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Pulmonary Manifestations of Malaria

Recognition and Management

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Abstract

Lung involvement in malaria has been recognized for more than 200 hundred years, yet our knowledge of its pathogenesis and management is limited. Pulmonary edema is the most severe form of lung involvement. Increased alveolar capillary permeability leading to intravascular fluid loss into the lungs is the main pathophysiologic mechanism. This defines malaria as another cause of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

Pulmonary edema has been described most often in non-immune individuals with *Plasmodium falciparum* infections as part of a severe systemic illness or as the main feature of acute malaria. *P. vivax* and *P. ovale* have also rarely caused pulmonary edema.

Clinically, patients usually present with acute breathlessness that can rapidly progress to respiratory failure either at disease presentation or, interestingly, after treatment when clinical improvement is taking place and the

parasitemia is falling. Pregnant women are particularly prone to developing pulmonary edema. Optimal management of malaria-induced ALI/ARDS includes early recognition and diagnosis. Malaria must always be suspected in a returning traveler or a visitor from a malaria-endemic country with an acute febrile illness. Slide microscopy and/or the use of rapid antigen tests are standard diagnostic tools. Malaria must be treated with effective drugs, but current choices are few: e.g. parenteral artemisinins, intravenous quinine or quinidine (in the US only). A recent trial in adults has shown that intravenous artesunate reduces severe malaria mortality by a third compared with adults treated with intravenous quinine. Respiratory compromise should be managed on its merits and may require mechanical ventilation.

Patients should be managed in an intensive care unit and particular attention should be paid to the energetic management of other severe malaria complications, notably coma and acute renal failure. ALI/ARDS may also be related to a coincidental bacterial sepsis that may not be clinically obvious. Clinicians should employ a low threshold for starting broad spectrum antibacterials in such patients, after taking pertinent microbiologic specimens. Despite optimal management, the prognosis of severe malaria with ARDS is poor.

ALI/ARDS in pediatric malaria appears to be rare. However, falciparum malaria with severe metabolic acidosis or acute pulmonary edema may present with a clinical picture of pneumonia, i.e. with tachypnea, intercostal recession, wheeze or inspiratory crepitations. This results in diagnostic confusion and suboptimal treatment. Whilst this is increasingly being recognized in malaria-endemic countries, clinicians in temperate zones should be aware that malaria may be a possible cause of 'pneumonia' in a visiting or returning child.

Human malaria is a parasitic disease caused by four plasmodium species, *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* that is transmitted by the female *Anopheline* mosquito.[1] The asexual blood stages (rings, trophozoites, schizonts) of the parasites cause clinical disease, whereas the sexual forms (gametocytes) are necessary to complete the parasite life-cycle in the mosquito. *P. falciparum* has two distinguishing pathologic features. Its asexual forms have a much higher propensity to parasitize red blood cells and produce heavy parasite burdens, and parasitized red cells adhere to the post-capillary venules of vital organs (cytoadherence), resulting in organ damage and dysfunction. The other malarias produce lower parasite burdens that are generally <2% of the red cell population, and do not cytoadhere.

The incubation periods of the four species vary somewhat, but range generally from 7 to 16 days. However, as part of their life-cycle, *P. vivax* and *P. ovale* produce liver hypnozoites (a dormant tissue parasitic stage) that may produce a first clinical attack weeks or months after mosquito inoculation or further clinical disease (relapse) after successful treatment of the blood stage infection. Therefore, malaria may be the cause of fever months or years after leaving a malaria-endemic area.

P. falciparum and *P. vivax* account for the vast majority of clinical cases worldwide. *P. falciparum* predominates in sub-Saharan Africa, and *P. vivax* in Latin America. There are also many areas of mixed species transmission.[2] Malaria is an important illness in temperate zones. Recent data suggest that the estimated number of cases of malaria in Western Europe is 10 000 per year, and some 1400 in the US.[3,4] When malaria presents as an acute febrile illness, species differentiation is not possible clinically, and many other febrile illnesses fall into the differential diagnosis.[5,6] Malaria must always be suspected as a possible cause of fever in a traveler or visitor from a malaria-endemic country. Accordingly, a malaria blood film must be examined.

1. Clinical Features

In the past, fascinating descriptions and classifications of malaria were used based on the clinical picture, and included such quaint diagnoses as bilious remittent fever, and pernicious fever with pulmonary symptoms. The latter was classified further as the bronchitic, pneumonic and bronchopneumonic types.[7,8] Appelbaum and Shrager[9] later described malaria pneumonitis. These descriptions are of historical value attesting to the clinical acumen of bygone physicians.

P. falciparum malaria causes severe disease that may lead to death. The other species cause acute febrile illnesses that rarely cause severe morbidity. The WHO has defined severe and complicated *P. falciparum* malaria in adults (table I).[10] There are certain differences in symptoms between adults and children, e.g. acute renal failure and pulmonary edema are rare in children, and coma is common to both adults and children. In a prospective case series of severe malaria in adults, pulmonary edema occurred in 9–21%, and acute renal failure in 28% of the patients.[11-13] In uncomplicated falciparum malaria, the risk of developing acute pulmonary edema was 0.1% in a cohort of 3300 American soldiers.[14] Pulmonary edema and hypoglycemia are both particularly common in pregnant women with severe malaria.

1.1 Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS) in Adult Malaria: Focus on Pulmonary Edema

The definitions of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) have now been standardized (table II). Malaria-associated ALI/ARDS results from a complex host inflammatory response both in the lung and systemically, involving pro- and anti-inflammatory cytokines, neutrophil and macrophage activation, the possible role of nitric oxide in ischemic hypoxia, and, for falciparum malaria, the additional role of red cell sequestration in the lung.[15-18] Consequently, the permeability of the alveolar capillary membrane increases and protein-rich fluid leaks into the lungs (exudative phase).[19] Lung function is compromised because of a ventilation perfusion mismatch whereby blood circulates through collapsed alveoli and edematous lung but does not participate in gas exchange.[20,21] ALI/ARDS may occur after parasite reduction and general clinical improvement; this may represent a post-treatment shift in the cytokine balance favoring increased lung inflammation.

