Respiratory Manifestation of Malaria: An Update

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ABSTRACT

Globally, malaria is the most important parasitic disease, representing a public health problem in more than 90 countries. In recent years, there has been an increased incidence of respiratory complications. Acute respiratory distress syndrome is the most severe form of the respiratory complications of malaria, with high mortality despite adequate therapeutic management. This syndrome is characterized by severe dyspnea, cough and refractory hypoxemia. Early ventilator and hemodynamic support with the execution of parenteral antimalarial treatment are key components of management. Therefore, the presence of dyspnea in malaria patient should alert physicians, as the development of respiratory distress is a poor prognostic factor.

Key-words: Malaria, respiratory complications, Acute respiratory distress syndrome
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INTRODUCTION

Malaria is an infectious disease transmitted by the female Anopheles mosquito spp., which produced five species of Plasmodium parasite: *Plasmodium ovale (P. ovale), Plasmodium falciparum (P. falciparum), Plasmodium vivax (P. vivax), Plasmodium malariae and Plasmodium knowlesi* (fig 1). It is a global public health problem, especially in poor, tropical and subtropical areas of the world. In 2015 World Health Organization (WHO) estimated that 3.2 billion people in 97 countries are at risk of contracting this disease, of whom 1.2 billion are at high risk. In 2015, there were 214 million cases new cases of malaria worldwide with an estimated 438 000 malaria deaths [1]. It is the tropical disease with the highest number of fatalities, most of them occurring in children under age of 5 years and pregnant women in Africa [2,3]. The complications of the malaria are often a subject to study, both for its frequency and for its high mortality (up to 30 % despite a correct treatment). Severe or complicated malaria is defined by clinical or laboratory evidence of vital organ dysfunction. The most frequent clinical manifestations of complicated infections are cerebral malaria, renal insufficiency, and metabolic acidosis, nonetheless, this description also includes two pulmonary manifestations in i.e. pulmonary edema and acute respiratory distress syndrome (ARDS) [4]. Like the rest of complications, most cases of ARDS occurred in patients with malaria are secondary to infection caused by the *P. falciparum* species, but cases have been reported in all species [5-10].

1.1. Epidemiology

The incidence of pulmonary complications of malaria has increased in recent decades. It is more frequent in non-immune patients between 20 and 40 years and in conditions of delay in treatment (beyond the seventh day of the onset of symptoms). About 4-18 % of the adult patients with *P. falciparum* malaria presents with respiratory symptoms, and post-mortem studies in non-immune patients reveal that 21-23 % develops pulmonary edema. Concerning ARDS, estimated incidence in case of *P. falciparum* is 5-25% and 1-10% in *P. vivax* [2,11]. Advanced age, immunosuppression and pregnancy are risk factors for developing this condition [8].

1.2. Pathophysiology

The essential steps in pathogenesis include invasion of red blood cells by malarial parasite with the subsequent development of anaemia by both, haemolysis and splenic sequestration of malaria-parasitized red blood cells. With the parasitic destruction there is a release of toxins that cause endothelial damage and activate pro-inflammatory cytokines such as interleukins (IL) - 1, 6-12, tumor necrosis factor (TNF)-α and platelet activating factor; These

cytokines facilitate the adhesions of cells (parasitized erythrocytes, leukocytes and platelets) to the endothelium, causing tissue hypoxia [12].

By the extrapolation of findings from cerebral malaria, it is considered that serious forms of malaria are secondary to hypoxia caused by occlusion of the microvasculature of vital organs by parasitized RBCs. These RBCs also adhere together to form structures called "rosettes" which contributes to reduced circulatory flow and multiple organ dysfunctions [13,12].

In pulmonary complications, it appears that the endothelial damage is multifactorial:
1. Development of an intense systemic inflammatory response by the activation of inflammatory cells cause an imbalance in the production of cytokines, pro-inflammatory dominates over anti-inflammatory [14].
2. Pulmonary accumulation of monocytes and intravascular inflammatory changes [10].
3. Extra-pulmonary factors include quinine treatment, thrombocytopenia, immune response of the patient, formation of rosettes (*P. falciparum*), and decreased production of nitric oxide [15-17].

