

## Review Articles

# Acute lung injury and acute respiratory distress syndrome in malaria

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### Abstract

Malaria is an important treatable cause of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in the tropics and in the returning traveller in the non-endemic areas. ARDS is an important complication in severe, complicated falciparum malaria and has been described in *P. vivax* and *P. ovale* malaria also. Malarial ALI/ARDS is more common in adults than in children. Pregnant women and non-immune individuals are more prone to develop this condition. Increased alveolar capillary permeability resulting in intravascular fluid loss into the lungs appears to be the key pathophysiologic mechanism. In malaria, ARDS can develop either at initial presentation or after initiation of treatment when the parasitaemia is falling and the patient is improving. Patients present with acute onset dysnoea that can rapidly progress to respiratory failure. The diagnosis of malaria is confirmed by slide microscopy supported by the use of rapid antigen tests. Patients with malarial ARDS should be managed in an intensive care unit. Careful attention must be paid to haemodynamic stabilisation and optimising fluid balance. Currently, specific treatment choices for malaria include parenteral artemisinins or intravenous quinine along with doxycycline. Respiratory failure requires endotracheal intubation and assisted mechanical ventilation. Co-existent bacterial sepsis is frequently present in patients with malarial ARDS even though an obvious focus may not be evident. Appropriate broad spectrum antibiotic therapy must be started when there is a clinical suspicion after procuring the microbiological specimens. ARDS in malaria is a disease with a high mortality. Early diagnosis, institution of specific antimalarial treatment and assisted ventilation can be life-saving.

**Key words** Acute lung injury – acute respiratory distress syndrome – malaria – *Plasmodium falciparum* – *Plasmodium ovale* – *Plasmodium vivax*

### Introduction

Even today, malaria remains a significant public health problem globally, especially in the tropical and subtropical areas. More than two billion people (36% of the world population) are exposed to the risk of contracting malaria<sup>1,2</sup>. Each year, malaria directly causes nearly one million deaths and about 500 million clinical cases, of which 2 to 3 million constitute

severe and complicated malaria<sup>3,4</sup>. Recent epidemiologic models, geographical and demographic data suggest that *Plasmodium falciparum* estimates outside Africa, especially in southeast Asia, are 200% higher than reported by the World Health Organization (WHO) — 118.94 million of global estimates of 515 million cases<sup>2,5</sup>. Malaria, like tuberculosis (TB) has a devastating socioeconomic impact on the affected countries. The term *disability adjusted life*

years (DALYs) has been introduced by the WHO, and one lost DALY means one lost year of “healthy life” on account of disease (either through death or illness/disability)<sup>6,7</sup>. It has recently been estimated that in India, the total DALYs lost due to malaria were 1.86 million years<sup>5</sup>.

While patients with uncomplicated malaria usually present with fever and non-specific symptoms, severe and complicated malaria is characterised by multi-organ involvement including acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)<sup>8-10</sup>. Recent years have witnessed a shift in the profile of patients with complicated malaria<sup>5,9</sup>; multiorgan system failure, ALI and ARDS are being increasingly reported in falciparum malaria<sup>8,9,11,12</sup> and in malaria caused by the species hitherto considered benign, *P. vivax*<sup>13-16</sup>, and in *P. ovale*<sup>17</sup> and *P. malariae*<sup>18</sup> also.

The more serious forms of malaria ravage the tropical countries where the disease is rampant. However, increasing international travel has resulted in severe complicated malaria and ARDS being witnessed in industrialised countries also especially in the returning travellers<sup>19-21</sup>.

### Pulmonary manifestations in malaria

Pulmonary symptoms such as cough with or without expectoration, dyspnoea, among others have been described in patients with malaria<sup>11,12</sup>. Historically, three clinical types of pulmonary manifestations have been variously described in patients with falciparum malaria, namely *bronchitic*, *pneumonic* and *bronchopneumonic* forms. It has been suggested that malarial pneumonitis is uncommon and these manifestations are probably due to coincident pneumonia, pulmonary oedema and perhaps, metabolic acidosis<sup>11,12</sup>.

### ALI and ARDS in malaria

Our understanding of ALI and ARDS has increased significantly in the last two decades. Called “adult

respiratory distress syndrome” in the earlier years, the entity is now called as “acute respiratory distress syndrome” as it can occur in children also. The ARDS is a disease with a high mortality and is a common cause of admission into intensive care units (ICUs) all over the world<sup>22-25</sup>.