The most significant malaria-induced lung pathology is acute pulmonary edema. It has the same dramatic clinical features as acute cardiogenic pulmonary edema, except that right-sided filling pressures are not elevated unless excess intravenous fluids have been given. Good clinical descriptions can be found in the literature from the 1960s that describe the rapid evolution of pulmonary edema and its poor prognosis in US Servicemen.[22-24]

Shortness of breath and cough are the main symptoms of malaria-induced lung disease; some patients also report chest tightness. Dyspnea may start abruptly and progress rapidly. Physical signs reflect the severity of underlying lung involvement and include labored breathing ('air hunger'), tachypnea, peripheral and central cyanosis, inspiratory crepitations, and expiratory wheezes. The jugular venous pulse is not raised unless there is concomitant fluid overload. In severely hypoxic patients, confusion and agitation may be present and cannot be differentiated from cerebral involvement. Dyspnea and an increased respiratory rate are usually the first features of impending pulmonary edema, preceding other clinical (e.g. inspiratory crepitations) or radiologic signs. A poor response to diuretics and oxygen (refractory hypoxemia) is usual, in contrast to cardiogenic pulmonary edema. Pulmonary edema may occur at presentation or after several days of treatment when parasitemia is falling and patients are improving clinically.[23,25] In patients who survive, recovery is often rapid.

Malaria-induced pulmonary edema is generally associated with severe disease in which respiratory compromise is part of the clinical picture of a toxic patient. However, it may also occur as the predominant manifestation of an otherwise unremarkable febrile illness.[23] The differential diagnoses are wide and include sepsis syndrome, pneumonia, metabolic acidosis, and cardiogenic pulmonary edema. Pulmonary edema is associated particularly with cerebral malaria.[10] Other important associations are high parasitemia, acute renal failure, hypoglycemia, metabolic acidosis, disseminated intravascular coagulation (DIC), hypoalbuminemia, and bacterial sepsis. Important iatrogenic factors are a delay in antimalarial drug treatment, overzealous use of intravenous fluids, and the failure to detect and effectively treat bacterial sepsis.[26-28] Death may occur rapidly, within hours, after the development of pulmonary edema, even with appropriate respiratory support.[29,30]

Table I. Clinical and laboratory features of severe and complicated falciparum malaria in adults

Clinical features
Coma (unrousable coma defines cerebral malaria)
Impaired consciousness
Prostration/extreme weakness
Multiple convulsions
Pulmonary edema
Acute renal failure
Spontaneous bleeding
Shock
Laboratory features
Hyperbilirubinemia (total bilirubin ≥3 mg/dL)
Severe anemia (in adults: hemoglobin <7 g/dL or hematocrit <20%)
Acute intravascular hemolysis with hemoglobinuria
Hypoglycemia (whole blood glucose <2.2 mmol/L)
Acidemia/acidosis (pH <7.35/plasma bicarbonate <15 mmol/L)
Hyperlactemia (plasma lactate >5 mmol/L)
Parasitemia ≥4% to ≥20% (depends on malaria-acquired immunity, e.g. ≥4% in a non-immune individual)

The reported mortality rates of strictly defined, adult severe malaria from tropical countries vary between 15% and 40%.[13,31] Although data are not extensive, mortality rates when ARDS is a complication appear higher despite artificial ventilation. In one study of Thai adults, death occurred in 7 of 10 ARDS patients compared with none in 15 with non-ARDS pulmonary edema.[12] In Colombia, the mortality of severe malaria is approximately 20%. In the absence of artificial ventilation – a not uncommon situation in many developing countries – mortality in severe falciparum malaria may exceed 80% (White NJ, unpublished observations).[23,24] Other poor prognostic features of severe malaria are jaundice with acute renal failure, shock, severe metabolic acidosis, and unrousable coma.[32]

Table II. Defining criteria for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

Timing	Oxygenation	PA chest x-ray	Pulmonary artery wedge pressure
Acute onset ALI	PaO_2/FiO_2 ≤300mm Hg[a]	Bilateral infiltrates[b]	≤18mm Hg or no clinical evidence of left atrial hypertension
Acute onset ARDS	PaO_2/FiO_2 ≤200mm Hg[a]	Bilateral infiltrates[b]	≤18mm Hg or no clinical evidence of left atrial hypertension

a Irrespective of the level of positive end-expiratory pressure.

b Abnormal CXR findings may lag behind functional disturbances.

CXR = chest x-ray; **FiO_2** = concentration of inspired oxygen; **PA** = posteroanterior; **PaO_2** = partial pressure of oxygen in arterial blood.

1.1.1 Pulmonary Edema in Benign Malaria

Pulmonary edema is a well described but rare feature in patients with *P. vivax* and *P. ovale* malaria, and may be associated with other severe clinical features like acute intravascular hemolysis and shock.[33-35] In contrast to falciparum malaria, the prognosis is usually good. Although clinically obvious pulmonary edema may be rare in the 'benign' malarias, recent work by Anstey et al.[16] has shown clearly that pulmonary inflammatory changes occur commonly in falciparum, vivax and ovale malaria, resulting in cough, an increase in small airways obstruction, and reductions in gas transfer.

In Colombia, pulmonary edema has been seen rarely in both vivax and mixed vivax/falciparum malaria. (Cañon V, unpublished data). In a small clinical series, seven patients had cough, shortness of breath, and inspiratory crepitations at presentation. All were in type I respiratory failure (PaO_2 <60mm Hg, low/normal $PaCO_2$) requiring mechanical ventilation for 2–5 days. The prognosis was good and there were no deaths.

1.1.2 Pulmonary Edema in Pregnant Women

In women who are in the second and third trimesters of pregnancy, pulmonary edema associated with malaria is a particular problem that leads to a high mortality.[10,36] It may occur after delivery of the placenta, especially if the woman is anemic or fluid-overloaded before labor. An increase in the respiratory rate is an ominous sign demanding careful clinical evaluation. Clinicians should be aware that hypoglycemia also causes tachypnea and should be excluded. Hypoglycemia is common in pregnant women with malaria and should be looked for actively with regular checks of blood glucose levels.