Some authors argue that the cause of endothelial damage in ARDS vary depending on the species of Plasmodium: while in the case of *P. falciparum*, the cause seems to be the same as in other complications (obstruction of microvascular endothelium adhesion of RBCs parasitized), however, in other species this appears to have a minor role [16]. Thus, in *P. vivax* and *P. ovale* infection, the endothelial damage would primarily be due to post-treatment induced inflammatory response caused by the death of parasites and capillary reperfusion with the release of soluble mediators (proinflammatory cytokines and parasitic antigens) [18,19]. Among the cytokines, TNF-α appears to have a predominant role in the pathogenesis of pulmonary edema: at one end it increases the adhesion of neutrophils to endothelium (by expression of adhesion molecules on the cell surface, particularly ICAM-1), and on the other hand, it alters the expression of sodium channels, increasing both endothelial and epithelial permeability [14,20]. This pulmonary edema is non-cardiogenic and sometimes aggravated by hypoalbuminemia and fluid overload which is often present in patients with malaria [11].

1.3. Clinical presentation
The pulmonary involvement in malaria can be asymptomatic or with few symptoms. About 20-50% of patients with malaria have a dry cough. Occasionally patient present with tachypnea, which may be due to the presence of fever, anemia or lung disease. Pneumonitis is rare with a reported incident of 1.5% in some case series [7], some authors suggest that it occurs as an intercurrent disease in conditions like pneumonia, pulmonary edema or metabolic acidosis [16]. Interstitial pneumonia has been reported with *P.vivax* infection [21].

The most serious pulmonary complication is the development of severe respiratory insufficiency by an increase in alveolar permeability, which is known as respiratory distress. When a number of criteria are met it is called ARDS, a serious entity with a multifactorial etiology (table 1). Although its clinical presentation may vary depending on the causative plasmodium species (table 2). ARDS in its typical clinical features consists of sudden dyspnea, coughing, and severe hypoxia that may be refractory to oxygen therapy and fatal. It is frequently accompanied by agitation and disorientation, which may be due to hypoxia or a concomitant cerebral malaria. Tachypnea is the earliest sign which can be seen on physical examination followed by peripheral cyanosis, wheezing on expiration and bibasilar crackles [2,22].

1.4. Diagnosis
In all patients with complicated malaria, *P. falciparum* should be ruled out comprehensively (either alone or in co-infection). Microscopic visualization of malarial parasites on thick and/or thin film is considered as 'Gold Standard' for diagnosis of malaria. When microscopy is not available, or there is a suspicion of false negative (when the patient has received incomplete antimalarial treatment), immunochromatographic antigen detection tests can be used, which is easier and rapid with a sensitivity of 90%. However, these tests do not replace the smear and the thick film, as they have a chance of false negatives results and have unpredictable efficiency at low and very high parasitemia [4].

The diagnosis of ARDS is based on clinical history and physical examination, an arterial blood gas analysis (showing hypoxemia and sometimes, metabolic acidosis) and evidence of bilateral alveolar infiltrates with a cardiac silhouette (except in cases with the pre-existing disease) on chest radiography (fig. 2); pleural effusion and thickening of fissures are rare findings. Malaria should be ruled out in all patients with respiratory distress residing or comes from the endemic area. The presence of a radiographic infiltrate in these patients with respiratory distress does not rule out the diagnosis of malaria, since up to 13% may present with concomitant pneumonia co-infection [6].

1.5. Treatment

1.5.1.General supportive measures

Patients who develop ARDS are at high risk of mortality, and they must be admitted to an intensive care unit (ICU), with continuous monitoring of systolic blood pressure, pulmonary arterial oxygen saturation, glucose levels and urine output [23]. In areas without ICU facility, hemodynamic and respiratory parameters (see below) should be stabilized while preparing for transfer to tertiary care service. Many tropical and subtropical rural areas lacks specialized health units, in these situation monitouring should include at least; temperature, heart rate, blood pressure and the level of consciousness [4]. The patient should be evaluated and corrected for all possible reversible causes of distress (acidosis, anemia). Establishment of primary prophylaxis for venous thromboembolism and gastrointestinal bleeding is a part of usual care. It is preferable to give nutrition enterally rather than parenterally to prevent catheter-associated infections [11,6]. There is not enough evidence to recommend standardized regimens of corticosteroids, mannitol or the use of exchange transfusion.

