Original Article

Outcome of Adult Malarial Co-infections in Eastern India

Saurabh Pandey, Priyanka Rai, Subhasish Kamal Guha, Ardhendu Maji, Subir Ghosh, Prantiki Halder, Manoj Kumar Gupta, Soumen Nath Halder, Dolanchampa Modak

Department of Tropical Medicine, School of Tropical Medicine, Kolkata, West Bengal, India

Abstract

Introduction: Co-infection with different agents such as bacterial, viral, and Rickettsia is being increasingly recognized due to greater availability and utilization of the diagnostic tests among malaria patients. **Methods:** Consecutive admitted malarial cases were included and were subjected to test for general investigations, bacteria, typhoid, dengue, chikungunya, and rest for specific diagnosis. All patients were followed up till discharge or death and appropriate statistical tests were performed. **Results:** A total of 152 malaria patients were recruited and 27 (18.8%) had concurrent infections. It included 40.7% dengue only**,** 18.7% pneumonia, 11.1% urinary tract infection (UTI), 7.4% enteric fever, 3.7% leptospirosis, chikungunya, and tuberculous meningitis each, and 3.7% each of dengue with pneumonia and UTI. The organisms isolated were *Streptococcus pneumoniae, Klebsiella pneumoniae, Escherichia coli, Salmonella typhi,* and *Mycobacterium tuberculosis.* The mean duration of fever was 6.33 ± 3.63 days with a range of 3–20 days. Blood culture grew in 2 cases *S. typhi* and *K. pneumoniae.* Dengue co-infections had significantly higher clinical and laboratory features of dengue and complications such as bleeding, jaundice, and cholecystitis, whereas rest concurrent infections had a significantly higher proportion of nausea and vomiting, convulsion, altered sensorium, productive cough, urinary symptoms, shock, acute kidney injury, anemia, and mean neutrophil count. There was significantly higher mortality among malaria–dengue concurrent infection group with 2 (15.4%) than malaria mono-infection group 3 (2.4%). **Conclusion**: Co-infections with malaria are not uncommon, especially dengue fever and other bacterial infections. The dominant clinical picture is of the superimposed infection. Decision should be clinically guided adjunct with specific diagnostic tests, and timely treatment has favorable outcome.

Keywords: Bacterial, co-infection, concurrent, dengue, Eastern India, leptospirosis, malaria

Introduction

India accounts for highest number of malaria cases in Asia and second in the world. It occurs throughout the year and peaks during monsoon and post monsoon season. The country has a dense population of vectors and surge of different vector-borne diseases during the season increases the chances of concomitant infections. Dengue malaria is the most common co-infection apart from bacterial and rickettsial infections.

Malaria itself causes transient immunosuppression leading to other co-infection with bacteria and parasites.[1] There are documented evidences of immunosuppression in the form of impaired cell-mediated immunity, phagocytic functions, opsonization, cell-dependent cytotoxicity, and humoral immunity.[2,3] These infections remain under suspected and diagnosed, leading to delayed recovery and unnecessary morbidity. In the present era of chronic diseases such as diabetes mellitus, hypertension, chronic kidney disease, and HIV infections, there is a considerable burden of immunosuppressed states. Therefore, a malarial infection might cause an additional immunosuppression leading to secondary infections. There are very few studies of malaria and dengue co-infection in Asia and even lesser regarding co-infections with other organisms, although secondary bacteremia is rare in adults. We studied the profile of co-infections of other organisms in malaria-infected individuals and to find out the features that suggests a co-infection along with outcome.