1.2 ALI/ARDS in Pediatric Malaria

The clinical overlap of falciparum malaria and pneumonia in a clinic setting was shown in a study of young Gambian children presenting with 'clinical pneumonia' defined as cough or difficulty in breathing and a raised respiratory rate, appropriate for age. During the high transmission season, one-third of 666 children had radiologic evidence of pneumonia (20% pneumonia alone, 13% pneumonia with malaria), ≈40% had malaria only, and ≈11% malaria with another illness. Although certain objective signs such as observed cough, chest wall recession, and auscultatory signs of consolidation were more likely in radiographically confirmed pneumonia, none was sufficiently discriminating to confidently exclude malaria, especially in the wet season.[37] Similar results were reported in a hospital-based study of 200 Kenyan children with an admission diagnosis of 'severe pneumonia.' The majority (137) had a positive malaria slide, 27 had pneumonia on the chest x-ray, and 23 had falciparum malaria and radiologically confirmed pneumonia.[38]

The respiratory pattern in African children with cerebral malaria has been studied by Crawley et al.[39] Of 295 Kenyan children with cerebral malaria, a substantial minority (40%) had an abnormal respiratory pattern, and a small proportion (5%) had more than one abnormal respiratory pattern during their illness. Four distinct patterns of respiration were observed: (i) deep breathing (n = 80) due to severe metabolic acidosis, which resolved following resuscitation with intravenous fluids and/or blood; (ii) hypoventilation with nystagmus and salivation (n = 18), due to EEG-confirmed, subtle status epilepticus, responding to anticonvulsant treatment; (iii) hyperventilation with extensor posturing (n = 20); and (iv) periodic respiration (n = 14) leading to respiratory arrest and death. The latter two patterns are compatible with progression of raised intracranial pressure leading to brain stem herniation. However, these suppositions have not been confirmed by autopsy studies.

1.3 ALI/ARDS Related to Concomitant Bacteremia

Bacteremia is a well recognized complication/association of severe malaria, and contributes to the overall clinical picture. In endemic areas there is undoubted diagnostic overlap. It may not have an obvious clinical source. Prevalence data for bacteremia vary widely, e.g. 0.2% (1/500) in Vietnamese adults (White NJ, unpublished data), 6% (10/175) in Thai adults, and 12% in two studies in African children.[28,40,41] In retrospective studies of adult falciparum malaria in France, Gachot et al.[27] and Bruneel et al.[42] found rates of community-acquired bacterial infection to be 12.5% (5/40) and 14% (13/95), on admission to their ICUs, respectively. A broad mix of pathogens have been isolated from studies, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escher-*

ichia coli, *Klebsiella* spp., *Acinetobacter* spp., and non-typhoid salmonellae.[43,44]

More research is required to better define patients who may have coexisting malaria and bacterial sepsis. Clinicians should be wary of the possibility of bacteremia in severely ill patients, and maintain a low threshold for starting broad spectrum antibiotics, especially if ALI/ARDS and/or shock are present.[27,42,45]

2. Diagnosis

The initial assessment of the sick malaria patient should focus on the basics of airway protection, adequacy of the circulation, and the level of consciousness. Venous access should be obtained and the following routine laboratory tests performed: (i) hematology, biochemistry including bicarbonate, blood glucose, plasma lactate; (ii) three blood cultures, other cultures as clinically indicated; and (iii) blood gases. A baseline ECG and chest radiograph are useful. Further investigations will be determined by the history, physical findings, and the differential diagnosis

2.1 Parasite Counts

Malaria is a parasitologic diagnosis. A blood film is the 'gold standard' for diagnosing malaria. Two films should be examined routinely in clinical practice. A thick film (figure 1) has high sensitivity for detecting parasitemia, while a thin film (figure 2) is better for species differentiation. Both may be used for quantifying the parasitemia, which is reported as the number of parasites per microliter (μL). When using the thick film, the number of parasites per 200 white cells is counted and multiplied by the total white cell count (WCC) divided by 200. However, it is the convention to approximate the parasitemia by assuming the total WCC is 8000/μL (i.e. multiplying the count by 40). For the thin film, the number

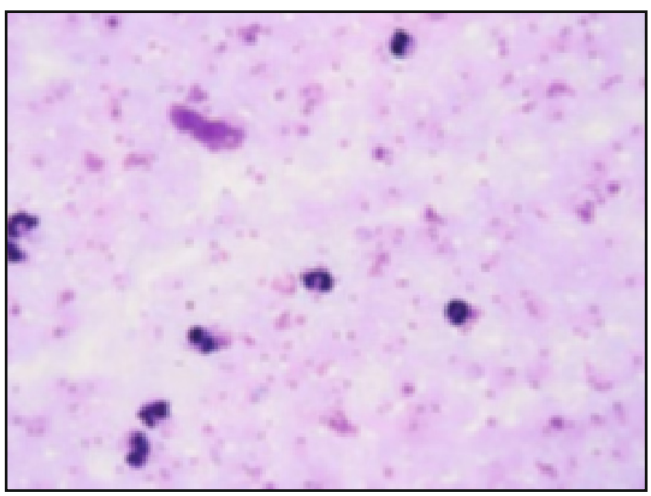

Fig. 1. A Giemsa-stained thick blood film showing asexual forms of *Plasmodium falciparum*.

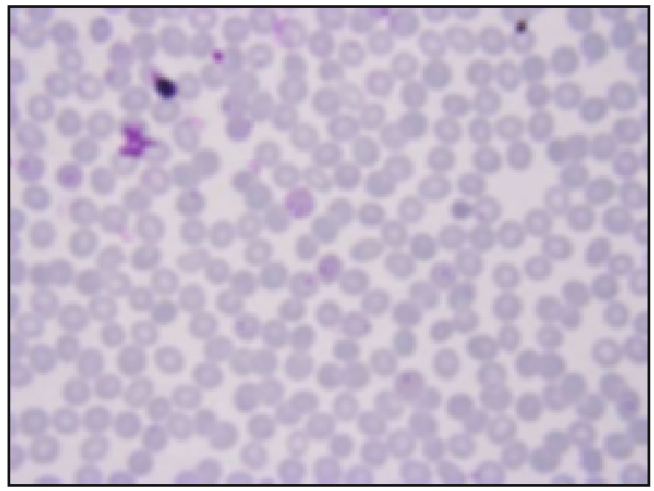

Fig. 2. A Giemsa-stained thin blood film showing showing ring forms of *Plasmodium falciparum*.

of parasitized red cells per 1000 red cells is counted and multiplied by the total red cell count, or by the hematocrit ×125.6. In practice, a good microscopist will detect low parasite counts down to 1 parasite per 500 white blood cells on a thick film. A negative slide result does not rule out malaria, but makes the diagnosis unlikely. Negative blood films should be repeated 12-hourly for 48 hours before malaria can be discounted from the differential diagnosis.