The initial reports describing ARDS lacked specific defining criteria. In 1988, an expanded definition was proposed that quantified the physiologic respiratory impairment using a four-point lung-injury scoring system<sup>26</sup>. Although the lung injury scoring system was widely employed for research purposes and in clinical trials, it was not found to be useful in predicting the outcome during the first 24 to 72 h after the onset of the ARDS and had limited clinical usefulness. The American-European Consensus Conference definition of ALI and ARDS was published in 1994<sup>27</sup> (Table 1). This definition is simple to apply

**Table 1. Definitions of acute lung injury and acute respiratory distress syndrome**

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#### *Acute lung injury*

Acute onset

$\text{PaO}_2/\text{FIO}_2 \leq 300^*$

$\text{SpO}_2/\text{FIO}_2 \leq 315^{*\dagger}$

Bilateral infiltrates on the frontal chest radiograph

PCWP  $\leq 18$  mm Hg, or no clinical evidence of left atrial hypertension

#### *Acute respiratory distress syndrome*

Acute onset

$\text{PaO}_2/\text{FIO}_2 \leq 200^*$

$\text{SpO}_2/\text{FIO}_2 \leq 235^{*\ddagger}$

Bilateral infiltrates on the frontal chest radiograph

PCWP  $\leq 18$  mm Hg, or no clinical evidence of left atrial hypertension

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\*Irrespective of level of positive end-expiratory pressure; †The  $\text{SpO}_2/\text{FIO}_2$  threshold of 315 yielded a sensitivity of 91% and specificity of 56% for accurately identifying acute lung injury<sup>28</sup>;

‡The  $\text{SpO}_2/\text{FIO}_2$  threshold of 235 yielded a sensitivity of 85% and specificity of 85% for accurately identifying acute respiratory distress syndrome<sup>28</sup>;  $\text{PaO}_2$  = Arterial oxygen tension;  $\text{FIO}_2$  = Fraction of inspired oxygen;  $\text{SpO}_2$  = Pulse oximetric measurement of oxygen saturation; PCWP = Pulmonary capillary wedge pressure (Source: References 27, 28).

in the clinical setting and also recognises that the severity of clinical lung injury varies according to the severity of arterial hypoxaemia<sup>27</sup>. Recently, pulse oximetric saturation (SpO<sub>2</sub>) to fraction of inspired oxygen (FIO<sub>2</sub>) ratio (S/F ratio) has been found to correspond to the arterial oxygen tension (PaO<sub>2</sub>) to FIO<sub>2</sub> ratio (P/F)<sup>28</sup>. The S/F ratio threshold value of 235 was found to have a sensitivity of 85% and specificity of 85% for a P/F ratio of 200 for the diagnosis of ARDS. Similarly, the S/F ratio threshold value of 315 was found to have a sensitivity of 91% and specificity of 56% for a P/F ratios of 300 for the diagnosis of ALI. These non-invasive substitutes for assessing oxygenation can be useful in the settings where arterial blood gas (ABG) analysis is not available and facilitate the monitoring of the course of the disease.

*Epidemiology*: Reliable epidemiological data are not available regarding the prevalence of ALI/ARDS in patients with malaria. The prevalence of ARDS in patients with malaria as documented in studies from India, published in peer reviewed journals is listed in Table 2<sup>29-38</sup>. Observations from these studies and other published reports<sup>11,12</sup> suggest that about 5% patients with uncomplicated falciparum malaria and 20%–30% patients with severe and complicated malaria requiring ICU admission may develop ARDS. It should be remembered, however, that different denominators have been used in various publications and meaningful comparison of such data is not possible. Furthermore, in many of the previously reported studies, the precise definition used for the diagnosis of ARDS is also not mentioned.

**Table 2. Prevalence of ARDS in patients with malaria**

Study (Reference)	Denominator used	No. of patients studied	% Prevalence of ARDS
Kochar <i>et al</i> (2006) <sup>29</sup>	Patients with severe <i>P. falciparum</i> and mixed ( <i>P. vivax</i> and <i>P. falciparum</i> ) malaria admitted to a classified malaria ward	192*	2.1
Mishra <i>et al</i> (2005) <sup>30</sup>	Slide-positive patients with malaria	150†	4.6
Mohan <i>et al</i> (2003) <sup>9</sup>	Patients with severe falciparum malaria admitted to an ICU in a tertiary care teaching hospital	480	2.9
Krishnan & Karnad (2003) <sup>31</sup>	Patients with severe falciparum malaria admitted to an ICU	301	3.3
Gupta <i>et al</i> (2001) <sup>32</sup>	Patients admitted to a respiratory ICU	28‡	21.4
Mehta <i>et al</i> (2001) <sup>33</sup>	Patients with acute renal failure due to falciparum malaria	24	29.1
Rajput <i>et al</i> (2000) <sup>34</sup>	Slide-positive patients with malaria	100§	4
Chishti <i>et al</i> (2000) <sup>35</sup>	Falciparum malaria patients admitted to a district hospital	64	6.25
Murthy <i>et al</i> (2000) <sup>36</sup>	Falciparum malaria patients admitted to a tertiary care teaching hospital	158	11.4
Kochar <i>et al</i> (1997) <sup>37</sup>	Patients with severe falciparum and mixed ( <i>P. vivax</i> and <i>P. falciparum</i> ) malaria admitted to a classified malaria ward	532	3.01
Katyal <i>et al</i> (1997) <sup>38</sup>	Falciparum malaria patients admitted to a medical college hospital	66	4.5

\*Data for the year 2001; †72 (48%) were *Plasmodium vivax*, 54 (36%) were *P. falciparum* and 24 (16%) were mixed infections; ‡28 of the 120 patients who received mechanical ventilation during the study period were diagnosed to have ARDS; §53% were *P. vivax*, 36% were *P. falciparum*, and 11% were mixed infections; ||Data for the year 1994; ARDS = Acute respiratory distress syndrome.