Methods

Study design and setting

The algorithm for patient recruitment and final sample is

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Address for correspondence: Dr. Saurabh Pandey, PMC Hospital, Malviya Road, Basti - 272 001, Uttar Pradesh, India. E-mail: saurabhp2013@gmail.com

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depicted in Figure 1. Patients admitted for evaluation of fever in Carmichael Hospital for Tropical diseases at School of Tropical Medicine, Kolkata, were tested for common causes of fever. It was conducted from July 2017 to June 2018. All the malaria cases with or without evidence of concomitant infections during hospital stay were enrolled in the study. Malaria diagnosis was made by thick and thin blood smear microscopy and rapid antigen test. Dengue infection was screened by NS1 antigen and confirmed by dengue-specific immunoglobulin M (IgM) antibody by serum ELISA and Chikungunya by IgM enzyme-linked immunosorbent assay (ELISA). The blood culture and IgM typhidot were performed by ELISA for enteric fever. Routine microscopy for urine was done. Urine and sputum microscopy and culture were done in clinically relevant cases. Other diagnostic tests were done according to the clinical scenario. All cases of early treatment failure of malaria were excluded from the study. Assessment parameters included history, physical examination, and laboratory parameters. Malaria was evaluated as severe and nonsevere by the WHO guidelines. Dengue was evaluated according to the WHO definition of uncomplicated dengue fever, dengue fever with warning signs, and severe dengue fever. The outcome was evaluated in terms of the presence of severe malaria, severe infection, major organs dysfunction, duration of hospital stay, and death. Appropriate statistical analysis was done.

Concurrent or concomitant infections were suspected among patients having persistent clinical features or new-onset clinical features within 3 days of standard antimalarial treatment. All hospital acquired infections which were diagnosed after the 4th day of admission were excluded from study. We utilized the following case definitions for diagnosis.

1. Scrub typhus: Eschar + scrub IgM ELISA positive or Scrub IgM ELISA positive with other serologies and blood culture negative or scrub IgM ELISA seroconversion on convalescent sera
2. Dengue: Clinical features of dengue with dengue IgM positive or seroconversion on convalescent sera
3. Malaria: Malaria parasite (trophozoites of *Plasmodium falciparum*, *Plasmodium vivax*, or mixed) visualized on thin blood smears
4. Enteric fever: Blood culture positive for *Salmonella typhi* or *Salmonella paratyphi* or fourfold rise in titer on the Widal test in convalescent sera
5. Leptospirosis: Leptospira IgM positive with other serologies and blood culture negative. Modified Faine's criteria for definitive diagnosis
6. Lower respiratory tract infection (LRTI): Fever with cough and evidence of localized pneumonic patch on examination and chest X-ray. Sputum organism isolation will be preferred
7. Urinary tract infection (UTI): Features of lower UTI with urinary pus cells more than 5 cells/mm^3 with or without isolation of organism on culture
8. Bacteremia: Presence or absence of features of sepsis with growth of organism on blood culture media
9. Concurrent infection: Presence of one or more listed criteria in the presence of demonstration of malarial trophozoite in peripheral blood smears of patients.

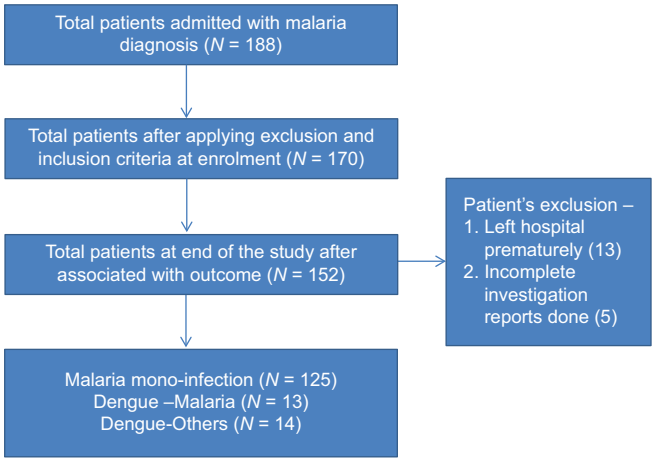

Figure 1: Recruitment of subjects in the study

All the patients were divided into three groups for comparison purpose – malaria mono-infection, malaria–dengue co-infection, and malaria-other co-infection group.