1.5.2.Fluid therapy

In recent years our knowledge regarding the use of fluids in ARDS has improved considerably and is more established now. Currently, a "conservative" (fluid intake is restricted and urinary output is increased in an attempt to decrease lung edema, shorten the duration of mechanical ventilation, and improve survival [24]) strategy is recommended, which decreases the incidence of pulmonary edema, multiple organ failure, days on ventilator and length of hospital stay [2,25]. WHO recommends the use of 5% dextrose or 0.9% saline at a rate of 3-4ml/kg/h in the pediatric population and 1-2 ml/kg/h in adults [4]. If necessary, crystalloids and vasopressors (such as dopamine) may be used to maintain a central venous pressure of 8-12 mmHg, avoiding the use of adrenaline owing to its ability to cause lactic acidosis [11,26]. For high venous pressure, loop diuretics, vasodilators, opiods or hemofiltration or dialysis, may be used to optimize cardiac output.

1.5.3.Ventilatory support

Mechanical ventilation strategies in malaria-associated ARDS are same as in ARDS caused by other causes, with the exception of permissive hypercapnia, since the carbon dioxide (CO_2) increases cerebral blood flow which in turns increases intracranial pressure, which has a deleterious effect on patients with malaria and altered level of consciousness [6]. For initial respiratory support oxygen therapy with FiO_2 of 0.5-0.6 by face mask can be used. Other measures options includes mechanical ventilation or noninvasive type continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP); Some studies have shown a better outcome with the latter in *P. vivax* ARDS [27]. Invasive mechanical ventilation should be conidered in the following cases:

a) Patients with altered level of consciousness.
b) Patients requiring an FIO2 greater than 0.6 (or higher pressures than CPAP at 10 cm H_2O) to maintain PaO_2 greater than 60 mmHg [8].

It is recommended to maintain expiratory: inspiratory ratio of 1:1 or 2:1. The FiO2 and positive end-expiratory pressure (PEEP) must be adjusted to maintain an adequate blood oxygenation [28]. Extracorporeal membrane oxygenation (ECMO) is a circuit that directly oxygenates the blood while eliminating CO2, improve gas exchange and accelerates healing of lung tissue. Its use can be considered in refractory cases of ARDS when positive pressure ventilation is not able to maintain an adequate gas exchange or when there is an unacceptable hypercapnia [29]. In malaria experience with ECMO is limited, and available data are case series, where it has been observed that it allows maintaining a low tidal volume (<6 ml/kg) and low oxygen concentrations, thereby reducing pulmonary damage associated with ventilation [30]. Besides the strict control of arterial pressure of CO_2, it also prevents the elevation of intracranial pressure [6]. Despite its benefits, ECMO is not risks free, and there are no standard guidelines that address its use in ARDS. Alves et al. recommend using ECMO only in cases of ARDS refractory to other measures [30]. Prone positioning increases oxygenation but it does not improve survival [31].

1.5.4. Antimalarial agents

All patients with confirmed severe malaria should receive early parenteral antimalarial treatment. Intravenous artesunate is a drug of choice for both adults and children and in pregnant women. WHO also recommends artesunate as a first-line treatment for severe malaria. Randamozied controlled trial showed that artesunate decrease mortality by 35% in adults and 22% in children when compared with quinine [32,6]. The initial dose is 2.4 mg/kg/12h (2 doses), followed by 2.4 mg/kg/d. If IV artesunate is not available, intravenous quinine can be used with careful monitoring of its most common side effects: hypoglycemia and arrhythmias. Tropical regions usually have greater availability of intramuscular artemether injection, but its absorption is erratic, and therefore its use in severe malaria should be avoided. Treatment should be administered parenterally for at least 24 h. Subsequently, if the clinical course is favorable and thick blood films for malaria parasites shows negative, patient can be switched to oral treatment, preferably with artemisinin-based combinations [4].