Quantifying the asexual parasitemia is a very imprecise indicator of the total parasite biomass, because of red cell adherence and sequestration from the circulation.[46] Nevertheless, there is a rough correlation between parasitemia and the severity of clinical disease. Falciparum schizonts and/or malaria pigment in ≥5% of neutrophils on a blood film are poor prognostic signs.[47,48] Serial parasite counts have some clinical utility in monitoring the progress of disease.

Rapid diagnostic tests (RDTs) are currently available for diagnosing malaria. They should be viewed as complementing expert microscopy, but are particularly useful if microscopy is unavailable.[49] A positive test with negative microscopy in a patient with a consistent clinical picture should be regarded as malaria, especially if there is a history of antimalarial drug ingestion. This is a scenario increasingly being seen in travelers who are able to buy artemisinin-based derivatives over the counter in many malaria-endemic countries.[50] RDTs are sometimes less sensitive than microscopy; therefore, a negative result does not exclude malaria.

2.2 Radiology

A chest radiograph may be helpful in differentiating pneumonia, cardiogenic pulmonary edema, and metabolic acidosis. Radiologic signs include a generalized increase in interstitial markings, followed by increasing areas of fluffy shadowing (alveolar pat-

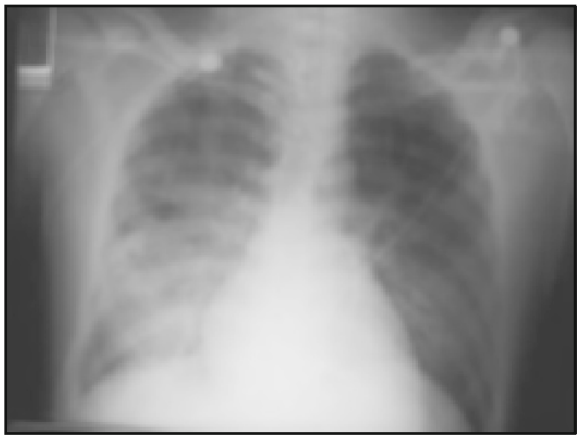

Fig. 3. A chest x-ray of a male patient ventilated for malaria-induced respiratory failure. There is bilateral shadowing in the mid- to lower lung zones.

tern) that may become extensive (figure 3). The cardiothoracic ratio is normal unless there is coincidental severe anemia or underlying heart disease. Less typical features include interstitial infiltrates alone, thickening of interlobular septal lines and lung fissures, and unilateral or bilateral pleural effusions.[22,51,52] Radiologic signs usually develop 6–24 hours after the onset of dyspnea; occasionally the reverse is true. There may also be radiologic signs of the complications of ventilation, e.g. pneumothorax or pneumomediastinum.[53]

3. Treatment

Malaria in Western clinical practice is relatively uncommon outside of specialist settings. The key to successful treatment is early recognition. Infectious disease services need to be involved early. Malaria mimics many diseases and may present with features strongly suggestive of a localized infection, e.g. fever and shortness of breath (pneumonia), fever and jaundice (hepatitis), fever and confusion or coma (meningitis or encephalitis), and fever and acute renal failure (leptospirosis). Therefore, every person with an imported fever or someone residing close to or working in an international airport must have a blood film done with or without an RDT. Once the diagnosis of malaria is established, effective treatment is crucial. There is widespread resistance of *P. falciparum* to chloroquine and sulfadoxine/pyrimethamine, and focal areas of quinine and mefloquine resistance (mostly Southeast Asia). Chloroquine is the treatment of choice for the other species, cognizant that there are areas of focal chloroquine-resistant *P. vivax,* e.g. in Indonesia and New Guinea.

In well resourced settings, ill patients should be managed in an intensive care unit. Detailed recommendations for severe malaria are available from the WHO, but these are orientated more towards tropical environments.[10] We highlight below practical points regarding the management of severe falciparum malaria.

3.1 Chemotherapy: Focus on *Plasmodium falciparum*

3.1.1 Artemisinin-Based Derivatives

Artemisinin-based derivatives are not currently available in the US, but are used widely in many parts of the world. They are the most potent antimalarial drugs and act rapidly to kill substantial numbers of parasites.[54] Oral preparations include artesunate, artemisinin, and a number of loose or fixed combinations, e.g. artesunate and amodiaquine, artesunate and mefloquine, CoArtemether® [1] (a fixed combination of artemether and lumefantrine) and Artekin® (a fixed combination of dihydroartemisinin and piperaquine).

For severe malaria, parenteral preparations have to be used. Artesunate for injection is prepared by adding sodium bicarbonate to artesunate powder, and may be given by a slow push intravenous injection or by the intramuscular route (anterior thigh). The currently recommended intravenous or intramuscular dose of artesunate is a 2.4 mg/kg loading dose, followed 12 and 24 hours later by 2.4 mg/kg, then 2.4 mg/kg daily until oral treatment can be substituted. Artemether can only be given by intramuscular injection (anterior thigh); the dose is 3.2 mg/kg followed 24 hours later by 1.6 mg/kg daily.

Both drugs are given until the patient is able to eat and drink normally; thereafter, oral artesunate (2 mg/kg/day) may be given to complete a course of 7 days. Alternatives to oral artesunate include artemether/lumefantrine (6 doses over 48 hours), doxycycline (100mg every 12 hours for 7 days); clindamycin (5 mg/kg every 8 hours for 7 days) may be used in pregnant women. Mefloquine should not be used, because this carries an increased risk of convulsions and psychosis.[55] Chloroquine or sulfadoxine/pyrimethamine should not be used, because of parasite resistance.

