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Severe and Complicated Malaria due to *Plasmodium vivax*

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Abstract

Contrary to the widespread belief that severe malaria is mainly caused by *Plasmodium falciparum*, malaria caused by *Plasmodium vivax* infection may also lead to severe clinical manifestations including a plethora of renal, pulmonary, hematologic, neurologic, and multiorgan dysfunction. Anemia and thrombocytopenia are considered as two major important markers of severity during the clinical course of severe *P. vivax* malaria. In highly endemic areas of *P. vivax* transmission, early diagnosis is crucial in preventing uncomplicated episodes progressing into severe and complicated clinical forms. In fact, given the wide geographic distribution of *P. vivax*, there is a large burden of disease, often not adequately acknowledged, and resulting from the combined effect of the large numbers of uncomplicated clinical episodes and the increasingly recognized severe and complicated clinical presentations.

Keywords: *Plasmodium vivax*, clinical manifestations, diagnosis, treatment, severe, complicated

1. Introduction

Globally, malaria remains one of the most important infectious diseases affecting humankind in terms of morbidity and mortality [1, 2]. *Plasmodium vivax* infection and *Plasmodium falciparum* represent the two most frequent and severe forms of human malaria. Individuals acquire the infection by the bite of the female *Anopheles* mosquitoes inoculating microscopic sporozoites that subsequently reach the liver via the bloodstream. Once in the liver, the sporozoites evolve into a schizont that produces merozoites and then releases them into the

bloodstream coinciding with the onset of the clinical syndrome of malaria [3]. Most importantly, most deaths associated with malaria occur in children living in highly endemic settings [3]. The large social and economic burden attributable to *P. vivax* in highly endemic settings results from the elevated number of cases that require medical care in an already impoverished economy diverting cash and family members from work to attend the sick [2, 3]. Uncomplicated *P. vivax* malaria refers to a febrile illness where there are no hemodynamic instability, no evidence of major hemolysis, no absence of severe anemia, no evidence of pulmonary edema or ARDS, and no evidence of severe metabolic acidosis, renal failure, hepatic dysfunction, focal neurological deficits or seizures, or multi-organ failure [4, 5]. Historically, severe malaria is often considered exclusively within the clinical spectrum of disease caused by infection due to *P. falciparum*. However, albeit less recognized, infection due to *P. vivax* can also lead to clinically severe manifestations and complications including (a) fatal bleeding due to traumatic or spontaneous rupture of an enlarged spleen, (b) seizures, (c) shock, (d) hepatitis with cholestasis, (e) renal failure, (f) severe anemia and thrombocytopenia, (g) respiratory distress and acute lung injury (ALI), (h) miscarriage and preterm delivery, and (h) multi-organ failure [6]. Of all these complications, the most significant source of morbidity is by far the occurrence of severe anemia and its consequences. Furthermore, in many geographic settings, coinfection of *P. vivax* and *P. falciparum* may occur in the same host, and this can be associated with severe clinical manifestations. Therefore, identifying coinfection in settings where there is co-circulation of both *Plasmodium* spp., the peripheral blood smear is of utmost clinical importance in the early course of a febrile illness in which malaria is a consideration [7]. *P. vivax* malaria was originally described clinically as “benign tertian malaria”; however, this is a misleading concept because *P. vivax* is not a benign disease. In fact, it is increasingly recognized as a major cause of morbidity and mortality in highly endemic settings.

The clinical spectrum of disease associated with *P. vivax* infection ranges from asymptomatic parasitemia and uncomplicated febrile illness to severe and fatal malaria. In this regard, the host response influences the clinical expression of the disease. Fever may occur with low parasite densities and may be identified 2–3 days before the parasites are detected in blood, underscoring the need for serial peripheral blood smear examinations [8]; *P. vivax* has a lower pyrogenic threshold (parasitic density required to evoke a fever) compared with *P. falciparum*. Globally, it is estimated that there are more than 80 million episodes of *P. vivax* malaria every year resulting in a considerable amount of morbidity and mortality. The prevailing neglect of the substantial public health impact of *P. vivax* that occurs in many settings in comparison with that of *P. falciparum* relies on its low incidence in Sub-Saharan Africa as a result of the evolutionary trait of the Duffy antigen negativity selected among many African populations [9].