**Pathology:** The fact that pulmonary oedema due to malaria responds poorly to diuretics, venodilators, and oxygen<sup>39</sup> and the recent haemodynamic, clinical and pathological evidence<sup>40-42</sup> suggests that this is a non-cardiogenic form of pulmonary oedema.

Autopsy studies<sup>39,43</sup> in patients with severe falciparum malaria and coma who died have revealed heavy, oedematous lungs, congested pulmonary capillaries, thickened alveolar septa, intra-alveolar haemorrhages, hyaline membrane formation, and serous pleural and pericardial effusions. Ultrastructural studies corroborate the histopathological findings<sup>44,45</sup>.

**Pathogenesis:** The key pathogenetic events underlying the various manifestations of severe complicated malaria include erythrocyte sequestration and destruction, the release of parasite and erythrocyte material into the circulation, and the host response to these events. It has been suggested that malarial parasites contain a toxin that is released at meront rupture, which results in the genesis of fever and other manifestations<sup>46</sup> and results in release and activation of cytokines, such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 (IL-1) from macrophages and monocytes. These cytokines are in turn postulated to induce release of other pro-inflammatory cytokines like interleukin-6 (IL-6) and interleukin-8 (IL-8) and upregulate the endothelial expression of certain vascular ligands that promote cytoadherence of infected erythrocytes in the venules of vital organs<sup>11,12,47</sup>. In addition to the role played by pro- and anti-inflammatory cytokines, neutrophil and macrophage activation, a potential role for nitric oxide in the genesis of ischaemic hypoxia has been postulated<sup>12,47,48</sup>.

As in the case with ALI/ARDS due to other causes, increased alveolar permeability is considered to be the key functional abnormality underlying ALI/ARDS due to malaria. However, the pathogenetic mechanisms underlying the development of ALI/ARDS in malaria are poorly understood. The obser-

vations such as the relatively low level of parasite sequestration in the lungs, occasional development of ALI/ARDS not only in *P. falciparum*, but also in *P. vivax* or *P. ovale* malaria, and the occurrence of ALI/ARDS alone or asynchronous with the development of other vital organ dysfunction suggest that some other as yet poorly understood mechanisms may be responsible for ALI/ARDS in malaria<sup>11,12</sup>.

Alterations in pulmonary physiology in falciparum, vivax and ovale malaria include airflow obstruction, impaired ventilation, reduced gas transfer, and increased pulmonary phagocytic activity<sup>49</sup>. Some workers<sup>50</sup> have proposed that ALI/ARDS in malaria is likely to be a continuous spectrum from subclinical lung involvement in uncomplicated malaria and severe malaria through to frank ALI/ARDS in severe malaria. The authors<sup>50</sup> postulated that in patients with severe malaria without ALI, endovascular obstruction caused by erythrocytes with reduced deformability, parasitised erythrocytes, and leucocytes; endothelial injury and interstitial oedema result in ventilation-perfusion mismatch and impairment of gas exchange. Furthermore, worsening or persistence of these gas exchange abnormalities after treatment and beyond the expected time of clearance of parasitised erythrocytes reflects a prolonged inflammatory response and the genesis of ALI/ARDS<sup>50</sup>.

The tentative pathophysiological basis of ALI/ARDS in malaria is depicted in Fig. 1. Unlike in ALI/ARDS caused by Gram-negative sepsis, large gaps in the knowledge exists in malarial ALI/ARDS regarding our understanding of parasite sequestration, neutrophil sequestration, cytokine levels, their ratios, causation of increased alveolar permeability, contribution of bacterial sepsis and the cellular and molecular basis for these events. Further research is required to understand these mechanisms.

**Clinical presentation:** ARDS is considered to be the most severe form of ALI in malaria<sup>11,12</sup>. Even in the early reports, pulmonary oedema has been described