Statistical analysis

Statistical Analysis was performed with Microsoft Excel spread sheet and imported to IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY: IBM Corp.). Continuous variables were expressed as means and standard deviations, and categorical variables were expressed as percentages. Test of proportion was used to find the standard normal deviate (Z) to compare the different proportions and Chi-square ($\chi 2$) test was performed to find the associations. In the cases where one of the cell frequencies was <5, corrected $\chi 2$ was used to find the association between variables. *T*-test was used to compare the means. $P < 0.05$ was taken to be statistically significant. ANOVA was applied in case of more than one group compared.

The ethical clearance for the study was obtained by the Institutional Ethics Committee of School of Tropical Medicine (CREC-STM/291).

Results

A total of 152 patients were included, of which 125 (82.2%) patients had mono-infection with malaria, whereas 27 (17.8%) had concurrent malarial infection. There were 14 (51.9%) males and 13 (48.1%) females among concurrent infection group. The mean age of the patients was 37.62 ± 14.88 years with a range of 15–75 years and the median age was 40 years. Six (22.3%) of the patients had comorbid conditions, out of which two patients had diabetes mellitus and the rest one case each had HIV and chronic steroid therapy.

Most of the patients were suffering from dengue (48.1%) along with malaria which was significantly higher ($Z = 5.02$; $P < 0.001$),

followed by LRTI (14.8%) and UTI (11.1%) [Table 1]. The mean duration of fever of the patients was 6.33 ± 3.63 days with a range of 3–20 days and the median duration was 5 days. Most of the patients had fever for less than a week (66.7%) which was significantly higher ($Z = 5.23$; $P < 0.001$). Only 2 (6.4%) had fever for more than 2 weeks which includes each patient having HIV-TB and leptospirosis.

The diagnosis of co-infection was suspected in the presence of either persistent or new-onset symptoms. The diagnosis in new-onset symptoms group included 1 case each of leptospirosis, dengue, UTI, and UTI with LRTI. The common features included fever (29.6%), myalgia (33.3%), cough (14.3%), and arthralgia and pain in the abdomen each (11.1%). Rash, conjunctival suffusion, and hematuria were seen in 1 case. Among the persistent features group, 12 cases were of dengue, 4 cases of LRTI, 2 cases of UTI, and 1 each case of chikungunya, enteric fever, and HIV-associated tuberculosis. Features included fever (4, 14.8) and myalgia, cough, and burning micturition (3, 11.1%). Blood culture grew *S. typhi* and *Klebsiella pneumoniae* in each patient. Rest blood cultures were sterile and organisms were isolated from sputum and urine culture.

Table 2 depicts a comparison of clinical features among the subset of patient groups. Among dengue and malaria, concurrent infection group in comparison to other groups had significantly higher retro-orbital headache, maculopapular rash, myalgia, arthralgia, epigastric pain in the abdomen, bleeding manifestations, bradycardia, bradycardia with hypotension, conjunctiva suffusion, and polyserositis. Among other concurrent infection groups, there was a significantly higher proportion of nausea and vomiting, convulsion, altered sensorium, productive cough, urinary symptoms, and lower mean systolic and mean diastolic blood pressure. There was significantly longer hospital stay among malaria with other infection groups.

Table 3 depicts the comparison of general investigations among groups. The dengue malaria concurrent infection group had a significantly higher proportion of leukopenia (53.8%) and mean value liver enzymes. The other infection and malaria concurrent infection group had a higher proportion of moderate-to-severe anemia (50.0%), mean total neutrophil count, leukocytosis, and mean bilirubin. Leukocytosis was seen in 2 cases of pneumonia. Mean Platelet count of malaria–dengue concurrent infection was 89214.29 ± 50386.47 cells/mm^3 and significantly higher than malaria mono-infection and bacterial co-infection groups. There was a significant improvement of platelet count among malaria–bacterial infection group after antimalarial therapy than dengue–malaria group.

