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An Analysis upon Prevalence of Bacterial Co-Infections with Malaria among Patients

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Abstract – Bacterial co-infection associated with malaria is potentially important but poorly documented. Published reports are mainly from African children while data from adult Indian population are limited.

To determine the spectrum of concurrent bacterial infection in malaria the present study was conducted in department of Medicine at Tripura Medical College. Out of eighty patients, 58 had falciparum, 15 had dual infection and 7 had vivax malaria. Blood culture failed to confirm bacteraemia in any sample with the exception of one case of complicated malaria showing the growth of Escherichia Coli. Urine culture also grew Escherichia Coli in 2.5% of enrolled patients. Anti salmonella IgM antibody was detected in 7.5% of the study population. Sputum culture was positive of streptococcus pneumoniae in single patient with radiological evidence of consolidation. CSF culture was sterile in cases with cerebral malaria. Thus the present study shows that bacteraemia is uncommon in adults with malaria compared to children of endemic areas. Presence of other co-existent infections should be sought in clinically suspected cases only. We propose a restrictive antibiotic policy in the setting of malaria.

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INTRODUCTION

Nvasive bacterial infections have been associated with high mortality in children with severe malaria in sub-Saharan Africa. Recently, malaria has been shown to strongly predispose children in areas of malaria endemicity to bacteremia. The risk of concurrent bacteremia and severe outcome has forwarded the use of antibiotics in combination with antimalarial therapy in patients with severe malaria. Antibiotics are, however, also administered to patients with uncomplicated forms of malaria due to fear of severe outcome, especially in travelers with imported malaria from areas where the disease is not endemic. The importance of bacterial confections has not been reported in mild malaria, nor has it been systematically described in adults and travelers.

The most frequent pathogens isolated in blood from children with severe *Plasmodium falciparum* malaria are nontyphoid *Salmonella* species (NTS) and other Gram-negative bacteria. To what extent there is a causal relationship between *Plasmodium* infection and bacteremia is currently unknown. Intestinal translocation of bacteria, immunosuppression, and increased erythrophagocytosis have been suggested as possible mechanisms for increased susceptibility to bacteremia in individuals with malaria.

A better understanding of the comorbidity and pathogenesis behind malaria and bacterial infections is needed. Current data are primarily based on studies in African children, where results can be challenging to interpret due to the high background asymptomatic parasite prevalence, and the bacteremia might be the actual primary and independent cause of disease. Studies of bacterial infections in travelers with malaria can therefore be highly informative since there is little risk of diagnostic misclassification.

Although stated in a few reports from intensive care units (ICUs), the frequency of bacterial confections has not been systematically assessed in travelers with malaria. Nonetheless, supplementary broad-spectrum-antibiotic therapy is often recommended for malaria patients in nonendemic settings, even though the bacteriological diagnosis might be indefinite. In Europe and the United States, 12,000 and 1,500 malaria episodes, respectively, are diagnosed yearly. Imported malaria requires special attention because of the potentially high mortality, as well as the risk of delayed diagnosis of *Plasmodium* infection due to limited awareness among clinicians in nonendemic settings. Conversely, the diagnosis of malaria could also delay the taking of blood culture and administration of antibiotic treatment.

Malaria is one of the oldest recorded diseases, with medical practitioners from ancient China, Greece, and Roman Empire writing about the disease. The oldest recorded mention of the disease is in an ancient Chinese medical text. The Greek medical practitioner Hippocrates recording the symptoms of the disease in detail: fever, splenomegaly, and anemia . Hippocrates was the first to note the connection between the symptoms of malaria and the proximity to swamps. The Romans, as well, appreciated the relation of malarial symptoms to swamps and their knowledge led to large scale swamp draining that prevented malaria from becoming a massive impediment to Roman citizens . Although the connection to swamps and warm weather was known for millennia, the causative agent of malaria was thought to be miasma from swamps. The term malaria derives “mal aria” or bad air . It was thought that the foul air from marshy areas would cause illness in those that lived nearby. It was only in the late 1800s that *Plasmodium falciparum* was determined to be an etiological agent of malaria .

