Journal of Tropical Diseases
ISSN: 2329-891X

Aggarwal et al., J Trop Dis 2013, 1:4
DOI: 10.4172/2329-891X.1000124

Review Article Open Access

Changing Trends in Malaria

Puneet Aggarwal*, Arka De, Nishanth Dev, Varun Rehani, Adesh Gadpayle and Swati Yadav

Post Graduate Institute of Medical Education and Research & Dr Ram Manohar Lohia Hospital, Department of Internal medicine, New Delhi, India

Abstract

Malaria continues to dominate the scene involving the infectious diseases even though the figures suggest that the incidence of malaria is decreasing. Transmitted by the bite of the anopheles mosquito, malaria has undergone varying epidemiological and clinical changes with *Plasmodium vivax* malaria becoming complicated along with the Falciparum malaria with multi-organ involvement and can be fatal at times. Early and accurate diagnosis of malaria is imperative for effective management. More recently, Rapid Diagnostic Tests (RDTs) have been introduced into routine use, and molecular methods like polymerase chain reaction are useful in certain situation. Artemesinin based combination therapy have become the drug of choice especially for complicated malaria with Synriam being the latest addition which is a fixed dose formulation containing the short acting arterolane and long acting piperaquine.

Keywords: Malaria; Epidemiology; *Plasmodium vivax*; Synrium

Introduction

Malaria, the disease which infected 500,000 [1] and killed over 60,000 men during World War II [2] still continues to be a significant public health problem in the 21st century world and causes 1-3 million deaths every year. Transmitted by the bite of the female anopheles mosquito, malaria is caused by members of the genus Plasmodium (P.) namely *P. vivax, P. falciparum, P. ovale, P. malariae and P. knowlesi.*

Changing Epidemiology

World Health Organization (WHO) estimates that global malaria incidence has decreased by 17% and death due to malaria by 26% from 2000-2010. 91% of deaths and 81% of the cases were reported from the African Region [3]. These improvements are attributed to human interventions, greater funding, greater use of insecticide treated bednets, indoor residual spraying, rapid diagnostic tests, and artemisinin-based combination therapies. Many epidemiologic changes have been noted in malaria-eliminating countries. Malaria cases are increasingly male, adult, clustered geographically, imported, among migrant and other hard-to-reach groups, and caused by *Plasmodium vivax* [4].

Despite these encouraging trends the sad fact is that 219 million cases and 660,000 deaths from malaria were reported by WHO in 2010 [5]. When undocumented deaths were taken into account, this number was a staggering 1.24 million. 65% of the cases occurred in children under 15 years of age [6]. Malaria is presently endemic in a broad band around the equator, in areas of the Americas, many parts of Asia, and much of Africa. The efforts of the Malaria Atlas Project, which aimed to map the global endemic levels of malaria and assess disease burdens, led to the publication of the *P. falciparum* endemicity map in 2010 [7].

The Indian Scenario

Malaria is one of the major public health problems in India with around 1.5 million confirmed cases reported annually by the National Vector Borne Disease Control Programme (NVBDCP) [8]. About 50% cases are attributed to Plasmodium falciparum as compared to only 14% in 1970 [9]. The increased proportion of falciparum cases is mainly due to the continued use of chloroquine despite the drastic increase in chloroquine resistant falciparum. Another significant factor is the role played by mosquito vectors including increasing resistance to insecticides seen in Anopheles culicifacies and Anopheles fluviatilis-the two main vectors in rural India [10]. The poor functioning of Government schemes like the Urban Malaria scheme has also contributed to the resurgence of malaria [11].

Changing Clinical Spectrum and Virulence of *P. vivax*

Traditionally, complicated or severe malaria was thought to be caused only by *P. falciparum* with *P. vivax* causing benign tertian malaria. The main problem with vivax malaria was relapses due to persistence of dormant hypnozoites in the liver. This was tackled by the administration of primaquine but there have been reports of increasing primaquine resistance from Indonesia and Oceania [12]. Vivax malaria has long been associated with complications like anemia, thrombocytopenia and rarely splenic rupture. Mortality and morbidity have however been low. This simplified scenario has been fast changing over the past decade with increasing reports of acute lung injury, pulmonary edema, acute kidney injury, shock, cerebral malaria, severe hyperbiliribunemia [13].

