

Integrated diagnostic and therapeutic approaches for bacterial co-infections in severe malaria

Mohammad Abbas¹, Mohammad Fakruddin^{2*}, Shainaz Tabassum³ and Farzana Begum⁴

¹Department of Anaesthesiology and Critical Care Medicine, Al Ameen Medical College and Hospital, Athani Road, Vijayapura-586108, Karnataka, India, ²Department of General Medicine, Al Ameen Medical College and Hospital, Athani Road, Vijayapura-586108, Karnataka, India, ³Department of Obstetrics and Gynaecology, Al Ameen Medical College and Hospital, Athani Road, Vijayapura-586108, Karnataka, India and ⁴Department of Paediatric, Gulbarga Institute of Medical Sciences, Veeresh Nagar, Sedam Main Road, Kalaburagi-585105, Karnataka, India

Received: 14th August 2025; **Accepted:** 25th September 2025; **Published:** 01st October 2025

Abstract: *Background:* Severe Malaria is medical emergency. Approximately 1 to 20 % of adults hospitalized with severe malaria across the globe are also have bacteraemia. Several guidelines for paediatric populations recommend the use of broad-spectrum antibiotics in addition to parenteral artesunate as incidence of bacteraemia and mortality is higher compared to adult population. However for adult populations it's unsure, some recommend use of Empirical antibiotics other do not. *Objectives:* Our aim was to review literature in patients admitted with severe malaria with bacteraemia and form recommendations for diagnosis as well as treatment. *Methods:* Collection of data on severe malaria in adult patients on PUBMED using key words like Severe malaria, Incidence, prevalence of co infections, bacterial infections, Diagnosis, management and outcome of bacterial infections in severe malaria. Data collection and recommendations covering the years 2010–2023 done. *Results:* The prevalence of concomitant bacteraemia in adults with severe malaria is approximately 1 to 20 %. Early identification of patients with severe malaria with high mortality using biomarkers like Procalcitonin, CRP, Microscopy (Parasitemia) and administration of empirical antibiotics, in addition to artesunate reduces mortality. Empirical antibiotic therapy is warranted in the patients whom diagnosis is unclear and immediate diagnostic modalities are unavailable or Suspicion of bacterial sepsis with organ dysfunctions and small subgroup of patients with very high parasitemia's and emphasizing the importance of quantitative blood smear microscopy assessment. *Conclusions:* Use of new diagnostic methods like haptoglobin, lipocalin-2 levels to identify the patients at higher risk of bacterial infections and Early Blood cultures and PCR based methods help in identify, initiate, tailor antibiotic therapy in patients with secondary bacteraemia and improve outcomes.

Keywords: Severe Malaria, Bacteraemia, Bacterial Sepsis, Diagnosis, Management.

Introduction

India is the only high-endemic country to report a sharp decline in the Annual Parasitic Incidence of malaria, along with significant improvements in morbidity and mortality. However severe malaria infection in endemic area is a major problem. Severe malaria is defined the presence of malaria infection with one of the following criteria - hyper parasitemia of >10%, shock, organ dysfunction or occurrence of anemia, coagulopathy in the absence of an identified alternative cause [1-4]. Acute febrile illnesses can be difficult to discriminate in a differential

diagnosis in resource-limited settings because of their overlapping clinical signs. Differentiating severe malaria alone or malaria with concomitant infections is very challenging as the clinical features and organ involvement are similar [5].

Malaria with persistent febrile illness accounts for chances of concomitant infections like bacterial, Viral (HIV), fungal, parasitic infections, which has significant morbidity and mortality if left untreated [5-7]. Different parts of the world has different prevalence of

bacterial co-infections ranging from 20% (Myanmar), 9.1% (Africa), 1% (Vietnamese and Asia) [4-5].

The increasing number of cases of malaria and bacterial co-infection is associated with factors including improper sewage disposal, poor personal hygiene, and poverty particular in rural areas [5]. Studies demonstrated that most patients with severe malaria, particularly those infected by *P. falciparum*, were co-infected by Gram-negative bacteria, typically *Salmonella typhi*, whereas among patients with *P. falciparum* and Gram-positive bacterial infection were primarily infected by *Staphylococcus aureus* [5-8]. The methodology to detect concomitant bacterial infections in malaria showed different sensitivity with PCR method being most sensitive method with detection rate of 3.6% compared to 1.6% by blood culture method [5].

A severely ill febrile adult with a low parasitemia could have severe malaria or sepsis with incidental parasitemia, and few studies demonstrated that higher parasitemia >20 % have higher incidence of bacterial coinfections in Vietnamese adults [9]. Therefore, co-infection by pathogens could lead to the over-prescription of antimicrobial agents, which are commonly recognized as a major cause of drug resistance. Hence detecting severe malaria and co bacterial infections in malaria by use of diagnostic

methods and treat it accordingly can reduce morbidity and mortality. We aimed to develop a consensus statement and guidelines for management of severe malaria with bacterial co infections in ICU [10-11].