Table 4 depicts a comparison of complications among patient subset groups. There was a significantly higher case of abnormal bleed (60.0%) and severe thrombocytopenia, jaundice, and cholecystitis (15.4%) among dengue malaria concurrent infections, whereas other infection malaria concurrent group had significantly higher cases of circulatory shock and acute kidney injury. In comparison to malarial mono-infection, there was a significantly higher case of abnormal bleed and severe anemia among dengue malaria concurrent infections, whereas other infection malaria concurrent group had significantly higher cases of circulatory shock, hemolysis, and hypoglyia. Overall, severe malaria cases were significantly higher among malaria and other infection groups (69.3%). Among 13 dengue cases, there were 7 (53.8%) uncomplicated cases and 3 (23.1%) each of dengue fever with warning signs and dengue shock syndrome. There was significantly higher mortality among malaria–dengue concurrent infection group with 2 (15.4%) in comparison to malaria mono-infection group 3 (2.4%) and no death seen in malaria and other infection groups.

Discussion

India is home to the second-highest burden of malaria after Africa. The most common season favoring malarial infection is monsoon and post monsoon. This season favors multiple vector-borne diseases, and thus, it is expected that a person remains exposed to culex, anopheles, Aedes mosquitoes, or a combination of these in a limited period of time resulting in co-infections. The most prevalent infection during the season in India is dengue fever, and hence, the most expected concurrent infection is with dengue. Review of literature

Table 1: Distribution of concurrent malarial infections

Co-infection with malaria	Frequency ($n=27$), *n* (%)	Associated organsims
Dengue only	11 (40.7)	*Dengue* virus
Dengue with pneumonia	1 (3.7)	*S. pneumoniae*
Dengue with UTI	1 (3.7)	*E. coli*
Chikungunya	1 (3.7)	*Chikungunya* virus
Leptospirosis	1 (3.7)	*Leptospira* sp.
Pneumonia	5 (18.5)	*K. pneumoniae, S. pneumoniae*
UTI	3 (11.1)	*E. coli*, *K. pneumoniae*
Both pneumonia and UTI	1 (3.7)	*K. pneumoniae*
Enteric fever	2 (7.4)	*Salmonella typhi*
HIV-associated tuberculous meningitis	1 (3.7)	*M. tuberculosis*

UTI=Urinary tract infection, *S. pneumoniae=Streptococcus pneumonia*, *E. coli=Escherichia coli*, *K. pneumonia=Klebsiella pneumonia*, *M. tuberculosis=Mycobacterium tuberculosis*

Table 2: Comparison of clinical features of the patients at the time of reporting to the hospital

Symptoms	Malaria mono-infection (*n*=125)	Malarial concurrent infection (*n*=27)	Malaria with dengue (*n*=13)	Malaria with others infection (*n*=14)
Fever (%)	100.0	100.0	100.0	100.0
Fever duration	5.54±3.47	6.33±3.63	5.07±1.49	7.69±4.73
Headache (%)	95.3	96.3	92.8	100.0
Retro orbital (%)	0.0	14.8	28.5	0.0
Myalgia (%)	7.0	11.4	64.2	38.4
Arthralgia (%)	0.0	33.3	57.1	7.6
Nausea and vomiting (%)	37.5	66.7	50.0	84.6
Pain abdomen (%)	6.3	37.0	50.0	23.1
Bleeding manifestations (%)	2.3	18.5	28.5	7.6
Convulsion (%)	6.5	7.4	0.0	15.3
Rash (%)	0.0	37.0	64.2	7.6
Altered sensorium (%)	9.6	22.2	7.1	28.5
Productive cough (%)	0.0	18.5	7.7	23.1
Urinary symptoms (%)	0.0	14.8	7.7	30.7
Bradycardia (%)	0.0	11.1	23.07	0.0
Hypotension (%)	14.4	37.4	38.5	38.5
Hypotension with bradycardia (%)	0.0	11.1	23.07	0.0
Mean SBP	117.35±178.73	93.26±22.12	95.43±22.86	90.92±21.96
Mean DBP	63.69±12.46	61.81±18.16	65.79±14.60	57.54±21.10
Mean pulse rate	95.69±18.30	94.93±20.16	91.71±21.58	98.38±18.74
Conjunctiva suffusion (%)	0.0	11.1	23.07	7.6
Splenomegaly (%)	59.3	66.5	61.5	71.4
Hepatomegaly (%)	59.4	63.2	69.2	57.2
Ascites (%)	0.0	11.1	23.07	0.0
Pleural effusion (%)	0.0	11.1	23.07	0.0
Mean hospital stay (days)	5.25±2.03	6.85±2.50	5.92±1.88	7.71±2.88