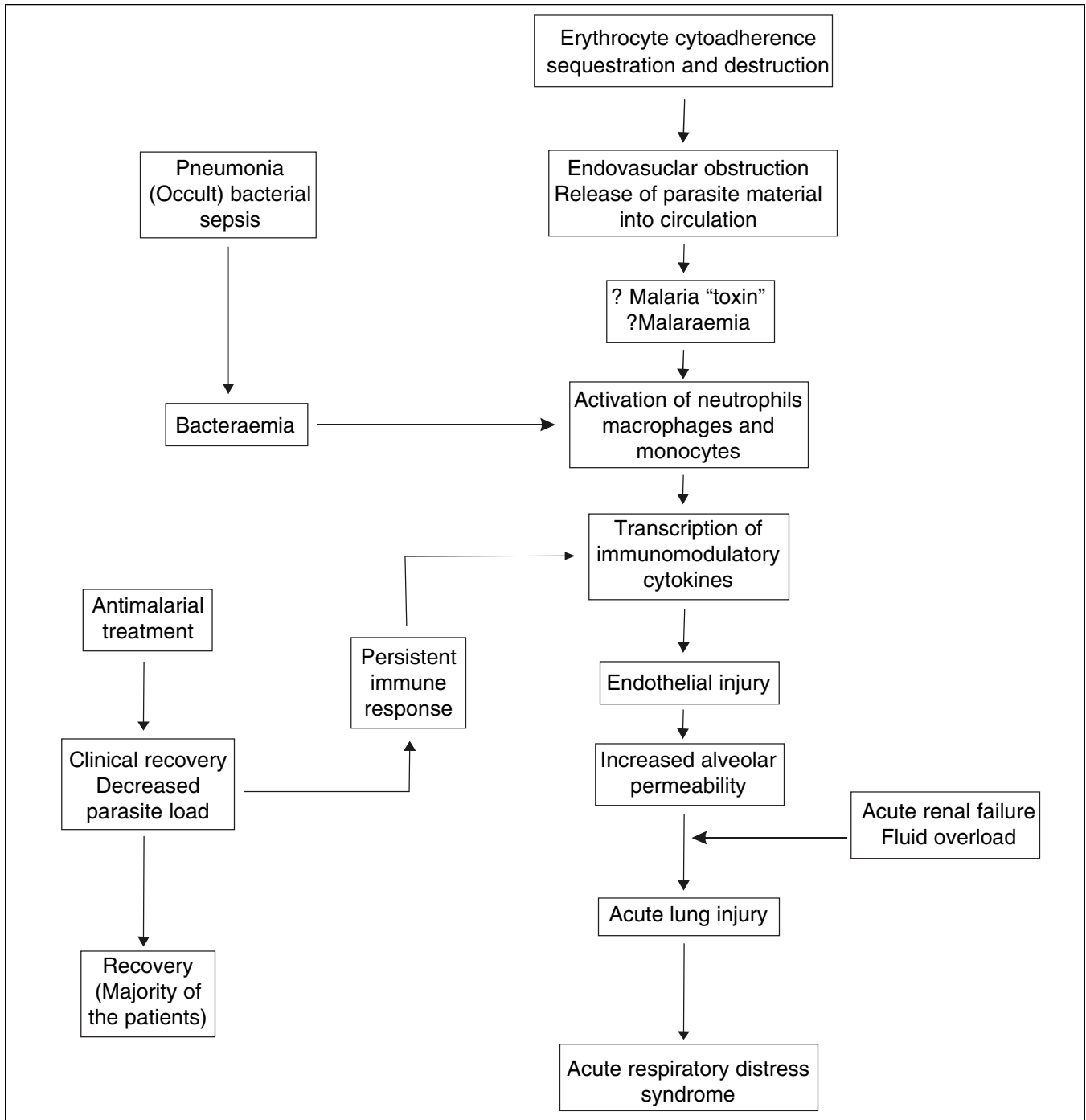


Fig. 1: Pathogenetic mechanisms underlying the development of acute lung injury and acute respiratory distress syndrome in malaria

as an important complication in patients with severe falciparum malaria and is frequently associated with cerebral malaria. It has been more frequently described in adults as compared to children. Sometimes

ARDS may be the only manifestation of otherwise uncomplicated falciparum malaria<sup>39,51</sup>.

ARDS can develop at any time during the course of

falciparum malaria, either at the time of initial presentation or after following several days of treatment, when patients appear to be improving and when the parasitaemia has fallen or cleared<sup>11,12,39</sup>. Pregnant women with severe falciparum malaria are particularly prone to develop ARDS. In pregnant women, the manifestations of pulmonary oedema due to malaria can develop before, during or after labour and is associated with a high mortality<sup>11,12</sup>.

When patients with falciparum malaria develop ARDS, they manifest abrupt onset dyspnoea, cough, and tightness in the chest that progresses rapidly over a few hours to cause life-threatening hypoxia. Disorientation and agitation is frequently present. Physical examination reveals signs of respiratory distress such as air hunger, use of accessory muscles of respiration, suprasternal and intercostal indrawing, central and peripheral cyanosis (reflecting the severity of arterial hypoxaemia), basal crepitations and expiratory wheezing<sup>23-26</sup>. In these patients, high parasitaemia, acute renal failure, hypoglycemia, metabolic acidosis, disseminated intravascular coagulation (DIC), and bacterial sepsis usually co-exist.

In a retrospective study, Gachot *et al*<sup>52</sup> described 40 patients with complicated falciparum malaria admitted to a medical ICU with (n = 12) or without (n = 28) ALI. Eight of the 12 patients with ALI had ARDS. Patients with ALI had more severe disease and had a higher simplified acute physiology score (SAPS) on admission ( $24.2 \pm 3.2$  vs  $13.7 \pm 0.7$ ,  $p < 0.0001$ ) and a longer mean time of treatment delay ( $8.8 \pm 2.5$  vs  $4.9 \pm 0.6$  days,  $p = 0.046$ ). Acute renal failure (10/12 vs 12/28,  $p = 0.018$ ), unarousable coma (8/12 vs 7/28,  $p = 0.012$ ), and metabolic acidosis (7/12 vs 4/28,  $p = 0.010$ ), number of complications ( $4.7 \pm 0.5$  vs  $1.6 \pm 0.1$ ,  $p < 0.0001$ ), septic shock (8/12 vs 2/28,  $p < 0.0001$ ) were significantly more common in patients with acute lung injury. Four patients (33%) with ALI died compared to one (12%) without ALI ( $p = 0.022$ ). Pulmonary artery catheterisation data obtained from patients with ALI (n = 5) revealed