The first historical evidence of malaria parasites was found in mosquitoes preserved in amber from the Palaeogene period about 30 million years ago. Human malaria is believed to have originated from Africa and coevolved with its hosts, mosquitoes and nonprimates. Human beings probably first became infected by mosquitoes which fed on gorillas and transmitted *Plasmodium falciparum* with their bites. *Plasmodium vivax* may have been transmitted from chimpanzees and gorillas. *Plasmodium knowlesi* has its origin in Asian macaque monkeys while *Plasmodium malariae* is highly specific to humans with some evidence of asymptomatic infection among wild chimpanzees.

Malaria, a mosquito borne infectious disease infects both humans and primates, and is caused by parasites of the genus *Plasmodium*. Globally, it remains the most important disease in tropical and sub-tropical countries, posing a huge burden on health and economic development. It has also been a major obstacle to sustainable development by the world’s poorest regions. Approximately 198 million cases of malaria were reported at the end of 2013 with 584,000 deaths (Bassat *et al.,* 2015).

Most bacterial infections are widespread but more prevalent in regions where sanitary conditions are poor and may invade the bloodstream after a wide variety of focal infections. Transient bacteraemia is usually non-alarming but may progress to septicaemia which can be life-threatening when immediate medical attention is not given. Septicaemia is a bloodstream infection usually caused by pathogenic bacteria and together with bacteraemia may be collectively referred to as invasive bacterial infections. Varieties of bacteria found to cause febrile illnesses in children include *Staphylococcus* spp, *Streptococcus* spp, *Enterobacter* spp, *Escherichia* coli, *Klebsiella pneumoniae*, *Pseudomonas* spp, *Enterococcus* spp, *Neisseria meningitides*, *Salmonella* spp, *Moraxella catarrhalis*, *Haemophilus influenzae* and *Campylobacter* spp

Among the commonly reported bacterial etiologic agents isolated from African children with bacteremia are; *Salmonella* species, *Streptococcus pneumonia* and other Gram-negative bacteria (Were *et al.,* 2011).

Malaria is a major disease of public health importance with high morbidity and mortality in tropical countries. The national vector born disease control program (NVBDCP) has reported 1.06 million cases of malaria and 519 malaria related deaths in India in the year 2012. The pathogenesis of severe disease is related to host and parasite interaction and recently malaria has also shown to strongly predispose individuals to bacteraemia.

There is lab evidence of impaired immune function in malaria. Opsonisation and phagocyte killing by macrophages becomes impaired after ingestion of parasite derived hemozoin. Deficient cell mediated cytotoxicity has been demonstrated even in patients of low level parasitemia. Patients with malaria have reduced circulating TLymphocyte, impaired proliferative T-Cell response and have plasma anti lymphocyte antibodies. Humoral immunity has also been shown to be impaired in malaria.

Therefore malaria and subsequent transient immune suppression can lead to opportunistic infections in previously immunocompetent individuals. *Streptococcus pneumonae*, gram negative bacteria, *staphylococcus aureus* and non typhoid salmonella (NTS) were most commonly isolated organisms among severe malaria cases, with NTS being the commonest. To what extent there is a causal relationship between plasmodium infection and bacteraemia is unknown, and there is no enough data regarding bacterial co-infection in mild malaria or in adult population. It has been observed that patients with *Plasmodium falciparum* infection who have concurrent bacteraemia have increased risk of severe malarial anaemia, cerebral malaria, ARDS and mortality. This has forwarded the use of antibiotics in-combination to antimalarial drugs in severe malaria without any convincing evidence that this can reduce the mortality.

LILTERATURE REVIEW

Malaria derived its name from the Italian word “Mal’aria” which means “bad air”, as the disease was associated with marshy areas. Malaria is an ancient disease and was previously described in Chinese medical writing. Some other earlier references to the disease include the accounts of the Hippocrates who described the symptoms of Malaria. In 1880 Charles Louis Alphonse Laveran, a French Army surgeon in Algeria discovered Malaria parasites in the blood of a patient and 18 years later, Dr Ronald Ross, a British medical officer in India discovered that the causative agent of malaria was transmitted by mosquitoes. Subsequently, Giovanni Battista Grassi, an Italian

Professor confirmed the vector to be Anopheles mosquitoes (CDC, 2012).