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1.5.5. Antibiotic treatment

Around 0.2 to 13% of malaria patients may have concomitant bacteremia, being the most likely to suffer serious bacterial infections [33]. Some authors propose that bacterial sepsis have a role in the ARDS pathogenesis, suggesting to initiate broad spectrum antibiotic treatment in all malaria patients who develop this ARDS [11]. WHO, in turn, recommended the use of antibiotics in all pediatric patients with altered level of consciousness to rule out bacterial infection, and in adults who have hypotension or a radiological infiltrate. The predominant infections in these patients are caused by respiratory pathogens (pneumococcus and Haemophilus influenzae) and enterobacteria; so a third-generation cephalosporins would be a good option [4,6].

1.6. Prognosis

The development of ARDS is a predictor of mortality in malaria [33,2]. About 40% of patients die despite appropriate treatment, without ventilatory support, the incident is, even more, higher, around 80-100%. The prognosis worsens when the causative agent is P. falciparum, given its frequent association with other complications [11].

Table 1: Features respiratory distress and adult respiratory distress syndrome of malaria

	Respiratory distress	**ARDS**
Definition	Respiratory distress with severe hypoxemia secondary to interstitial lung involvement by increased alveolar permeability [2]	The following must be met [34]: ▪ Establishment of distress within the first week of onset of known lung damage ▪ bilateral opacities on chest radiography or CT, not completely justified by pleural effusion, atelectasis or pulmonary nodules ▪ Respiratory failure is not fully explained by heart failure or fluid overload ▪ Deterioration in oxygenation
Causes	▪ hyperventilation secondary to severe metabolic acidosis ▪ hyperlactatemia[a] ▪ concomitant pneumonia ▪ fluid overload ▪ severe anemia ▪ ARDS	▪ sepsis ▪ aspiration pneumonia ▪ bacterial / viral infection ▪ idiopathic

ARDS: adult respiratory distress syndrome; CT: computed tomography

[a] lactic acid produced by the parasite, tissue hypo-perfusion or renal failure. It is the most common type of distress in African children, and it is also common in adults [32]. It seems that hyperventilation contributes to pulmonary edema, although both may appear simultaneously [10].
*[b] in absence of risk factors for ARDS, an objective assessment is required to rule out hydrostatic pulmonary edema (e.g. by echocardiography).*
[d] as define by the relationship between the arterial partial pressure of oxygen (PaO 2) / fraction of inspired oxygen (FiO 2) or the relationship between the peripheral oxygen saturation (SpO2 measured by pulse oximetry) and FiO2 (SpO 2 / FiO 2). The degree of hypoxemia defines the severity of ARDS.

Table 2: Clinical differences of adult respiratory distress syndrome based causitive Plasmodium species

	P. knowlesi , P. falciparum	*P. vivax, P. ovale*
Onset of ARDS	From the start of symptoms	2-3 days of initiation antimalarial treatment (up to 14 days)
Parasitaemia	Present with elevation	Negative or declining
Associated complications	cerebral malaria, renal failure, acidosis, hypoglycemia, CID	Acute renal failure is the only usual complication