mean arterial pressure  $58 \pm 5$  mm Hg, mean pulmonary artery pressure  $21 \pm 2$  mm Hg, mean pulmonary artery occlusion pressure  $11 \pm 2$  mm Hg, cardiac index  $6.5 \pm 0.8$  l/min/m<sup>2</sup>, systemic vascular resistance index  $601 \pm 100$  dynes.s.cm<sup>-5</sup>/m<sup>2</sup>, and pulmonary vascular resistance index  $137 \pm 77$  dynes.s.cm<sup>-5</sup>/m<sup>2</sup>. The authors<sup>52</sup> also suggested that bacterial co-infection significantly contributed to mortality and highlighted the importance of early initiation of empirical antibiotic treatment<sup>52</sup>.

### ALI and ARDS in benign malaria

Pulmonary involvement in vivax and ovale malaria is increasingly being recognised although less frequently than in falciparum malaria<sup>11,12</sup>. While some of these cases could be attributed to mixed infections, published data also point out that ALI/ARDS can develop primarily due to vivax, ovale and malariae malaria<sup>13-18</sup>. As compared with patients with severe complicated falciparum malaria with ALI/ARDS, the prognosis is relatively better in ALI/ARDS in patients with benign forms of malaria.

### Role of concomitant bacterial sepsis

Bacterial sepsis is an important contributor to the genesis of ALI/ARDS in severe falciparum malaria. In patients with severe falciparum malaria, the prevalence of bacteraemia in published studies has varied from 6%–15%<sup>11,12</sup>. However, an obviously evident focus of sepsis may not be discernible in many patients. Further research is required to understand the contribution made by bacterial sepsis in patients with severe falciparum malaria. This important observation, implies that, in endemic areas, practicing clinicians should have a low threshold to initiate broad spectrum antibiotics in falciparum malaria patients with ALI/ARDS and shock as it can be life-saving<sup>11,12</sup>.

### Diagnosis

*Parasite detection:* Malaria is essentially a parasito-



logical diagnosis. The thick (for detection of parasitaemia) and thin (for species identification) peripheral blood smear examinations must be carried out. Thick smear examination also facilitates quantification of the parasitaemia. The number of parasites per 200 white blood cells can be counted and multiplied by the total white cell count divided by 200. Similarly, in thin film, the *erythrocyte parasite index* can be calculated by counting the number of parasitised erythrocytes per 1000 erythrocytes and multiplying this either by the erythrocyte count or by haematocrit multiplied by 125.6<sup>11,12</sup>.

Though certain degree of correlation exists between the severity of the disease and parasitaemia, it should be remembered that, quantification of the asexual parasitaemia does not accurately reflect the parasite load. Due to erythrocyte adherence and sequestration, the peripheral smears may not reveal the parasite and a negative blood smear result does not rule-out malaria. Repeat smear examination can be rewarding in ascertaining the diagnosis of malaria in severely ill patients presenting with ALI/ARDS of obscure aetiology in endemic areas. Various rapid diagnostic tests (RDTs) that are available for malaria are helpful in complementing good smear microscopy and should not be considered as replacements for smear examination.

*Arterial blood gas analysis:* Arterial blood gas analysis reveals arterial hypoxaemia that may be refractory to oxygen therapy. Concomitant metabolic acidosis may be present.

*Chest radiograph:* In patients with ALI/ARDS due to malaria, chest radiographs may reveal bilateral frontal opacities (alveolar pattern), increased interstitial markings mimicking observations in patients with ARDS due to other causes. The cardiac size is usually normal unless there is co-existent severe anaemia or underlying heart disease. Rarely, thickening of lung fissures, interlobular septal lines and pleural effusion have also been described. In patients receiving assisted ventilation, complications such as, pneumothorax and pneumome-

diastinum may be evident<sup>11,12</sup>.

### Differential diagnosis

Malaria must be differentiated from other acute febrile conditions with dyspnoea (e.g. bacterial pneumonia, pleurisy), with jaundice, thrombocytopenia, or acute renal failure (e.g., leptospirosis, sepsis syndrome), with confusion or coma (e.g., other causes of meningitis, encephalitis). In endemic areas, malaria is an important treatable cause of ALI/ARDS and should be differentiated from ALI/ARDS due to other treatable causes such as leptospirosis<sup>53</sup>, tuberculosis<sup>54</sup>, enteric fever<sup>55</sup>, among others. Rarely, ALI has been described in a patient co-infected with severe falciparum malaria and leptospirosis<sup>56</sup>.

### Management

Patients with severe complicated malaria with ALI/ARDS should ideally be managed in an ICU because of the high mortality associated with this condition.