Barcus et al. reported that 3.2% of patients admitted in north eastern Indonesia Papua with *P. Vivax* infection had severe malaria [14]. Tjitra et al. reported that of all malaria admissions in a hospital in Timika, southern Papua, Indonesia, severe disease was present in 23% of *P. vivax* cases (675/2,937) as compared to only 20% of *P. falciparum* cases (1,570/7,817); mixed infections accounted for the highest percentage (31%). Severe anemia was the commonest complication associated with *P. vivax* malaria. Importantly *P. vivax* also resulted in respiratory distress in 78 patients and coma in 42 patients. 1.6% vivax cases died during admission as compared to 2.2% cases of falciparum cases and 2.3% cases with mixed infection [15].

Kochar et al. in 2005 reported 11 cases of severe *Plasmodium vivax* malaria in Bikaner. Complications included cerebral malaria, acute kidney injury, shock, severe anemia, hemoglobinurea, bleeding diathesis, acute respiratory distress syndrome and jaundice [16].

***Corresponding author:** Puneet Aggarwal, Post Graduate Institute of Medical Education and Research & Dr Ram Manohar Lohia Hospital, Department of Internal medicine, New Delhi, India, Tel: +919810626392; E-mail: puneetaggarwal4u@gmail.com

Received October 02, 2013; **Accepted** November 22, 2013; **Published** November 25, 2013

Citation: Aggarwal P, De A, Dev N, Rehani V, Gadpayle A, et al. (2013) Changing Trends in Malaria. J Trop Dis 1: 124. doi: 10.4172/2329-891X.1000124

Out of 303 children with malaria in Bikaner, Kochar et al. 63.1% of children with vivax malaria had severe disease as compared to 42.7% with falciparum malaria. The risk was greater in the 0-5 year age group where 75.7% *P. vivax* malaria cases had severe disease. Severe cases were more in female children [17].

Bhattacharjee et al. studied 763 *P. vivax* malaria cases at a tertiary centre in National capital region, India and reported a multi-system involvement with abdominal manifestations (including hepatosplenomegaly, hepatomegaly, splenomegaly and ascites) in 45.8% cases, hepatic dysfunction and jaundice in 16.7%, moderate to severe anemia in 89.9%, thrombocytopaenia in 82.1% cases, petechiae in 26.8% cases, gross bleeding in 5.3% cases, respiratory findings (tachypnoea, pleural effusions and acute respiratory distress syndrome in 13.1% cases, deranged renal function in 9.5% cases, circulatory collapse in 4.1% cases, cerebral malaria in 5.9% cases, hypoglycaemia in 53% cases, multi-organ dysfunction was detected in 6.54% cases. They too noted that younger children (0-5 years) had more severe complications [18].

Clinico-pathological Correlation

These studies suggest that both sequestration and non sequestration-related complications can occur with *P. vivax*. *P. vivax* incites a greater inflammatory response than *P. falciparum* with same degrees of parasitemia [19]. Studies in the Amazon belt of Brazil indicate that TNF (Tumor Necrosis Factor) and IFN- gamma (Interferon Gamma) are increased in *P. vivax* infections. They also correlate with severity of disease in a linear manner and their levels decrease with recovery [20]. Infection may lead to a proinflammatory state which in turn might incite a cytokine imbalance. Despite these insights the sad truth is that little is known about the pathogenesis of vivax malaria and the reasons behind the increase in virulence. The availability of the *P. vivax* genome may help us know more about this neglected pathogen that though labeled as benign is often malignant.

Diagnosis

Early and accurate diagnosis of malaria is imperative for effective management. Even today, the most widely used method is to diagnose malaria "clinically" particularly in areas of high transmission and low resources like parts of Africa. However, this method is obviously unreliable as the clinical features of malaria are highly non specific. The gold standard is microscopic diagnosis- demonstration of the parasite on thick smear with identification of species on thin smears. However the technical infrastructure and personnel required for microscopy is often difficult to provide for. Apart from being labor intensive, it is also time consuming and delayed reporting leads to delay in institution of treatment.