SBP=Systolic blood pressure, DBP=Diastolic blood pressure

Table 3: Comparison of laboratory features of the patients at the time of reporting to hospital

Symptoms	Malaria mono-infection (*n*=125), *n* (%)	Malarial concurrent infection (*n*=27), *n* (%)	Malaria with dengue (*n*=13), *n* (%)	Malaria with others infection (*n*=14), *n* (%)
Anemia (moderate–severe)	40 (32)	9 (33.3)	2 (15.4)	7 (50.0)
Thrombocytopenia	58 (46.4)	15 (55.6)	8 (61.5)	7 (50.0)
Leukopenia	10 (8.0)	8 (29.6)	7 (53.8)	1 (7.6)
Neutrophilic leukocytosis	5 (4.0)	2 (7.4)	0	2 (14.3)
Mean hemoglobin	11.27±2.39	11.90±2.30	12.54±2.30	11.21±2.19
Mean TLC	5391.80±2573.64	6329.63±2610.31	5114.29±2218.40	7638.46±2419.21
Mean platelet count	110,000.04±83,000	99,962.96±46,464.61	89,214.29±50,386.47	111,538.46±40,588.62
Mean bilirubin	1.37±1.45	1.39±1.14	1.22±0.81	1.57±1.43
Mean SGOT	49.59±38.21	69.89±70.83	84.36±90.91	54.31±37.56
Mean SGPT	44.34±35.37	50.85±45.75	62.43±60.82	38.38±14.26
Mean creatinine (mg/dl)	1.51±2.38	1.31±0.38	1.16±0.25	1.48±0.43
Number of falciparum cases (%)	30.4	29.6	15.4	42.8
Number of vivax cases (%)	69.6	70.4	84.6	57.2

TLC=Total lymphocyte count, SGOT=Serum glutamic-oxaloacetic transaminase, SGPT=Serum glutamic pyruvic transaminase

of dengue–malaria co-infection in Asia by Selvaretnam *et al*. showed that majority of report literature were from India (26/36).[3] The other co-infections in this review include hepatitis A and E, chikungunya, leptospirosis, scrub typhus, filariasis, and typhoid, but the number is outnumbered by dengue co-infection. The reported literature from India further adds new data, and the percentage of co-infection ranges from 1.54% to 10.25%, with a mean value of around 4%.[4-14] In our study, 9.2% had concurrent dengue infection among malaria patients with an additional 10% having other concurrent infections including enteric fever, leptospirosis, chikungunya, LRTI, and UTIs. Both of the concurrent infection data are consistent with the published literature from India and abroad.

Table 4: Comparison of complications among patient groups

Complications	Mono-infection (*n*=125)	Malaria–dengue (*n*=13)	Malaria-others (*n*=14)
Anemia (moderate–severe)	40 (32.0)	5 (38.5)	6 (46.2)
Thrombocytopenia	58 (46.4)	7 (53.8)	6 (46.2)
Severe thrombocytopenia	30 (24.0)	3 (23.1)	2 (15.4)
Abnormal bleeding	4 (3.2)	3 (23.1)	1 (7.7)
AKI	40 (32.0)	3 (23.1)	7 (50)
Jaundice	28 (22.4)	12 (92.3)	2 (15.4)
Hepatitis	47 (37.6)	5 (38.5)	2 (15.4)
Shock (SBP <90 mmHg)	18 (14.4)	5 (38.5)	5 (38.5)
Altered sensorium	7 (5.6)	1 (7.7)	1 (7.7)
Seizures	5 (4.0)	0	1 (7.7)
Hypoglycemia	1 (0.8)	0	1 (7.7)
Hemolysis	4 (3.2)	1 (7.7)	0 (0.0)
Cholecystitis	3 (2.4)	2 (15.4)	1 (7.7)