In adults with severe malaria, intravenous artesunate reduced the case fatality rate by 35% compared with intravenous quinine.[56] Quinine was also associated with a 3-fold higher risk of developing hypoglycemia. Therefore, intravenous artesunate should be used as the first-line drug for treating severe malaria in adults.

In pregnant women, parenteral artemisinins are better options than quinine in the second and third trimesters because quinine is associated with a higher risk of recurrent hypoglycemia. In the first trimester of pregnancy, the lower risk of quinine-induced hypoglycemia has to be balanced against the relative lack of safety

1 The use of trade names is for product identification purposes only and does not imply endorsement.

data of the artemisinins. Pending more data, the artemisinins or quinine may be used in the first trimester. Because of the clear-cut advantage of artesunate over quinine in nonpregnant adults, artesunate should be the artemisinin of first choice.[57]

3.1.2 Quinine

Quinine is the mainstay of treatment in many countries, and is effective at the doses used for severe malaria despite areas of focal resistance.[58] It should be administered as an intravenous infusion (any crystalloid fluid may be used) over 4 hours; it may also be given by intramuscular injection to the anterior thigh. It must *never* be given as a bolus injection, because of its cardiotoxicity.

Quinine is given as a loading dose of 20 mg/kg salt followed by 10 mg/kg salt every 8 hours. Patients are on infusion for 4 hours, off infusion for 4 hours, and back on infusion for 4 hours. Alternatively, quinine may also be given as a continuous infusion. The infusions should be continued until the patient is able to eat and drink normally. Oral quinine may be used to complete a total of 7 days' treatment. If this is not well tolerated, doxycycline or another antimalarial can be given, as above.

3.1.3 Quinidine

In the US, quinidine is used instead of quinine. It is more cardiotoxic,[59] and recommendations on its use and monitoring are available from the US Centers for Disease Control and Prevention (CDC), which should be consulted. The following dosage regimens are a verbatim copy selected from the US CDC web site (accessed September 2006).[60] "Since 1991, quinidine gluconate has been the only parenterally administered antimalarial drug available in the US. It is recommended to give a loading dose of 6.25mg base/kg (= 10mg salt/kg) of quinidine gluconate infused intravenously over 1–2 hours followed by a continuous infusion of 0.0125mg base/kg/min (= 0.02mg salt/kg/min).[16] An alternative regimen is an intravenous loading dose of 15mg base/kg (= 24mg salt/kg) of quinidine gluconate infused intravenously over 4 hours, followed by 7.5mg base/kg (= 12 mg/kg salt) infused over 4 hours every 8 hours, starting 8 hours after the loading dose (see package insert). Quinidine levels should be maintained in the range of 3–8 mg/L. At least 24 hours of quinidine gluconate infusion are recommended (or 3 intermittent doses); once the parasite density is < 1% and the patient can take oral medication, the patient can complete the treatment course with oral quinine at a dosage of 10mg salt/kg every 8 hours (for a combined treatment course of quinidine/quinine for 7 days in Southeast Asia and 3 days in Africa and South America)."

"Parenteral quinidine gluconate is cardiotoxic and should be administered in an intensive care setting with continuous cardiac and frequent blood pressure monitoring. At the dosages required for the treatment of falciparum malaria, quinidine gluconate may cause ventricular arrhythmia, hypotension, hypoglycemia, and prolongation of the QTc interval. The quinidine gluconate infusion should be slowed or stopped for an increase in the QRS complex by >50%, a QTc interval >0.6 seconds, a QTc interval that is prolonged by more than 25% of the baseline value, or hypotension unresponsive to fluid challenge."

These two dose regimens are very different and there is concern that the low-dose regimen may be insufficient for a life-threatening disease.[61]

3.2 Malaria Complications

3.2.1 Respiratory Compromise

Breathless patients should be assessed and given oxygen administered by the most appropriate method. Oxygen delivery using nasal canulae or a face mask may suffice. However, the experience from Southeast Asia is that breathless patients develop respiratory failure rapidly, necessitating prompt mechanical ventilation. Positive pressure ventilation with positive end-expiratory pressure (PEEP) is used and combined with early hemofiltration for patients in acute renal failure. This combined strategy appears optimal in this setting where both respiratory and renal failure are relatively common (Day NPJ and White NJ, unpublished observations, 1992–96).[56] Intubation should be smooth and quick to avoid a rise in partial pressure of carbon dioxide in arterial blood ($PaCO_2$). Metabolic acidosis in malaria results in hyperventilation, resulting in a low or normal $PaCO_2$, which in turn maintains cerebral vasoconstriction. A rise in $PaCO_2$ would result in cerebral vasodilatation and expansion of an already engorged brain that is full of static adherent parasitized red blood cells. Such an expansion within the defined space of the cranium would lead to a dramatic rise in intracranial pressure.

Current guidelines for the mechanical ventilation of patients call for the use of low tidal volume ventilation, adjusting PEEP and the concentration of inspired oxygen to reduce the risk of barotrauma, oxygen toxicity, and a decrease in cardiac output.[62-64] This may lead to a rise in arterial carbon dioxide, so-called 'permissive hypercapnea.' There are no studies examining this issue in ventilated patients with severe falciparum malaria, but hypercapnia may be undesirable in comatose malaria patients because this will further increase the cranial blood flow and intracranial pressure. In Colombia, where non-sequestrating *P. vivax* is a cause of ALI/ARDS, low tidal volume ventilation is used routinely with PEEP. One potential disadvantage of low tidal volume ventilation is that deep sedation and sometimes patient paralysis may be required.

Noninvasive positive pressure ventilation (NPPV) has gained acceptance for the management of respiratory failure due to, for

example, cardiogenic pulmonary edema and COPD.[65] However, NPPV requires a cooperative patient and is unsuitable in severely ill patients and those with impaired consciousness.