P. vivax causes almost half of all of the 70–390 million clinical cases of malaria each year. In countries endemic for both major *Plasmodium* species, *P. vivax* infection may account for up to 38% of patients hospitalized with malaria. In Indonesian Papua, *P. vivax* accounted for 24% of malaria admissions in all age groups, of whom 47% (415/887) are infants [6]. The need for hospitalization among these cases indicates significant morbidity, and at least moderately

severe disease. Thus, clinicians should be aware of the spectrum of severe disease and of potential multi-organ affection among patients presenting with *P. vivax* malaria [10–37].

2. Parasitology and epidemiology

Infection due to *P. vivax* challenges human health in many settings, particularly in Southeast Asia, in some areas of the Pacific Islands, and in many areas in Latin America, particularly in Venezuela and Brazil [38, 39]. This type of malaria infection affects approximately 100–400 million people each year within a population living at risk of 2.5 billion. Interestingly, *P. vivax* occurs with an extremely low prevalence throughout much of Africa likely as selective pressure led to the emergence of the Duffy antigen negativity or red blood cells across African populations, particularly in West Africa. However, *P. vivax* produces substantial morbidity in some settings at subtropical and temperate latitudes in Asia [11].

P. vivax is responsible for approximately 3.3–30.3% of complications of malaria. In Colombia, *P. vivax* is responsible for almost 75% of cases of malaria. In the country, mortality from 130 to 150 cases per year is recorded, because this situation has been considered the disease as a public health concern with a growing number of complications [10, 11]. *P. vivax* accounted for 24% of malaria admissions in all age groups, including 47% of them among infants. In a recent autopsy-based report from Brazil, at least four of 17 (23.5%) *P. vivax*-associated deaths in Brazil were attributable to alternative causes at the time of death, including meningitis and yellow fever, underscoring the ability of this infection to manifest with severe disease often mimicking other conditions traditionally considered to produce severe clinical manifestations. Mortality rates in those hospitalized in Indonesian Papua with microscopy-confirmed *P. vivax* were reported as 0.8–1.6%, similar to that of *P. falciparum* infection (1.6–2.2%). The adjusted odds ratio of death from severe anemia in Papua, Indonesia, was 5.9 for those with *P. falciparum* and 4.4 for those with *P. vivax* infection [12, 13]. Differences in intensity of transmission might contribute to the variation in the spectrum of disease severity, as it occurs with falciparum malaria. Prospective studies from Papua New Guinea conducted to address mortality associated with *P. vivax* infection have shown a mortality rate of 1.6% among hospitalized patients with *P. vivax* and of 2.2% among those infected with *P. falciparum*. These facts illustrate the similarities in terms of clinical outcomes between both types of human malaria. Further studies are needed to define *P. vivax* attributable mortality in endemic areas along with clinical studies to elucidate the precise pathophysiological and clinical spectrum of disease and from a public health perspective, the overall magnitude of morbidity and mortality associated with *P. vivax* malaria [14].

3. Pathogenesis and disease transmission

The clinical spectrum of disease of *P. vivax* infection in humans is influenced by many factors: the parasite, parasite-host interactions, host factors, and socioeconomic environment in which

these infections occur [3–5]. For example, low socioeconomic status is associated with higher risk of developing severe anemia [3]. Studies of specific organs have also shown that the inflammatory response during infection with *P. vivax* is of greater magnitude compared with that seen in *P. falciparum* infection and also with a parasite biomass similar or greater. Moreover, cytokine production in *P. vivax* infections is quantitatively more robust than in *P. falciparum* infections with a similar parasite biomass.