*General therapeutic measures:* Adequate supportive management is currently considered to be an essential component responsible for the decline in mortality observed in patients with ARDS<sup>23-26,57</sup>. Measures for prevention of nosocomial infections must be scrupulously followed. Adequate nutritional support must be ensured preferably through the use of enteral nutrition as it does not cause the serious risk of catheter induced sepsis. Efforts should also be directed to prevent gastrointestinal bleeding and pulmonary thromboembolism<sup>23-26,58</sup>. Patients with ARDS should ideally have pulmonary and systemic arterial lines inserted for haemodynamic monitoring and rational fluid replacement therapy. Monitoring arterial oxygen saturation (SaO<sub>2</sub>) is preferred to PaO<sub>2</sub> monitoring because oxygen delivery is the important determinant of tissue oxygenation<sup>22</sup>.

*Fluid and haemodynamic stabilisation & management:* Adequate organ perfusion must be ensured in

patients with ARDS in order to prevent abnormal tissue oxygenation and organ failure. The intravascular volume must be maintained as low as possible while maintaining an adequate cardiac index and mean arterial pressure. Taking the pulmonary capillary wedge pressure (PCWP) as the guideline, adequate circulation and blood pressure is ensured using volume infusion (crystalloids), vasopressors<sup>23–26,58–60</sup>.

The optimal fluid management strategy in ARDS is not yet settled with the choice ranging between a 'conservative' and a 'liberal' fluid management strategies. In a prospective randomised controlled study<sup>61</sup>, the conservative and a liberal fluid management strategies in patients with ALI were compared. The cumulative fluid balance (mean  $\pm$  SE) during the first seven days in patients receiving the conservative strategy was  $136 \pm 491$  ml compared to  $6992 \pm 502$  ml in the liberal strategy group ( $p < 0.001$ ). Even though there was no significant difference in the primary outcome of 60-day mortality between the conservative and liberal strategy groups (252.5 vs 28.4%;  $p = 0.3$ ), the conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation (number of ventilator-free days  $14.6 \pm 0.5$  vs  $12.1 \pm 0.5$ ;  $p < 0.001$ ) and intensive care without increasing non-pulmonary-organ failures. A similar strategy is likely to be beneficial in ALI/ARDS due to malaria.

A recently published randomised controlled trial<sup>62</sup> compared the benefits and risks of haemodynamic monitoring guided by a pulmonary artery catheter with haemodynamic monitoring guided by a central venous catheter. It was observed that pulmonary artery catheter guided therapy did not improve survival or organ function and was associated with more complications than central venous catheter guided therapy. These observations suggest that pulmonary artery catheter should not be routinely used for monitoring patients with ALI<sup>62</sup>. In patients with severe falciparum malaria, attempts should be directed at

maintaining the central venous pressure at 8–12 mm Hg<sup>59</sup>. The left sided cardiac filling pressures must be kept as low as consistent with cardiac function<sup>23–26,58,60</sup>. Evidence is available suggesting that adrenaline exacerbates lactic acidosis. Since lactic acidosis is an independent risk factor for death in severe malaria, the use of adrenaline is best avoided in these patients and other vasopressors such as dopamine should be preferred<sup>41</sup>.

*Specific treatment:* In patients with severe complicated malaria, early institution of specific anti malarial therapy is life-saving. In these patients parenteral therapy is indicated and the initiation of treatment should not be delayed in patients with proven or strongly suspected malaria. Specific antimalarial therapy as advocated in the WHO guidelines 2006<sup>63</sup>, or the U.K. national guidelines 2007<sup>64</sup> must be used. Two classes of drugs are currently used for the parenteral treatment of severe complicated malaria: the cinchona alkaloids (e.g. quinine and quinidine) and the artemisinin derivatives (e.g. artesunate, artemether and artemotil). The currently employed treatment regimens are shown in Tables 3a and 3b.

In pregnant women with severe complicated falciparum malaria, parenteral artemisinins appear to be a better choice than quinine in the second and third trimesters because quinine is associated with a higher risk of recurrent hypoglycaemia<sup>11,12</sup>. During the first trimester, the artemisinins or quinine may be used and the choice should be made keeping in mind the lower risk of quinine-induced hypoglycaemia and the relative lack of safety data on the use of the artemisinins<sup>11,12</sup>.

*Respiratory supportive therapy:* Initially, spontaneous ventilation using a face mask with a high flow gas delivery system can be used to deliver a  $FIO_2$  of up to 0.5 to 0.6. Continuous positive airway pressure (CPAP) may be added to improve  $PaO_2$  without increasing  $FIO_2$ <sup>23–26,60</sup>. If a  $FIO_2$  of more than 0.6 and CPAP of more than 10 cm  $H_2O$  are needed to achieve



**Table 3a. WHO guidelines for antimalarial treatment for severe, complicated malaria \***


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<i>Artesunate</i>	2.4 mg/kg body weight iv or im given on admission (time = 0), then at 12 and 24 h, then once a day <sup>†‡</sup>
<i>Artemether</i>	3.2 mg/kg body weight im given on admission then 1.6 mg/kg body weight per day <sup>‡</sup>
<i>Quinine</i>	20 mg salt/kg body weight on admission (iv infusion or divided im injection), then 10 mg/kg body weight every 8 hourly; infusion rate should not exceed 5 mg salt/kg body weight per hour <sup>‡</sup>

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\*Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with whichever effective antimalarial is first available; <sup>†</sup>Recommended choice in low transmission areas or outside malaria endemic areas; <sup>‡</sup>Recommended for children in high transmission areas. There is insufficient evidence to recommend any of these antimalarial medicines over another (Source: Reference 63).