Since the late 1990s rapid diagnostic tests have become available for the diagnosis of malaria. These tests use immunochromatographic methods to detect malarial parasites in lysed blood. Usually the test comes in the form of a dip-stick or test strip that bears monoclonal antibodies against the targeted malarial antigen. The antigens commonly targeted are the falciparum specific HRP-II (Histone Rich Protein- a water-soluble protein produced by trophozoites and young falciparum gametocytes) and plasmodial LDH (Lactate Dehydrogenase). The advantages of RDTs (rapid diagnostic tests) are that they can be performed by people with minimal training and give rapid results (under 15 minutes). Their sensitivity is comparable to microscopic detection of *P. falciparum* on thick smears (about 0.001% parasitemia) [21]. However, they are unable to quantify parasite density, differentiate between *P. vivax, P. ovale* and *P. malariae*, and between the sexual and asexual stages [22]. Tests may remain positive despite parasite clearance following chemotherapy eg- *P. falciparum* HRP- 2 kits may show positive results for upto 3 weeks following successful treatment.

In India, RDT kits for detection of P. falciparum are provided by NVBDCP in areas where microscopy results cannot be reported within 1 day of sample collection [23]. There are several other methods for the diagnosis of malaria. However they are not used routinely. They include PCR (Polymerase Chain Reaction-the most sensitive and specific method) and microscopy using flurochromes like acridine orange on blood smears or centrifuged blood.

Treatment

Although chloroquine resistance in *P. vivax* is being increasingly reported from South East Asia, Indonesia, Oceania, Central and Southern Americas, the treatment of choice for all non falciparum malarias still continues to be chloroquine except in Indonesia and Papua New Guinea. In India, chloroquine is recommended at a dose of 25 mg/kg divided over 3 days along with primaquine 0.25 mg/kg for 14 days to prevent relapse. Primaquine is contraindicated in G6PD (Glucose 6-Phosphate Dehydrogenase) deficient individuals, infants and pregnant women. However, severe vivax malaria should be treated in the lines of severe falciparum malaria [23]. Falciparum malaria should be treated with ACT (Artemisinin Combination Therapy) along with primaquine 0.75 mg/kg single dose on day 2. Artemisinin derivatives should not be used as monotherapy in uncomplicated malaria due to the fear of development of resistance when these rapid acting derivatives are used without long acting anti-malarials.

Treatment in pregnancy

In India, falciparum malaria in pregnancy is treated with quinine in the 1st trimester and with ACT in the 2nd and 3rd trimesters. Chloroquine is used for vivax malaria [23].

Severe Malaria Treatment

New drug: synriam

Synriam is a fixed dose formulation containing the short acting arterolane and long acting piperaquine. Arterolane is the first fully synthetic, non- artemisinin, oral, rapidly acting anti-malarial drug. Piperaquine acts against both *P. vivax* and *P. falciparum* (including chloroquine resistant strains) [24]. Given once daily for three days, it was approved by Drug Controller General India for use in uncomplicated falciparum malaria in 2011. The combination was compared with artemether-lumefantrine in a phase III, double blinded, randomised, multicentre trial in 186 patients of uncomplicated falciparum malaria. As compared with 98.9% patients with artemether- lumefantrine synriam cured 97.9% patients. Median fever clearance time and parasite clearance time for arterolane- piperaquine was 18hours and 36 hours respectively as compared with 24 hours and 34 hours respectively for artemether-lumefantrine [25].

Conclusion

Arterolane-piperaquine has been found to be safe in phase II and phase III trials [25,26]. The most common adverse effects are head ache and GI side effects; in general the safety profile is comparable to that artemether-lumefantrine combination. There are no specific contraindications except hypersensitivity to any of the ingredients.