P. vivax infections relapse at intervals of 3–4 weeks, and progressive anemia is associated with recurrent episodes of hemolysis and dyserythropoiesis. In areas with chloroquine resistance, this is further aggravated by the elimination of delayed parasite infection and risk of reactivation. The low number of *P. vivax* parasites indicates that severe anemia may not be produced by the destruction of infected erythrocytes. This is further evident from the fact that it has been shown that during *P. vivax* malaria therapy studies have shown that for each infected erythrocyte destroyed, 32 uninfected erythrocytes are cleared from the bloodstream. This contrasts with the loss of only a few infected red blood cells during *P. falciparum* malaria. The mechanisms underlying this difference are not known; the proportion of uninfected erythrocytes destroyed compared to the proportion of extravascular subject (e.g., splenic) pooling is also not known. Recent studies show an increased fragility microfluidics of infected erythrocytes [14–16]. Pathogenic mechanisms leading to severe symptoms not known exactly, but it have suggested that a failure of the immune system to control parasite replication or immunopathological response resulting from excessive inflammation; they are considered as contributing factors in this response malaria parasites and parasite-infected red blood cells that activate dendritic cells activate dendritic. Parasite antigen presenting T helper (Th) 1 cells triggers a pro-inflammatory response. The inflammatory response required to eliminate parasites may produce tissue damage and activation of phagocytes with production of a cytokine cascade [17].

4. Clinical manifestations

When evaluating patients presenting with a clinical syndrome compatible with malaria, there are no specific signs or symptoms to assist clinicians in distinguishing infection due to *Plasmodium vivax* or *Plasmodium falciparum*; or when there is coinfection by the two species. Fever in young children may produce seizures. Some individuals progress rapidly to respiratory failure caused by either pulmonary edema or even acute respiratory distress syndrome (ARDS). Among those with rapid clinical deterioration, we should always consider the concomitant risk of gram-negative bacteremias among individuals with either *P. vivax* or *P. falciparum* infection [6, 7]. The main serious manifestation in most series of vivax malaria in children is severe anemia, defined as hemoglobin <5 g/dl in children and <7 g/dl in adults [18]. The pathogenesis of severe malaria is caused by erythrocyte destruction after the invasion of the parasite by its multiplication and also by morphological deformity of the infected red blood cell with opsonization and antibody-dependent lysis of erythrocytes. Indeed, *P. vivax*-infected red blood cells are minimally tacky and are more deformable than *P. falciparum* erythrocytes resulting in relatively low red cell sequestration in microvasculature and bone sinuses and the

passage of a greater proportion of erythrocytes through the reticuloendothelial spleen and other organs infected [19]. Recurrent episodes of *P. vivax* infection in highly endemic settings contribute to a higher risk of severe anemia [20, 21]. Acute respiratory distress syndrome (ARDS) occurs often in patients with severe *P. vivax* [22, 23]. Among patients with *Plasmodium vivax* infection and presenting with severe clinical manifesting it is important to identify splenic rupture early. In fact, the incidence of splenic rupture is as high as 24%. Factors leading to Splenic rupyure include: rapid hyperplasia and parenchymal splenic capsule, forming small infarcts bleeding, loss connective tissue fibrosis and alterations of primary immunity [6, 10].

Acute kidney injury may occur in both children and adults, and it may result for oliguric renal failure or even from acute tubular necrosis [24, 25]. Many patients present with multi-organ failure and hemodynamic instability requiring vasopressor support and often mechanical ventilation. Others may develop acute kidney injury from hypovolemic shock secondary to splenic rupture. All of these potential clinical scenarios should be considered among those with severe *P. vivax* infection and particularly among those with rapid clinical deterioration often requiring intensive care support. In some settings, *P. vivax* may present with concomitant bacterial infection including non-typhoidal salmonellosis or even with enteric fever [26–29]. Finally, patients may also develop seizure disorder or focal neurologic deficits during the clinical course of *P. vivax* mono-infection or when coinfecting with *P. falciparum* [30–32]. Early recognition and institution of appropriate interventions are crucial to improve overall clinical outcomes.

5. Diagnosis of severe vivax malaria

Appropriate management of individuals with *P. vivax* requires confirmation of the diagnosis by peripheral smear examination. Coinfection with *P. falciparum* should be entertained in settings where there are co-circulations of both *Plasmodium* species [30]. Early institution of anti-parasitic therapy is instrumental. Additionally, ruling out coinfection with bacterial diseases such as non-typhoidal salmonellosis or by other enteric-gram-negative bacteria is of utmost clinical relevance. Supportive management in intensive care units should be early instituted among those with rapid progression to multi-organ failure and among those with persistent hypotension despite volume resuscitation or requiring vasopressors due to persistent hemodynamic instability. Search for potential splenic rupture needs to be considered at the time of initial presentation, or during the course of illness, among those with rapid clinical deterioration or those developing severe anemia.