**Table 3b. U.K. guidelines for antimalarial treatment for severe, complicated malaria**


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*Quinine*<sup>\*†</sup> Loading dose of 20 mg/kg quinine dihydrochloride in 5% dextrose or dextrose saline over 4 h. Followed by 10 mg/kg every 8 hourly for first 48 h (or until patient can swallow).

Frequency of dosing should be reduced to 12 hourly if intravenous quinine continues for more than 48 h.

Alternative rapid quinine loading regimen (adults only) 7 mg/kg quinine dihydrochloride over 30 min using an infusion pump followed by 10 mg/kg over 4 h.

*Doxycycline*<sup>†</sup> 200 mg (or clindamycin<sup>†</sup> 450 mg three times a day for pregnant women, 7 to 13 mg/kg three times a day for children), given orally for total of 7 days from when the patient can swallow.

*Artesunate*<sup>\*§||</sup> 2.4 mg/kg given as an intravenous injection at 0, 12 and 24 h then daily thereafter.

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\*Parenteral quinine therapy should be continued until the patient can take oral therapy when quinine sulphate 600 mg should be given three times a day to complete 5 to 7 days of quinine in total; <sup>†</sup>Quinine treatment should always be accompanied by a second drug such as doxycycline or clindamycin; <sup>‡</sup>Artesunate has not been licensed in the European Union. Treatment should never be delayed whilst obtaining artesunate: every patient with severe malaria should be started on quinine immediately in the first instance; <sup>§</sup>Appropriate for adults only on expert advice in certain situations where the benefits outweigh the potential disadvantages of using unlicensed drug. This includes patients with parasite counts over 20%, very severe disease, deterioration on optimal doses of quinine, cardiovascular disease that increases the risks from quinine or patients with falciparum malaria from southeast Asia where relative quinine resistance is likely; <sup>||</sup>A 7-day course of doxycycline should also be given; U.K. = United Kingdom (Source: Reference 64).

PaO<sub>2</sub> of more than 60 mm Hg, use of non-invasive positive pressure ventilation (NPPV) or tracheal intubation and mechanical ventilation must be considered<sup>23–26,60</sup>. The aim of mechanical ventilation is to maintain gas exchange with minimal complications.

NPPV has been tried in patients with ALI/ARDS due to malaria<sup>13</sup>. However, NPPV requires a conscious cooperative patient and it may not always be useful in patients with severe complicated malaria who present with altered sensorium or are comatose.

Though sparse published data on the appropriateness of various ventilatory strategies in ARDS due to malaria are available, certain generalisations can be made basing on observations from ARDS due to other causes. The lung protective ventilatory strategy used in the Acute Respiratory Distress Syndrome Network (ARDSNet) study is shown in Table 4<sup>65</sup>. Sparse data are available comparing volume-controlled and pressure-controlled modes in patients with ARDS<sup>22,25</sup>. Whether pressure-controlled or volume-controlled mode of ventilation is used, tidal

**Table 4. Protective lung ventilation protocol from the ARDS net study**

Variable	Setting	
Ventilator mode	Volume assist-control	
Tidal volume (initial)	6 ml/kg of predicted body* weight initially. Tidal volume is adjusted according to plateau pressure	
Plateau pressure	< 30 cm H <sub>2</sub> O	
Rate	6–35 breaths/min	
Ratio of the duration of inspiration to the duration of expiration	1:1–1:3	
Oxygenation target		
PaO <sub>2</sub>	7.3–10.7 kPa (55–80 mm Hg)	
SaO <sub>2</sub>	88–95 (%)	
FIO <sub>2</sub> and PEEP†	FIO <sub>2</sub>	PEEP
	0.3	5
	0.4	5–8
	0.5	8–10
	0.6	10
	0.7	10–14
	0.8	14
	0.9	14–18
	1.0	18–24

\*Predicted body weight of male patients =  $50 + 0.91[\text{height (cm)} - 152.4]$ , predicted body weight of female patients =  $45.5 + 0.91[\text{height (cm)} - 152.4]$ ; † Set according to pre-determined combinations (PEEP range 5–24 cm H<sub>2</sub>O); PEEP—Positive end-expiratory pressure; FIO<sub>2</sub>—Fraction of inspired oxygen (Source: Adapted from reference 65).

volume should be set in the region of 6 ml/kg predicted body weight (“lung protective ventilation”) and the plateau pressures (end-inspiratory pause pressures) should be limited to 30 cm H<sub>2</sub>O to prevent lung overdistension. These have been the only methods of ventilation proven to be of value in improving survival in patients with ARDS in randomised clinical trials<sup>22,25,65–68</sup>.

Presently, peak end expiratory pressure (PEEP) is set at a level above the lower inflection point to about 15 cm H<sub>2</sub>O in patients with ARDS. It is also a common practice to increase the ratio of duration of inspiration to the duration of expiration ratio to 1:1 or 2:1 (inverse

ratio ventilation) with close monitoring of intrinsic PEEP (PEEPi) and haemodynamic parameters during pressure control ventilation<sup>23–26,65–68</sup>. There is no consensus on the optimum PEEP value. However, PEEP and FIO<sub>2</sub> are adjusted to arrive at the optimum PaO<sub>2</sub>.