3.2.2 Fluid Balance

Attention to fluid balance is an important element in management because of the risk of exacerbating pulmonary edema. However, dehydrated and/or anemic patients need to be resuscitated adequately with crystalloids and blood, as guided by invasive hemodynamic monitoring using a central venous pressure (CVP) line and a Swan Ganz catheter.[53] There is a fine line between trying to keep the lungs 'dry' and not compromising cardiac and renal function. The recommendations in malaria are to maintain the central venous and pulmonary artery occlusion pressures at 0–5cm H_2O, and 12mm Hg, respectively.[66]

Patients who are in shock despite apparent normovolemia should be evaluated with particular attention to finding a source of sepsis, excluding a myocardial infarction (a possibility in elderly patients), and checking for acidemia/acidosis (blood gases, plasma lactate). Unusual causes should also be sought, e.g. occult gastrointestinal bleeding, uremic pericardial effusion, and a pneumothorax. Studies in Vietnamese adults with severe malaria have shown that adrenaline exacerbates lactic acidosis, a finding not associated with dopamine.[67] Because lactic acidosis is an independent risk factor for death in severe malaria, adrenaline is best avoided unless other pressor agents (dopamine, norepinephrine [noradrenaline]) have failed.

There are data from sepsis patients that hypoproteinemia predicts the development of ARDS and is also a marker of a poor prognosis. Clinical data suggest that infusions of albumin combined with frusemide (furosemide) are beneficial. This approach merits further evaluation in malaria patients.[68]

3.2.3 Acute Renal Failure

Malarial acute renal failure (ARF) behaves in a similar way to acute tubular necrosis (ATN) of diverse etiology. Factors leading to prerenal failure, e.g. dehydration and shock, should be corrected. Frusemide is often used to 'rescue' the kidney from developing ATN, but there is no evidence that this approach is effective. The use of low 'renal' dose dopamine is also questionable. It did not result in improved renal function in Vietnamese adults with malaria ARF.[69] Most patients with renal impairment respond to effective antimalarial treatment and rehydration.[70] Established malaria ARF is hypercatabolic and characterized by rapid increases in urea. In such patients, dialysis should be instituted promptly.[71] The clinical indications for dialysis are essentially those for other causes of acute renal failure, and include manifest uremia (changes in sensorium, flapping tremor, pericarditis, gastrointestinal bleeding), fluid overload, hyperkalemia (>7 mmol/L and/or related ECG signs), blood urea >25–30 mmol/L, a serum creatinine of 500–700 μmol/L, and severe acidemia (blood pH <7.1) or acidosis (serum bicarbonate <12 mmol/L).[64,70,72] Hemofiltration is the preferred treatment modality, significantly reducing the mortality rate compared with peritoneal dialysis in Vietnamese adults.[73]

3.2.4 Concomitant Bacteremia

Malaria patients may have a concomitant bacteremia on admission. There are no evidenced-based guidelines, but clinicians should employ a low threshold for starting broad spectrum antibacterials to cover both Gram-negative and Gram-positive organisms[23,24,43] in patients with shock, and ALI/ARDS. Infections acquired in the intensive care unit, e.g. line infections and ventilator-related pneumonia, require energetic management. Nosocomial pathogens are likely to be resistant to routine antibacterials.[74]

3.2.5 Anemia and Hypoglycemia

Anemia and hypoglycemia are two important complications. The WHO recommendations for commencing a blood transfusion in the tropics are a hematocrit level of <20% in adults and <15% in children.[10] These are based partly on the very important practical consideration of obtaining pathogen-free blood. No target hemoglobin level is suggested in the WHO guidelines. The blood transfusion recommendations for adult patients with sepsis are to transfuse when the hemoglobin decreases to <7 g/dL and to aim for a hemoglobin level of 7–9 g/dL.[63] Although this recommendation is based on work conducted in non-malaria-endemic populations without malaria and before the widespread use of leukoreduction, they are reasonable targets to aim for pending revised, evidenced-based recommendations.[75,76] Most adult malaria patients in endemic countries will otherwise be healthy and tolerate low hemoglobin levels. For patients with stable ischemic heart disease, restricting blood transfusion as recommended above appears safe.[77] There are no data on patients with severe malaria and concomitant acute myocardial infarction or unstable angina, so strict recommendations cannot be made. Using blood transfusions in patients with acute myocardial infarction has been reviewed by Hébert and Fergusson,[78] and should be consulted.

Hypoglycemia may go unrecognized in a severely ill patient. Regular measurements of blood glucose are essential – hourly during quinine transfusions, and 4-hourly during administration of artemisinins. Clinical manifestations include a change in behavior, deteriorating level of consciousness, convulsions, and increased respiratory rate. Hypoglycemia is a particular problem in pregnant women.

3.3 Other Therapies

Exchange transfusion has been suggested as an ancillary treatment to remove infected red cells, inflammatory cytokines and

toxins, and to replenish patients with healthy red cells. Various clinical series have reported beneficial results but a randomized trial has never been conducted.[10,32] Certain treatments, some of which have been used in non-malaria ARDS, have been shown to be harmful in severe malaria (e.g. dexamethasone)[40] or of no benefit (e.g. prostacyclin).[10]

4. Conclusion

Clinicians should always suspect malaria in febrile patients with a history of travel or residence in the tropics. Malaria is best diagnosed by the microscopic examination of a thick and thin blood film. Lung involvement in malaria may be the main feature of an otherwise unremarkable febrile illness or may be part of a severe systemic illness. Severe malaria caused by *P. falciparum* must be treated promptly with an effective antimalarial drug. Artesunate is the drug of choice in severe malaria but is not yet widely available; intramuscular artemether, quinine or quinidine (US only) are alternatives. Quinidine is cardiotoxic and requires ECG monitoring. In well resourced settings, severely ill patients should be managed in an intensive care unit; complications like ALI/ARDS, ARF, and hypoglycemia should be treated energetically. Bacterial sepsis may be present in a minority of patients with severe malaria; it may not be clinically manifest and should be treated empirically if clinically suspected. Pregnant women are particularly prone to developing pulmonary edema and hypoglycemia. Intravenous artesunate is the treatment of choice in the second and third trimesters. Quinine or the artemisinins may be used in the first trimester. Pending more data, quinine and the artemisinins are options for treating first-trimester severe malaria.