6. Treatment of severe vivax malaria

A summary of core concepts in the management of severe malaria due to *P. vivax* is depicted in **Table 1**. Clinical trials to assess optimal treatment regimens of *P. vivax* malaria are limited. At this point in time, in many settings, treatment of vivax malaria consists of chloroquine or

an artemisinin-based combination therapy. In those settings where chloroquine resistance remains low, chloroquine may be used as monotherapy with continuous clinical monitoring. However, in most settings, an artemisinin-based combination therapy has become the standard of care due to the growing recognition of vivax malaria causing severe disease, also due to the risk of coinfection with *P. falciparum* (in settings with co-circulation of both species), and finally due to the increasing rates of resistance to chloroquine. Some areas consider a universal policy of treatment with an artemisinin-based combination therapy (artemether-lumefantrine) that is considered the treatment of choice since this drug combination is well tolerated and safe to pregnant women and children [34]. Additionally, there is an increasing recognition of treatment failure when using chloroquine or the combination of chloroquine/sulfadoxine-pyrimethamine [35–37].

Clinical category	Core concepts
Respiratory failure	Protect airway Provide supplemental oxygen Rule out other causes of concomitant respiratory failure (i.e., bacterial pneumonia, pulmonary embolism, or others)
Acute pulmonary edema	Oxygen supplementation BIPAP or mechanical ventilation via endotracheal intubation if needed. Patient often requires PEEP given the possibility of ARDS
Shock	Potentially caused by either hypovolemia due to bleeding or septic shock from gram-negative bacteremia Obtain blood cultures; administer broad spectrum antibiotics; correct hemodynamic disturbances Rule out splenic rupture with abdominal ultrasound or computed tomography Surgical consultation
Acute renal failure	Exclude prerenal causes Fluid replacement Hemodialysis or hemofiltration if indicated (i.e., worsening acute kidney injury, acute tubular necrosis, concomitant severe acidosis, and/or hyperkalemia)
Seizures	Protect airway Benzodiazepines Other antiseizure medications: Dilantin
Acidosis	Exclude or treat hypoglycemia, hypovolemia, and sepsis If severe, performing hemofiltration or hemodialysis is indicated
Severe anemia	Blood transfusion
Antiparasitic treatment	First-line treatment Second-line treatment of complicated malaria Quinine dihydrochloride combined with either clindamycin (300 mg) or doxycycline (100 mg) tablets Presumptive anti-relapse therapy with primaquine is required to eradicate the liver stage of <i>P. vivax</i> (hypnozoite), similar to <i>P. ovale</i> in both low-transmission and high-transmission settings

Table 1. Clinical spectrum and management of severe/complicated *P. vivax* malaria.

The spread of drug-resistant *P. vivax* to parts of Indonesia, other parts of Southeast Asia, and South America highlights the urgent need to revisit the spectrum of disease and of the burden of vivax malaria in order to implement control measures and allocate adequate resources against this neglected infectious disease [1, 37].

7. Conclusion

Malaria infection remains as a leading infectious diseases affecting humankind due to its associated large burden of disease. There is a growing recognition that *P. vivax* contributes to a large proportion of this burden. In particular, coinfection of *P. vivax* and *P. falciparum* seems to be synergistic in terms of leading to severe disease, complications, and death among the most vulnerable populations. The spectrum of disease severity associated with *P. vivax* infection ranges from respiratory failure to renal failure. However, the most important marker of disease severity across borders is produced by hematological abnormalities including severe anemia and thrombocytopenia. Further research is warranted to address the large epidemiologic burden of disease associated with *P. vivax* and to identify preventive strategies. From a clinical perspective, there is a need for further clinical studies to identify strategies to optimize the clinical management of vivax malaria.

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