Malaria is caused by intraerythrocytic protozoan parasites belonging to *Plasmodium* species (phylum Apicomplexa). Human malaria is caused by five different species of *Plasmodium: P. falciparum, P. malariae, P. ovale, P. vivax* and *P. knowlesi* (Alam, 2014). The species differ in their geographical distribution, morphology, immune response, relapse patterns and drug response. *P. falciparum* causes tropical malaria, *P. vivax and P. ovale* cause tertian malaria whilst *P. malariae* causes quartan malaria. Relapses are characteristic in *P. vivax and P. ovale* infections.

The most widespread species are *P. vivax* and *P. falciparum*, the latter is attributable to the severest forms of malaria whilst infections of other species are rarely life-threatening. *P. ovale* is restricted to West Africa sub-region whereas *P. malariae* is found worldwide at low prevalence. Occasionally, humans become infected with a zoonotic species, *P. knowlesi* (Daneshvar *et al.,* 2009).

MALARIA AND BACTERIAL CO-INFECTION -

An association between malaria and susceptibility to invasive bacterial infection has been known for almost a century, and has been repeatedly documented in different settings across Sub-Saharan Africa (Medana *et al*. 2011). This association was first described for malaria and non-Typhoid Salmonella (NTS) bacteraemia, which remains the most frequent cause of malaria associated bacteraemia in many studies, but also includes susceptibility to other Gram negative bacteria.. The linking of NTS to malaria has been documented from studies in Africa. Oundo *et al.* (2002) realized in their study in Kenya that, septicaemia infection caused by some species of *Salmonella* were mostly common and severe at peak season of malaria than any other time.

It has been observed that malaria infection was often associated with NTS bacteraemia even in countries where NTS infection was very rare in healthy individuals. Supporting the concept that the malaria was the cause of the susceptibility to NTS infection, observations in British Guyana demonstrated that once malaria was cured with quinine, co-infected individuals were often able to spontaneously clear NTS infection without additional treatment.

Studies of the epidemiology of malaria-NTS co-infection have clearly shown that the incidence of malaria and NTS bacteraemia are strongly correlated whereas stool carriage of NTS is not as closely related to the incidence of NTS bacteraemia. Where malaria transmission has declined over time, similar trends have been observed in NTS bacteremia.

Clinical observations have prompted speculation that malaria may cause susceptibility to bacteraemia through immunoparesis impairment of phagocytic cell function (Essuman *et al.,* 2010) complement consumption or increased gut permeability. Several subsequent studies have suggested that increased susceptibility to NTS bacteraemia may persist after clearance of microscopically detectable malaria infection or that susceptibility is greater at moderate than high parasite density. Other studies have suggested that the association is particularly strong in the case of severe malarial anemia (Dorovini *et al.,* 2011).

METHODOLOGY

Eighty consecutive patients of 18 years and above with freshly diagnosed cases of malaria admitted in the department of medicine were included in the study. The subjects were enrolled after obtaining informed consent. The study was approved by institutional ethical committee. The diagnosis of malaria was based on findings of malaria parasites in peripheral smear by Giemsa stained thick and thin blood smears or malarial antigen assay (RDT) in smear negative patients. We excluded the patients who had history of prior antibiotic administration, patients known to be suffering from immunosuppressive disease or undergoing treatment with immunosuppressants. Similarly remote infections if persisting during the episode of malarial illness was also excluded.

All patients were assessed clinically by relevant history, physical examinations. Routine hematological and biochemical tests were done to assess severity. Clinical categorization was done based on WHO 2000 guidelines. All subjects also underwent chest x-ray, urine culture, and blood culture and salmonella typhi IgM antibody test. CSF analysis was carried out whenever required.