ARDS: adult respiratory distress syndrome; DIC: disseminated intravascular coagulation.
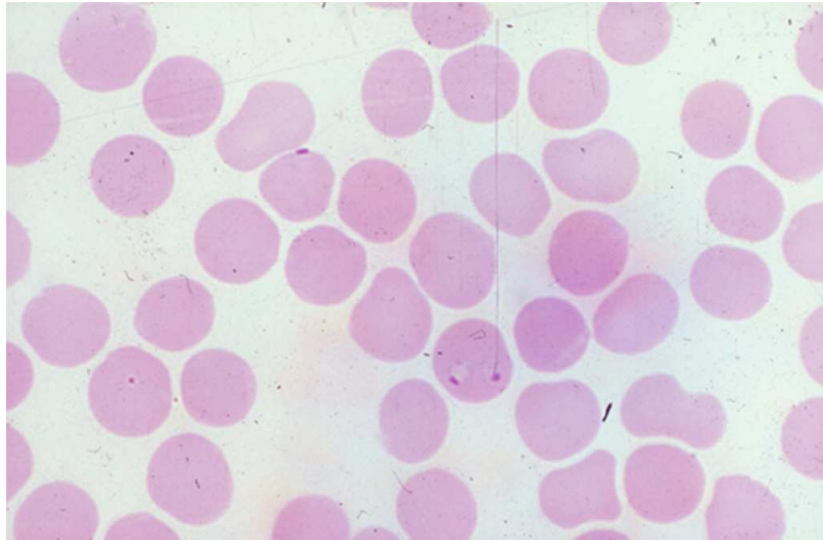
Figure 1. Peripheral blood smear stained with Giemsa stain showing multiple parasitized red blood cells by trophozoites of Plasmodium falciparum. This species is responsible for most of the pulmonary complications of malaria
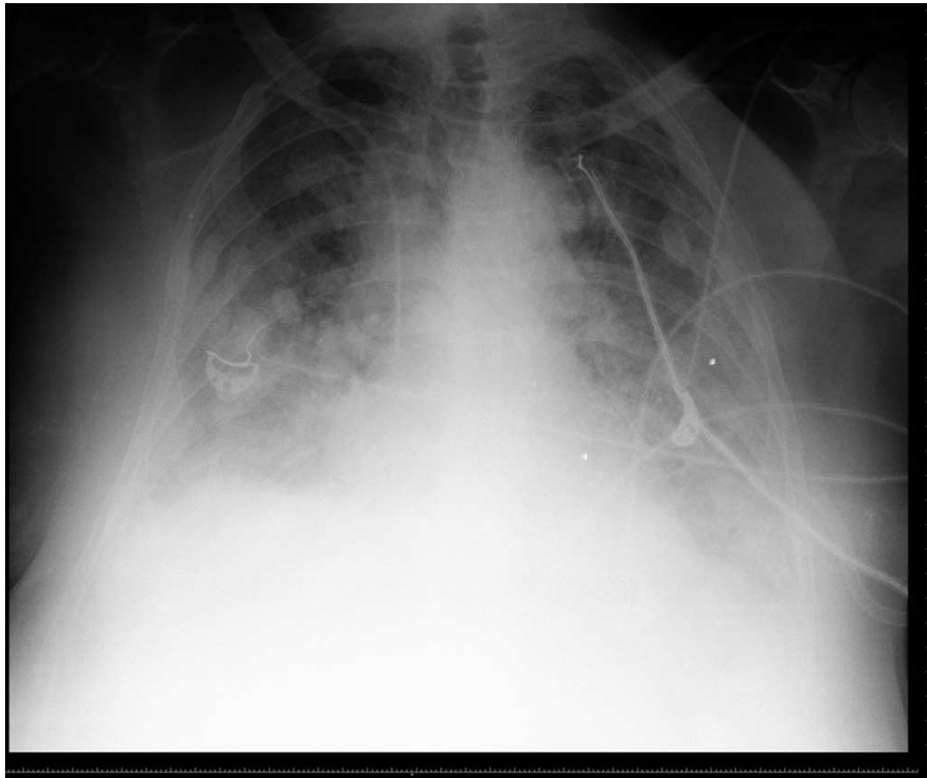
Figure 2. Chest radiograph of a patient with acute respiratory distress syndrome secondary to severe *P. falciparum* malaria. Respiratory symptoms began 72 h after the onset of a parenteral antimalarial treatment

CONCLUSION

In recent years, there has been an increased incidence of pulmonary forms of severe malaria. ARDS is the most severe clinical form because it has a poor prognosis despite appropriate treatment. Whenever there is a clinical suspicious of ARDS in severe malaria, ventilatory and hemodynamic support should be initiated at early stages preferably in an ICU with the execution of parenteral antimalarial treatment.

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