References

1. Bray RS (2004) Armies of Pestilence: The Effects of Pandemics on History. James Clarke 102.
2. Byrne JP (2008) Encyclopedia of Pestilence, Pandemics, and Plagues: A-M. ABC-CLIO 383
3. WHO (2011) World malaria report 2011. Geneva: World Health Organization.
4. Cotter C, Sturrock HJ, Hsiang MS, Liu J, Phillips AA, et al. (2013) The changing epidemiology of malaria elimination: new strategies for new challenges. Lancet 382: 900-911.
5. Nayyar GM, Breman JG, Newton PN, Herrington J (2012) Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. Lancet Infect Dis 12: 488-496.
6. Murray CJ, Rosenfeld LC, Lim SS, Andrews KG, Foreman KJ et al. (2012) Global malaria mortality between 1980 and 2010: A systematic analysis. Lancet 379
7. Guerra CA, Hay SI, Lucioparedes LS, Gikandi PW, Tatem AJ, et al. (2007) Assembling a global database of malaria parasite prevalence for the Malaria Atlas Project. Malar J 6: 17.
8. Dhingra N, Jha P, Sharma VP, Cohen AA, Jotkar RM, et al. (2010) Adult and child malaria mortality in India: a nationally representative mortality survey. Lancet 376: 1768-1774.
9. Shah NK, Dhillon GP, Dash AP, Arora U, Meshnick SR, et al. (2011) Antimalarial drug resistance of Plasmodium falciparum in India: changes over time and space. Lancet Infect Dis 11: 57-64.
10. Sharma VP (1996) Re-emergence of malaria in India. Indian J Med Res 103: 26-45.
11. Roll Back Malaria. Situation analysis of malaria control in five selected pilot areas in the country for the implementation of roll Back Malaria (RBM) initiative.
12. Fernando D, Rodrigo C, Rajapakse S (2011) Primaquine in vivax malaria: an update and review on management issues. Malar J 10: 351.
13. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, et al. (2007) Vivax malaria: neglected and not benign. Am J Trop Med Hyg 77: 79-87.
14. Barcus MJ, Basri H, Picarima H, Manyakori C, Sekartuti, et al. (2007) Demographic risk factors for severe and fatal vivax and falciparum malaria among hospital admissions in northeastern Indonesian Papua. Am J Trop Med Hyg 77: 984-991.
15. Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, et al. (2008) Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Med 5: e128.
16. Kochar DK, Saxena V, Singh N, Kochar SK, Kumar SV, et al. (2005) Plasmodium vivax malaria. Emerg Infect Dis 11: 132-134.
17. Kochar DK, Tanwar GS, Khatri PC, Kochar SK, Sengar GS, et al. (2010) Clinical features of children hospitalized with malaria--a study from Bikaner, northwest India. Am J Trop Med Hyg 83: 981-989.
18. Bhattacharjee P, Dubey S, Gupta VK, Agarwal P, Mahato MP (2013) The clinicopathologic manifestations of Plasmodium vivax malaria in children: a growing menace. J Clin Diagn Res 7: 861-867.
19. Anstey NM, Russell B, Yeo TW, Price RN (2009) The pathophysiology of vivax malaria. Trends Parasitol 25: 220-227.
20. Andrade BB, Reis-Filho A, Souza-Neto SM, Clarêncio J, Camargo LM, et al. (2010) Severe Plasmodium vivax malaria exhibits marked inflammatory imbalance. Malar J 9: 13.
21. WHO (1999) New perspectives Malaria Diagnosis.
22. Quintana M, Piper R, Boling HL, Makler M, Sherman C et al. (1998) Malaria diagnosis by dipstick assay in a Honduran population with coendemic Plasmodium falciparum and Plasmodium vivax. Am J Trop Med Hyg 59: 868–871.
23. Guidelines for diagnosis of treatment of Malaria in India (2011) Government of India.
24. Aditya S, Nandha R, Sekhri K ,Tyagi S (2013) Arterolane maleate and piperaquine phosphate: A new option in the treatment of P. falciparum malaria. J drug dis and therap 1: 66-69.
25. Efficacy. Synriam new age cure for malaria.
26. Valecha N, Krudsood S, Tangpukdee N, Mohanty S, Sharma SK et al. (2012) Arterolane maleate plus piperaquine phosphate for treatment of uncomplicated falciparum malaria: A comparative, multicentre, randomised clinical trial. Clin Infect Dis 55: 663-671.