad parasitaria más importante, representando un problema de salud pública en más de 90 países. En los últimos años se ha observado un aumento en la incidencia de las complicaciones pulmonares. Su forma clínica más grave es el síndrome de distrés respiratorio agudo, que tiene una elevada mortalidad a pesar de un adecuado abordaje terapéutico. Se presenta como un cuadro de disnea súbita, tos e hipoxemia refractaria, requiriendo ingreso en unidades de cuidados intensivos, tratamiento antipalúdico parenteral precoz, y soporte ventilatorio y hemodinámico. Todo paciente con malaria que presente disnea requiere vigilancia estrecha, ya que el desarrollo de distrés respiratorio es un factor de mal pronóstico.



## Introduction

Malaria is an infectious disease transmitted by the *Anopheles* spp. female mosquito and produced by 5 species of the *Plasmodium parasite*: *Plasmodium falciparum* (*P. falciparum*), *Plasmodium vivax* (*P. vivax*), *Plasmodium ovale* (*P. ovale*), *Plasmodium malariae* and *Plasmodium knowlesi* (Fig. 1). It is a global public health problem, especially in the tropics and subtropics, as reflected in the estimates made in 2015 by the World Health Organization (WHO): 3.2 billion people in 97 countries at risk of contracting the disease, 214 million cases and 438,000 deaths. It is the tropical disease with the highest number of fatalities, most of them occurring in children under 5 and pregnant women in Africa.[1,2]

Complications of malaria are often subject to study, not so much for its frequency as its high mortality (up to 30% despite a correct treatment). Whenever there is evidence of organ dysfunction, either by clinical data or by laboratory data, it is called severe or complicated malaria. The most common clinical signs and symptoms are cerebral malaria, renal failure and metabolic acidosis, but 2 pulmonary manifestations are also included in its definition: pulmonary oedema and acute respiratory distress syndrome (ARDS).[3] Most cases of ARDS occurring in malaria patients are, like the rest of complications, secondary to *P. falciparum* species infection, but cases have been reported in all species.[4–10]

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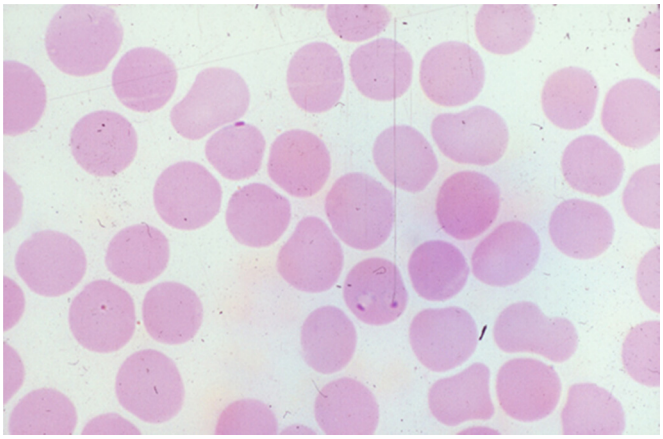

**Fig. 1.** Peripheral blood smear stained with Giemsa where multiple parasitism by *Plasmodium falciparum* trophozoites of a red blood cell is observed. This species is responsible for most of the pulmonary complications of malaria.

## Epidemiology

The incidence of pulmonary complications of malaria has increased in recent decades, being more frequent in non-immune patients between 20 and 40 years of age and in situations of delayed treatment (after the seventh day from symptoms onset). A 4–18% of adult patients with *P. falciparum* malaria present with respiratory symptoms and post-mortem studies in non-immune patients reveal that 21–23% develop pulmonary oedema. Regarding ARDS, an incidence of 5–25% is estimated in the case of *P. falciparum* and 1–10% in *P. vivax*.[2,11] Advanced age, immunosuppression and pregnancy are risk factors for developing this entity.[7]

## Physiopathogeny

The essential pathogenesis of malaria is the parasite invasion of red blood cells with the subsequent development of anaemia due to both, haemolysis as well as splenic sequestration of the parasitized red blood cells. Parasitic destruction releases toxins that cause endothelial damage and activate proinflammatory cytokines such as interleukin (IL)-1, 6 and 12 occurs, the *tumour necrosis factor* (TNF)α and platelet activating factor; these cytokines promote cell adhesion (parasitized red blood cells, leucocytes and platelets) to the endothelium, causing tissue hypoxia.[12]