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References

1. Gilles HM, Warrell DA, editors. Bruce-Chwatt's essential malariology. London: Arnold, 1993
2. WHO. World malaria situation in 1994. Wkly Epidemiol Rec 1997; 72: 269-76
3. Loutan L. Malaria: still a threat to travellers. Int J Antimicrob Agents 2003; 21: 158-63
4. Shah S, Filler S, Causer LM, et al. Malaria surveillance: United States, 2002. MMWR Surveill Summ 2004; 53: 21-34
5. Luxemburger C, Nosten F, Kyle DE, et al. Clinical features cannot predict a diagnosis of malaria or differentiate the infecting species in children living in an area of low transmission. Trans R Soc Trop Med Hyg 1998; 92: 45-9
6. Murphy GS, Oldfield III EC. *Falciparum malaria*. Infect Dis Clin North Am 1996; 10: 747-75
7. Falconer AW, Anderson AQ. Clinical types of subtertian malaria. Lancet 1917; I: 607-10
8. Hughes SB, Bomford RR. Clinical features and treatment of malaria in British troops in West Africa. BMJ 1944; 1: 73
9. Appelbaum IL, Shrager J. Pneumonitis associated with malaria. Arch Intern Med 1944; 74: 155-62
10. World Health Organization, Communicable Diseases Cluster. Severe falciparum malaria. Trans R Soc Trop Med Hyg 2000; 94 Suppl. 1: S1-90
11. Mohanty S, Mishra SK, Pati SS, et al. Complications and mortality patterns due to *Plasmodium falciparum* malaria in hospitalized adults and children, Rourkela, Orissa, India. Trans R Soc Trop Med Hyg 2003; 97: 69-70
12. Aursudkij B, Wilairatana P, Vannaphan S, et al. Pulmonary edema in cerebral malaria patients in Thailand. Southeast Asian J Trop Med Public Health 1998; 29: 541-5
13. Tran TH, Day NP, Nguyen HP, et al. A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. N Engl J Med 1996; 335: 76-83
14. Sheehy TW, Reba RC. Complications of falciparum malaria and their treatment. Ann Intern Med 1967; 66: 807-9
15. Clark IA, Cowden WB. Why is the pathology of falciparum worse than that of vivax malaria? Parasitol Today 1999; 15: 458-61
16. Anstey NM, Jacups SP, Cain T, et al. Pulmonary manifestations of uncomplicated falciparum and vivax malaria: cough, small airways obstruction, impaired gas transfer, and increased pulmonary phagocytic activity. J Infect Dis 2002; 185: 1326-34
17. Day NP, Hien TT, Schollaardt T, et al. The prognostic and pathophysiologic role of pro- and antiinflammatory cytokines in severe malaria. J Infect Dis 1999; 180: 1288-97
18. Taylor WR, White NJ. Malaria and the lung. Clin Chest Med 2002; 23: 457-68
19. Bellingan GJ. The pulmonary physician in critical care. 6: the pathogenesis of ALI/ARDS. Thorax 2002; 57: 540-6
20. Charoenpan P, Indraprasit S, Kiatboonsri S, et al. Pulmonary edema in severe falciparum malaria: hemodynamic study and clinicophysiologic correlation. Chest 1990; 97: 1190-7
21. Lewis CH, Martin G. Understanding and managing fluid balance in patients with acute lung injury. Curr Opin Crit Care 2004; 10: 13-7
22. Tong MJ, Ballantine TV, Youel DB. Pulmonary function studies in *Plasmodium falciparum* malaria. Am Rev Respir Dis 1972; 106: 23-9
23. Brooks MH, Kiel FW, Sheehy TW, et al. Acute pulmonary edema in falciparum malaria. N Engl J Med 1968; 279: 732-7
24. Deaton JG. Fatal pulmonary edema as a complication of acute falciparum malaria. Am J Trop Med Hyg 1970; 19: 196-201
25. Safdar A, Hartman BJ, Connor BA, et al. Pulmonary edema in malaria. Int J Infect Dis 1999; 3: 217-9
26. Hall AP. The treatment of severe falciparum malaria. Trans R Soc Trop Med Hyg 1977; 71: 367-78
27. Gachot B, Wolff M, Nissack G, et al. Acute lung injury complicating imported *Plasmodium falciparum* malaria. Chest 1995; 108: 746-9
28. Berkley J, Mwarumba S, Bramham K, et al. Bacteraemia complicating severe malaria in children. Trans R Soc Trop Med Hyg 1999; 93: 283-6
29. James MF. Pulmonary damage associated with falciparum malaria: a report of ten cases. Ann Trop Med Parasitol 1985; 79: 123-38
30. Punyagupta S, Srichaikul T, Nitiyanant P, et al. Acute pulmonary insufficiency in falciparum malaria: summary of 12 cases with evidence of disseminated intravascular coagulation. Am J Trop Med Hyg 1974; 23: 551-9
31. Lalloo DG, Trevett AJ, Paul M, et al. Severe and complicated falciparum malaria in Melanesian adults in Papua New Guinea. Am J Trop Med Hyg 1996; 55: 119-24
32. White NJ. The treatment of malaria. N Engl J Med 1996; 335: 800-6
33. Curlin ME, Barat LM, Walsh DK, et al. Noncardiogenic pulmonary edema during vivax malaria. Clin Infect Dis 1999; 28: 1166-7
34. Lee EY, Maguire JH. Acute pulmonary edema complicating ovale malaria. Clin Infect Dis 1999; 29: 697-8
35. Perren A, Beretta F, Schubarth P. ARDS in *Plasmodium vivax* malaria. Schweiz Med Wochenschr 1998; 128: 1020-3
36. Looareesuwan S, Phillips RE, White NJ, et al. Quinine and severe falciparum malaria in late pregnancy. Lancet 1985; II: 4-8

37. O'Dempsey TJ, McArdle TF, Laurence BE, et al. Overlap in the clinical features of pneumonia and malaria in African children. Trans R Soc Trop Med Hyg 1993; 87: 662-5

38. English M, Punt J, Mwangi I, et al. Clinical overlap between malaria and severe pneumonia in Africa children in hospital. Trans R Soc Trop Med Hyg 1996; 90: 658-62

39. Crawley J, English M, Waruiru C, et al. Abnormal respiratory patterns in childhood cerebral malaria. Trans R Soc Trop Med Hyg 1998; 92: 305-8