AKI=Acute kidney injury, SBP=Systolic blood pressure

Data on invasive and secondary concomitant bacterial infections are a well-known feature in children, but robust data are clearly missing in adults.[4] In our study, 9.2% of malaria-infected adults had developed concurrent bacterial infection, with 1.4% of patients having bacteremia. A study by Phu *et al*. found that 1.7% of patients developed bacteremia among severe falciparum malaria patients.[15] A study by Das *et al*. showed that concurrent infections in severe malaria cases were pneumonia, UTI, and enteric fever around 3.2% each.[16] Another study from India by Bhattacharya *et al*. demonstrated the presence of bacteremia in 9% of cases of malaria (all *P. vivax*) in adults.[3] A study by Trivedi *et al*. showed concurrent bacterial infections in 5% of malaria cases with 1 case of bacteremia. Multiple patients had antibody against typhoid but no clinical case diagnosis. It is therefore evidenced that bacteremia and concurrent infection is being reported. A robust multicentric study from India found 9.3% of malaria cases to have bacteremia and common organisms were *S. typhi and paratyphi, Gram-negative bacilli*, *and Staph aureus*.[17]

The common clinical syndrome of malaria includes fever with chills, malaise, anemia, splenomegaly, thrombocytopenia, and organ involvement which is also seen in dengue, scrub typhus, leptospirosis, and in the later part of enteric fever. These illnesses have few contrasting features from malaria too and it includes rash, conjunctival suffusion, lymphadenopathy, eschar, bleeding manifestations, and gastrointestinal and musculoskeletal involvement. Mostly, the symptoms are nonspecific, and therefore, demonstration of parasite remains important for the diagnosis of malaria. A study by Barua *et al*. and Mohaptra *et al*. found that clinical features of concurrent infection were dominantly of dengue and presence of anemia (especially hemolytic) in dengue case favored concurrent infection with malaria.[11,13] It is also observed that concurrent infection of dengue–malaria were more severe in terms of presentation, morbidity as well as laboratory features especially anemia, thrombocytopenia, jaundice, hepatitis and renal dysfunction.[5,13] The possible reason demonstrated is heightened production of tumor necrosis factor-alpha and interleukin-6 productions in comparison to their mono-infections.[13]

Our study showed that malaria–dengue concurrent infection presented like dengue fever with all classical features of dengue with an additional greater thrombocytopenia during febrile phase as well as jaundice. Among malaria bacterial infection group, there was significantly greater anemia, shock, acute kidney injury, and neutrophilic leukocytosis in comparison to malaria mono-infection and dengue co-infection. A study by Phu showed bacteremia was seen in patients with high parasite load (>20% parasitemia), and hence, clinical picture is dominated by severe malaria in the form of renal and hepatic dysfunction.[15] They also found neutrophilic leukocytosis to be nonreliable marker for bacteremia and was seen in around 10% cases apart from the fact that it is sometimes seen in severe malaria. In our study, neutrophilic leukocytosis was present in 4% of malaria cases (all severe) and 14.3% cases of malaria and bacterial concurrent infection with 1 case of leptospirosis. The presence of sepsis-like state in malaria, especially vivax, might be representing a concurrent bacteremia, especially in patients with comorbidities.[3] In our study, sepsis-like condition with shock was seen in 50% of bacterial co-infection patients which is in concordance. There was a significant rise in platelet count after antimalarial therapy in malaria–bacterial infection group in comparison to dengue–malaria infection group, indicating active disease process of dengue fever during the concurrent infection. In our study, there was significantly higher mortality in dengue–malaria concurrent infection group in comparison to other groups (15.4% vs. 2.4%), indicating a heightened severity of either disease leading to worsen outcome.