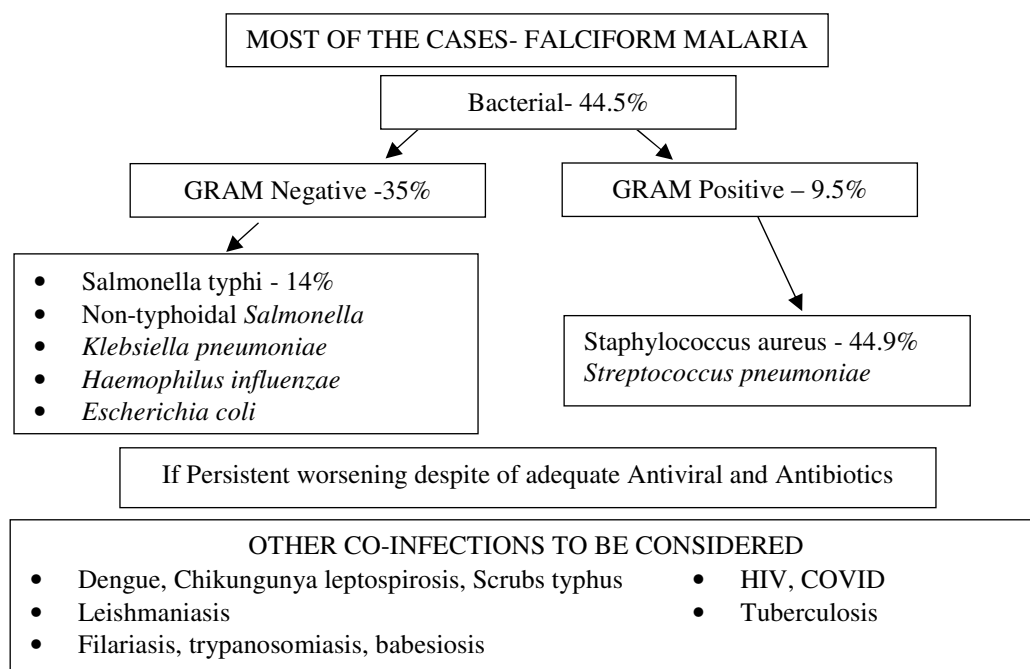
Material and Methods

A panel of expert author including doctors, scientists, teachers, and researchers from India was established to discuss the subject, track relevant literature, exchange experiences, and draft guidelines. A thorough review of literature was done using available resources including PubMed, Prevalence of bacterial infections and antibiotic therapy used and outcome along with National and International guidelines of diagnosis and management of Severe Malaria. Key words used during data collection were bacterial infections in malaria, concomitant infections Malaria, Biomarkers in Severe malaria, Severe Malaria diagnosis and Management.

Results

The group of intensivists agreed upon that diagnosing and early management of bacterial infections significantly improves outcomes. Prevalence of Various co-infections in severe malaria mentioned in flowchart-1 [5]. Incidence of various bacterial infections in severe malaria (worldwide).

Flowchart-1: Prevalence of Various co-infections in severe malaria



In India Overall incidence of coinfections in malaria patients shown in table-1 [12].

Table-1: Incidence of co-infections in malaria		
Over all Malaria co-infections in India – Eastern regions	Co-infections	Incidence in India
	Pneumonia	18.7%
	Urinary tract infection (UTI)	11.1%,
	Enteric fever	7.4%,
	Leptospirosis, chikungunya, and tuberculous meningitis	3.7%