40. Warrell DA, Looareesuwan S, Warrell MJ, et al. Dexamethasone proves deleterious in cerebral malaria: a double-blind trial in 100 comatose patients. N Engl J Med 1982; 306: 313-9

41. Evans JA, Adusei A, Timmann C, et al. High mortality of infant bacteraemia clinically indistinguishable from severe malaria. QJM 2004; 97: 591-7

42. Bruneel F, Hocqueloux L, Alberti C, et al. The clinical spectrum of severe imported falciparum malaria in the intensive care unit: report of 188 cases in adults. Am J Respir Crit Care Med 2003; 167: 684-9

43. Prada J, Alabi SA, Bienzle U. Bacterial strains isolated from blood cultures of Nigerian children with cerebral malaria. Lancet 1993; 342: 1114

44. Walsh AL, Phiri AJ, Graham SM, et al. Bacteremia in febrile Malawian children: clinical and microbiologic features. Pediatr Infect Dis J 2000; 19: 312-8

45. Bruneel F, Gachot B, Timsit JF, et al. Shock complicating severe falciparum malaria in European adults. Intensive Care Med 1997; 23: 698-701

46. Pongponratn E, Turner GD, Day NP, et al. An ultrastructural study of the brain in fatal *Plasmodium falciparum* malaria. Am J Trop Med Hyg 2003; 69: 345-59

47. Silamut K, White NJ. Relation of the stage of parasite development in the peripheral blood to prognosis in severe falciparum malaria. Trans R Soc Trop Med Hyg 1993; 87: 436-43

48. Nguyen PH, Day N, Pram TD, et al. Intraleucocytic malaria pigment and prognosis in severe malaria. Trans R Soc Trop Med Hyg 1995; 89: 200-4

49. Cropley IM, Lockwood DN, Mack D, et al. Rapid diagnosis of falciparum malaria by using the ParaSight F test in travellers returning to the United Kingdom: prospective study. BMJ 2000; 321: 484-5

50. Jackson Y, Chappuis F, Loutan L, et al. Malaria treatment failures after artemisinin-based therapy in three expatriates: could improved manufacturer information help to decrease the risk of treatment failure? Malar J 2006 Oct 4; 5: 81

51. Cayea PD, Rubin E, Teixidor HS. Atypical pulmonary malaria. Am J Roentgenol 1981; 137: 51-5

52. Godard JE, Hansen RA. Interstitial pulmonary edema in acute malaria: report of a case. Radiology 1971; 101: 523-4

53. Beale R, Grover ER, Smithies M, et al. Acute respiratory distress syndrome ("ARDS"): no more than a severe acute lung injury? BMJ 1993; 307: 1335-9

54. White NJ. Assessment of the pharmacodynamic properties of antimalarial drugs in vivo. Antimicrob Agents Chemother 1997; 41: 1413-22

55. Nguyen TH, Day NP, Ly VC, et al. Post-malaria neurological syndrome. Lancet 1996; 348: 917-21

56. Dondorp A, Nosten F, Stepniewska K, et al. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005; 366: 717-25

57. WHO. Guidelines for the treatment of malaria. WHO/HTM/MAL/2006.1108

58. Pukrittayakamee S, Supanaranond W, Looareesuwan S, et al. Quinine in severe falciparum malaria: evidence of declining efficacy in Thailand. Trans R Soc Trop Med Hyg 1994; 88: 324-7

59. White NJ, Looareesuwan S, Warrell DA. Quinine and quinidine: a comparison of EKG effects during the treatment of malaria. J Cardiovasc Pharmacol 1983; 5: 173-5

60. Centers for Disease Control and Prevention (CDC). Treatment of malaria (guidelines for clinicians), part 3: treatment – severe malaria [online]. Department of Health and Human Services, CDC. Available from URL: http://www.cdc.gov/Malaria/diagnosis_treatment/clinicians3.htm [Accessed 2006 Sep]

61. White NJ, Warrell DA. Dosage for malaria treatment. Lancet 1996; 348: 1312

62. Calfee CS, Matthay MA. Recent advances in mechanical ventilation. Am J Med 2005; 118: 584-91

63. Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Surviving Sepsis Campaign Management Guidelines Committee. Crit Care Med 2004; 32: 858-73

64. Cordingley JJ, Keogh BF. The pulmonary physician in critical care: 8. Ventilatory management of ALI/ARDS. Thorax 2002; 57: 729-34

65. Liesching T, Kwok H, Hill NS. Acute applications of noninvasive positive pressure ventilation. Chest 2003; 124: 699-713

66. Day NP, Nguyen HP, Pham PL. Renal disease: II. Malaria and acute renal failure. J R Coll Physicians Lond 1997; 31: 146-8

67. Day NP, Phu NH, Bethell DP, et al. The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. Lancet 1996; 348: 219-23

68. Martin GS, Mangialardi RJ, Wheeler AP, et al. Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. Crit Care Med 2002; 30: 2175-82

69. Day NP, Phu NH, Mai NT, et al. Effects of dopamine and epinephrine infusions on renal hemodynamics in severe malaria and severe sepsis. Crit Care Med 2000; 28: 1353-62

70. Wilairatana P, Westerlund EK, Aursudkij B, et al. Treatment of malarial acute renal failure by hemodialysis. Am J Trop Med Hyg 1999; 60: 233-7

71. Trang TT, Phu NH, Vinh H, et al. Acute renal failure in patients with severe falciparum malaria. Clin Infect Dis 1992; 15: 874-80

72. Warrell DA, Cox TM, Firth JD, et al., editors. Oxford textbook of medicine. 4th ed. Oxford University Press, 2003: 3286-7

73. Phu NH, Hien TT, Mai NT, et al. Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. N Engl J Med 2002; 347: 895-902

74. Vincent JL. Nosocomial infections in adult intensive-care units. Lancet 2003; 361: 2068-77

75. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999; 340: 409-17

76. McIntyre L, Hébert PC, Wells G, et al. Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? Canadian Critical Care Trials Group. J Trauma 2004; 57: 563-8

77. Hébert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group. Crit Care Med 2001; 29: 227-34

78. Hébert PC, Fergusson DA. Do transfusions get to the heart of the matter? JAMA 2 2004; 292: 1610-2

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