Concern has been expressed over the issue of permissive hypercapnia because elevated arterial carbon dioxide levels may be undesirable in comatosed malaria patients since this can increase the cranial blood flow and result in raised intracranial pressure<sup>12</sup>. Further research is required to ascertain the efficacy and safety of various mechanical ventilatory strategies in patients with ARDS due to malaria.

*Other treatment strategies:* The potential role of corticosteroids<sup>69,70</sup>, mannitol<sup>64,71</sup>, and exchange transfusion<sup>64,72</sup> in the treatment of severe complicated malaria is controversial and there are no clear-cut guidelines for their use.

*Treatment of complications of malaria:* Other complications such as acute renal failure that are usually co-existent must also be looked for and managed. In patients with malarial acute renal failure, renal replacement therapy should be initiated early and nephrotoxic drugs should be avoided. The indications for dialysis support in patients with acute renal failure due to malaria are similar to that for acute renal failure due to other causes. Haemofiltration appears to be superior to peritoneal dialysis<sup>73</sup>.

Anaemia is an important complication of severe falciparum malaria. If the patient is anaemic, transfusion of packed erythrocytes must be considered, as this would improve oxygenation. The WHO guidelines<sup>63</sup> recommend blood transfusion when the haematocrit falls below 20% and 15% in adults and children respectively. While the ideal target haemoglobin or haematocrit are difficult to generalise, packed erythrocyte transfusion may be employed to achieve a target haemoglobin value of 7 to 9 g/dl as in the case of patients with sepsis due to other causes<sup>22</sup>.

Hypoglycaemia, a common, correctable factor that contributes to mortality in patients with severe falciparum malaria, especially in pregnant women. Hypoglycaemia must be specifically looked for by frequently monitoring blood glucose levels and corrected.

Since bacterial sepsis is often co-existent, foci of underlying infection should be aggressively treated with intravenous antibiotics and surgery where required. Wherever possible, the antibiotic choice should be guided by the culture and sensitivity reports.

In patients with severe falciparum malaria, thrombocytopenia and activation of blood coagulation system have been frequently described<sup>74,75</sup>. However, activation of coagulation does not progress to frank pathological disseminated intravascular coagulation (DIC) in majority of the cases. Co-existent bacterial sepsis may also contribute to the development of DIC. Presently, there is no single diagnostic test for the definitive diagnosis of DIC. Serial measurements of a battery of laboratory investigations, such as platelet count, global clotting times (activated partial thromboplastin time and prothrombin time), measuring clotting factors and inhibitors (such as antithrombin), and a test for fibrin degradation products or a scoring system developed by the subcommittee on DIC of the International Society of Thrombosis and Haemostasis<sup>76</sup> can be used for the diagnosis of DIC. When DIC is present, supportive treatment should be aimed at replacement of platelets and coagulation factors, anticoagulant treatment, and restoration of anticoagulant pathways. As per the recently published International Guidelines for Management of Severe Sepsis and Septic Shock<sup>22</sup>, platelet transfusion is indicated when the platelet count is less than or equal to 5000/mm<sup>3</sup> irrespective of bleeding status. When the platelet count is 5000/mm<sup>3</sup> to 30000/mm<sup>3</sup>, platelet transfusion is indicated only if there is a significant bleeding risk.

### Outcome

Definitive data on the survival in patients with ARDS due to malaria receiving intensive care are lacking. Available data suggest that mortality is high in patients with ARDS due to malaria even with appropriate respiratory supportive therapy. When facilities for assisted ventilation are not available, the mortality may exceed 80% in patients with falciparum malaria and ARDS<sup>11,12</sup>. Presence of falciparum schizonts and/or malaria pigment in 5% or more of neutrophils on a blood film are considered to be poor prognostic signs<sup>12,77,78</sup>. In a study<sup>9</sup> of patients with falciparum malaria with acute respiratory

failure requiring assisted ventilation from India, involvement of two or more organ systems ( $p < 0.05$ ) and high erythrocyte parasite index (%) ( $p < 0.05$ ) were predictors of death.

### Conclusion

Malaria is an important curable cause of ALI/ARDS. In endemic areas, or in returning travellers in non-endemic areas, malaria should be considered as a possible aetiological cause in patients presenting with ARDS of obscure aetiology. Thick and thin peripheral blood smear examination usually confirms the diagnosis; sometimes, repeat examination may be helpful in detecting the parasite. Early institution of antimalarial treatment can be life-saving and initiation of treatment should not be delayed in patients with proven or strongly suspected malaria. Patients with ALI/ARDS are seriously ill and need to be managed in an ICU setting. They require assisted mechanical ventilation, monitoring and correction of anaemia, hypoglycaemia and prompt institution of renal replacement therapy and dialysis if acute renal failure is also present. Further research is required to understand the pathogenetic mechanisms underlying the genesis of ALI/ARDS and evolve appropriate mechanical ventilatory strategies.

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