Blood Culture - The site selected for venipuncture was disinfected using 70% isopropyl alcohol followed by iodine to prevent contamination by bacterial flora of skin. The top of the collection bottle was cleaned using 70% isopropyl alcohol immediately before collection. Two samples were collected over a 30–60 min interval. 10 ml of blood was drawn into a syringe and was aseptically introduced into commercially available glucose broth w/0.05% SPS. Majority of the blood cultures were drawn on the day of admission. Any growth was identified according to standard laboratory methods. Bacteraemia was considered as the isolation one non-contaminant bacteria from the admission blood culture. Coagulase negative *staphylococci,* anaerobic diptheroid positive findings were regarded as contaminants if detected in one

bottle only. Urine was cultured on macconkey agar plates according to standard laboratory procedures.

Statistical Analysis - Data were entered into Microsoft excel 2010 and analysed by using the SPSS version. Analysis include the computation of descriptive statistics. Data were expressed as mean ± SEM. Differences between means were analysed by unpaired Student's t test. A p-value of<0.05 was considered to reveal a significant difference.

RESULTS

A total of 80 patients were studied comprising of 59 males and 21 females. Baseline characteristics of the study population including malarial species are shown in Table 1. *Plasmodium falciparum* was most common species (72.5%), followed by mixed plasmodium infection (18.7%) and *P. Vivax* (8.7%). Out of them 22.5% had complicated malaria and 77.5% had uncomplicated malaria. Noncerebral severe malaria was the commonest manifestation in the cohort of complicated malaria. There was no significant difference in the duration of illness between patients of uncomplicated malaria when compared to the patients with other subtypes of severe malaria. There was also no significant difference in the levels of Total count (TLC), Differential leucocyte count (DLC), platelet and FBS between uncomplicated and complicated malaria. However, the difference in levels of haemoglobin, serum creatinine, serum bilirubin and SGPT, SGOT were statistically significant in patients with severe malaria.

Subject	Complicated Malaria (*n*=18)		Un-complicated Malaria
	CM	NCSM	
Total no. of patient	4	14	62
Male/ Female	16/2		
Mean Age	33.38 ±11.23		30.48 ±8.93
P. *Falciparum* (*n*=58)	3	8	47
P. *Vivax* (*n*=7)	0	1	6
Mixed *(PF+PV) (n*=15)	1	5	9
Duration of illness (Day)	3.9±2.3		4.5±1.5
Mortality	1	0	0
Note: CM-Cerebral malaria, NCSM-non cerebral severe malaria			

Table 1: Demographic and Clinical Categories of study population.

DISCUSSION

This study of eighty adult patients with malaria has been categorized into various degrees of severity in order to analyse bacteraemia in individual groups. Establishing the importance of bacterial co-infection is essential for clinical management and can also contribute to an increased understanding of the pathogenesis of co infection. Out of 80 patients, bacteraemia were detected only in one case with gram negative bacteria which is in contrast to the high prevalence of bacteraemia reported in children with malaria. Published reports also reveal non typhoid salmonella being the commonest isolate in patients of severe malaria and associated with highest mortality.

CONCLUSION

The purpose of this study was to determine the prevalence of co-infection of malaria and bacteraemia and also to assess the risk factors for bacterial infections. Malaria coupled with bacterial infections are a major public health concern as the tendency of misdiagnosis is eminent and therefore tends to increase morbidity and mortality.

In conclusion the frequency of bacterial co infection was low in our study as compared to higher prevalence previously described in children of endemic areas. Thus bacteraemia being uncommon in adult patients of severe malaria antibiotic therapy should be individualized based on the clinical profile.

In conclusion, in this retrospective study on patient diagnosed with acute malaria, the frequency of bacterial confection was low. Our data suggest a weaker association between malaria and bacteremia in patient than previously described in studies of children in areas of endemicity. Identifying a marker indicating the need for antibiotic treatment would be highly useful. In our study, the CRP level had only a fair predictive value of bacterial infection. Our findings support a restrictive antibiotic policy for returning travelers with malaria. The majority of patients were adults, and further investigations regarding factors such as divergent immune responses, chronic infections, gastrointestinal permeability's, and bacterial translocation with both an age-related focus and/or an endemic setting perspective are needed.

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