One of our cases was concurrent infection of malaria with chikungunya with classical presentation in the form of large joint arthritis, rash around joint, and facial hyperpigmentation. A Tanznian study showed absence of distinguishable features of chikungunya from malaria in co-infection cases and diagnosis was based on serology. A review of literature also

showed absence of clinical studies, and rather, the diagnosis was considered on the basis of serology alone.[18] Similarly, we had a case of leptospirosis which was diagnosed when fever and rash along with myalgia partially responded to antimalarial therapy and it was diagnosed on basis of Modified Faines' criteria and responded well to the treatment. A study showed positive serology of leptospira in 10% of cases of malaria, but again, clinical data were missing.[19]

The diagnosis of malaria is straightforward by the demonstration of parasites in peripheral blood smears, whereas dengue fever requires serology such as leptospirosis, scrub typhus, and enteric fever apart from organism isolation. After 5th day of dengue fever, IgM is required or fourfold rising titer of IgG in convalescent sera and NS1 is usually undetectable by the 5th day.[18] The problem with serology in the Indian context is with recurrent epidemics, thereby creating background positivity and cross-reactivity with other common organisms including scrub typhus and chikungunya.[19,20] Therefore, serology should only be used in relevant clinical backgrounds. Polymerase chain reaction should be prioritized in the diagnosis of concurrent infections in relevant clinical background in already diagnosed cases of malaria.[19] Multiple reports showed asymptomatic dengue transmission during the rainy season in India and other countries,[18-20] and thus, diagnosis of this infection is epidemiologically important but not clinically.

In the Indian context, a clinical symptom- and basic laboratory-based algorithm is required to diagnose co-infection cases rather than a serology based alone. The presence of intercurrent pandemics poses a real challenge in diagnosing acute fever on the basis of serology alone and especially in malaria-endemic zone, co-infection cases do occur and require appropriate treatment, but avoiding inappropriate antibiotics use becomes equally important in the present context of antimicrobial resistance era. Therefore, we propose an algorithm for diagnosis of co-infections at resource-limited settings in India and similar tropical countries [Figure 2].

Conclusion

Co-infections are common among admitted patients of malaria and dengue was most common indicating bite from multiple mosquitoes during rainy season. Secondary bacterial infections were also common with discrete cases of other vector-borne diseases. The secondary infection should be suspected in cases where symptoms are not easily explained by malaria mono-infection, and clinical-based decision adjunct with relevant diagnostic tests should guide the diagnosis and timely treatment has good outcomes.

Research quality and ethics statement

The authors followed applicable EQUATOR Network (http://www.equator network.org/) guidelines during the conduct of this research project. The ethical clearance for the study was obtained by the Institutional Ethics Committee of School of Tropical Medicine (CREC STM/291).

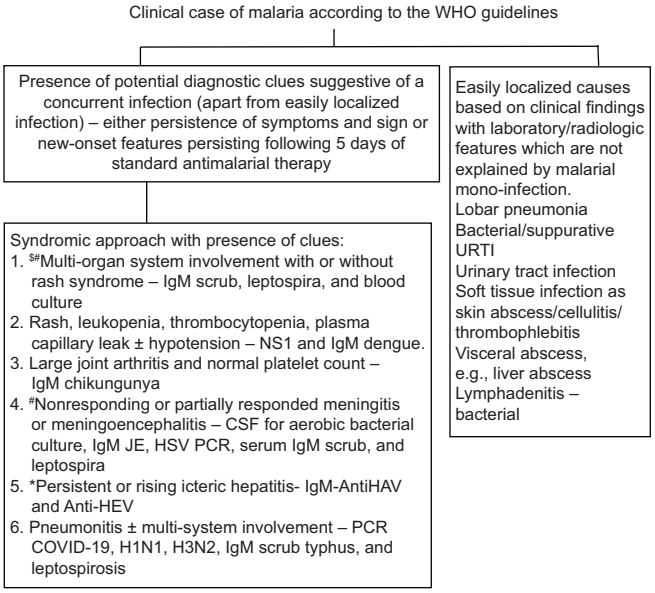

Figure 2: Algorithm for symptom based diagnosis of concurrent infections with malaria. #Blood culture should be sent in these conditions in all diagnosed cases of malaria. $Presence of rash without organ involvement can be attributed to dengue, chikungunya, leptospirosis, scrub typhus as common etiology tested in tropical countries. *Rising or persistent jaundice and hepatitis can be feature of acute fulminant hepatic failure also

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Conflicts of interest

There are no conflicts of interest.

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