By extrapolation from studies in cerebral malaria, it is considered that serious forms of malaria are secondary to hypoxia due to occlusion of the microvasculature of vital organs by parasitized red blood cells. These RBCs also adhere together to form structures called "rosettes" contributing to a reduced circulatory flow and multiorgan dysfunction.[12,13]

Regarding the pulmonary complications, it appears that the endothelial damage is multifactorial:

a) Development of an intense inflammatory response by activation of inflammatory cells and cytokines. An imbalance occurs in the production of cytokines, with proinflammatory being predominant versus antiinflammatory.[14]
b) Pulmonary accumulation of monocytes and intravascular inflammatory changes.[6]
c) "Extrapulmonary" factors: treatment with quinine, thrombocytopenia, patient's immune response, formation of "rosettes" (*P. falciparum*), decreased production of nitric oxide.[15–17]

Some authors argue that the origin of endothelial damage in ARDS varies depending on the *Plasmodium* species: while in the case of *P. falciparum* the cause seems to be the same as in other complications (microvascular endothelium obstruction due to adhesion of the parasitized red blood cells), in other species this seems to have a minor role.[14] Thus, in *P. vivax* and *P. ovale* infections, endothelial damage is primarily caused by an post-treatment inflammatory response induced by parasite death and capillary reperfusion, with the release of soluble mediators (proinflammatory cytokines and parasitic antigens).[10,18] Among the cytokines, TNFα appears to have a predominant role in the pathogenesis of pulmonary oedema: firstly, it induces neutrophil hyper-adhesion to the endothelium (by expression of adhesion molecules on the cell surface, particularly ICAM-1), and secondly, alters the expression of the sodium channels, thus increasing epithelial and endothelial permeability.[14,19] In any case, endothelial dysfunction is a disruption of the alveolar-capillary barrier integrity, allowing the passage of proteins into the interstitium with an increase in interstitial pressure that causes the passage of fluids to the alveolar space. This is a non-cardiogenic pulmonary oedema, sometimes aggravated by hypoalbuminaemia and fluid overload often present in patients with malaria.[11]

## Clinical signs and symptoms

Pulmonary involvement in malaria can be asymptomatic or oligosymptomatic. 20–50% of patients with malaria have dry cough. Sometimes they present with tachypnoea, which may be due to fever, anaemia or lung disease. Pneumonitis is rare, −1.5% in some series,[4] and some authors suggest that it is due to intercurrent pneumonia, pulmonary oedema or the existence of metabolic acidosis.[15] There have been reports of interstitial pneumonia caused by *P. vivax*.[20]

The most feared complication is the development of severe respiratory insufficiency due to an increased alveolar permeability, known as respiratory distress. When a number of criteria are met, it is called ARDS, a serious multifactorial aetiology entity (Table 1). Although its clinical presentation may vary depending on the causal species of *Plasmodium* (Table 2), the typical clinical features of ARDS consists of sudden dyspnoea, coughing and severe hypoxia, which can be refractory to oxygen therapy and compromise the patient's life. Often accompanied by agitation and disorientation, which may be due to hypoxia itself or concomitant cerebral malaria. On physical examination, tachypnoea is usually the earliest sign, followed by central and peripheral cyanosis, bibasilar crackles and expiratory wheezing.[2,21]

## Diagnosis

In all patients with uncomplicated malaria the presence of *P. falciparum* (alone or in co-infection) should be ruled out exhaustively. The *gold standard* diagnostic method in malaria is parasite visualization in the thick film and the peripheral blood smear. If a microscope is not available or false negatives are suspected (when the patient has received incomplete antimalarial treatment) immunochromatographic antigen detection tests that are simple and quick to perform can be used. These have a 90% sensitivity (approx.). However, these tests do not replace the smear and the thick film, as they have false negatives and do not allow to quantify parasitaemia.[3]

The diagnosis of ARDS is based on clinical history and physical examination, performing an arterial blood gas test (showing hypoxaemia and, sometimes, metabolic acidosis) and a simple chest radiography, showing evidence of bilateral alveolar infiltrates with normal cardiac silhouette (except in cases with concomitant disease) (Fig. 2); pleural effusion and thickening of fissures are rare finds. Malaria should be ruled out in all patients with respiratory distress residing in an endemic area or coming from it. The presence of a radiographic infiltrates in these patients with distress does not