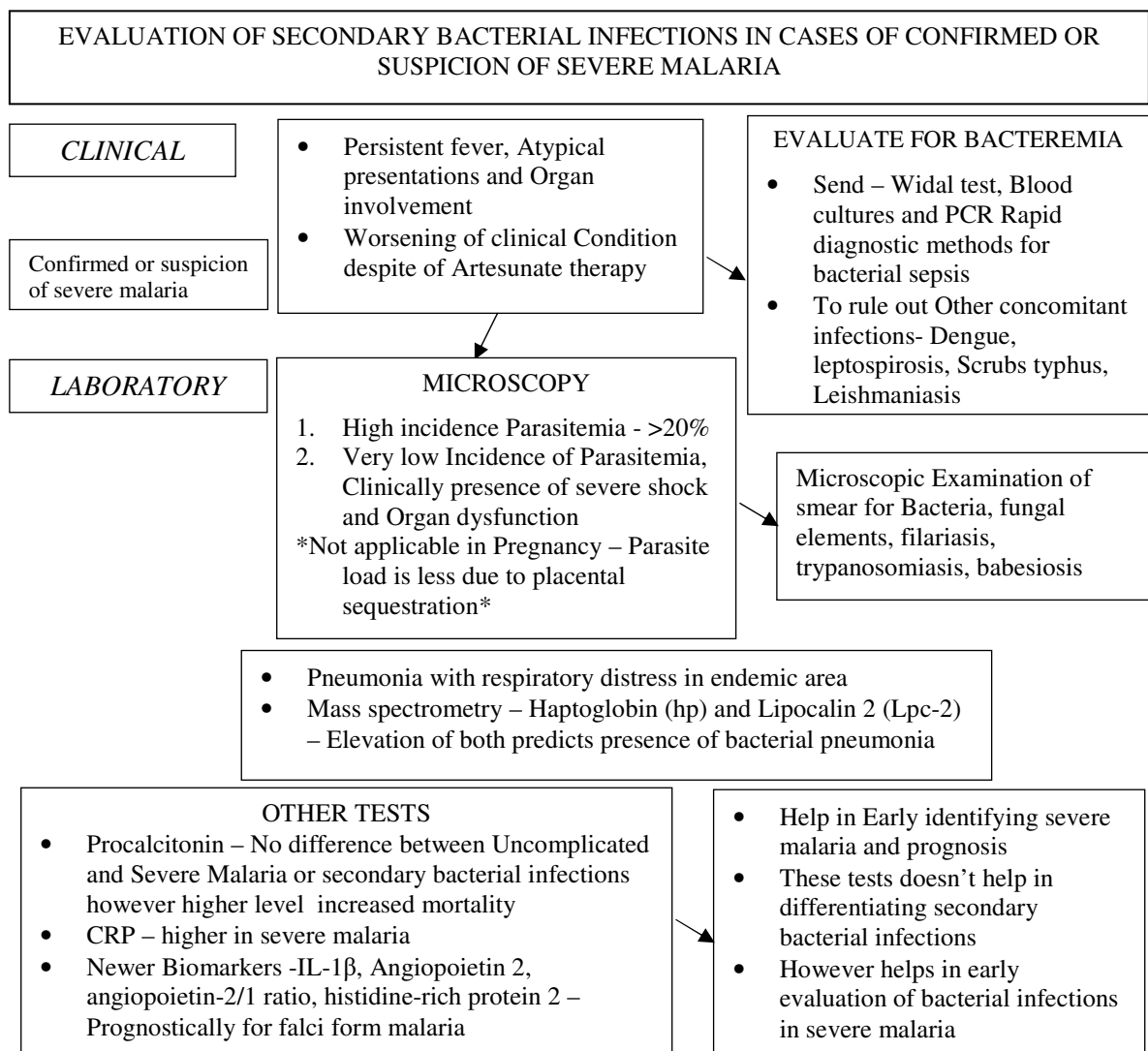
Diagnosis of severe malaria clinically is challenging as the presentation is similar to several other infections like Bacterial. It is always

important to diagnose malaria using sensitive methods for proper diagnosis as it prevents use of multiple antibiotics for empirical therapy.

Methods for laboratory diagnosis of malaria include microscopy (visualization of parasites in stained blood smears and identifying type of parasite) and rapid diagnostic tests (RDTs; which is based on antigen or antibody reactivity) [13-14].

- Histidin-rich-protein-2/HRP2 (*P. falciparum*-specific);
- Parasite lactate dehydrogenase / pLDH (either *P. falciparum*-, *P. vivax*-, or pan-[all species] specific);
- Aldolase (pan-specific).

Flowchart-2: Evaluation of secondary bacterial infections in cases of confirmed or suspicion of severe malaria



Smear examination via light microscopy is the typical tool for diagnosis of malaria; RDTs, PCR, flow cytometry would be used if microscopy is not available [1]. Through smear examination, diagnosis can be made and the extent of parasitemia can be ascertained. As higher incidence of parasitemia (>20%) is associated with more secondary bacterial infections [9]. Microscopy provides details in categorizing bacterial infections, identifying fungal elements as well as identifying intra cellular bacterial pathogen. The algorithm to diagnose secondary bacterial infections in suspected cases or confirmed as follows (Flowchart-2).

In endemic areas in patients presents with respiratory distress studies conducted by Foko et al suggested to use Haptoglobin (hp) and Lipocalin 2 (Lpc-2) levels by Mass spectrometry helps in differentiating bacterial pneumonia with respiratory distress due to severe malaria [14-15]. The elevation of haptoglobin and Lpc-2 were high in bacterial pneumonia. Lpc-2 >163 ng/mL had 9 times the odds of having a positive blood culture and similarly haptoglobin level >1.1 mg/mL was associated with 14.8 times higher respiratory distress due to bacterial pneumonia.

The role of Lpc-2 in innate defense against bacterial infection is well established. The transcription of the Lpc-2 gene has been shown to be up-regulated in activated macrophages through Toll-like receptor 4 ligation and to interfere with bacterial iron uptake. More importantly, Lpc-2 transcription is increased by *S. pneumoniae* and *Haemophilus influenza* colonization in nose [14-15]. Lipocalin 2 (Lpc-2) is the better protein biomarker of severe pneumonia with bacteremia in malaria. However combination of LPC-2 and Haptoglobin is overall best marker.

Studies have shown Higher levels of CRP and Procalcitonin levels was associated severe malaria and higher mortality, however there was not much difference in differentiating between Severe malaria and secondary bacterial infection. These markers can be used to diagnose severe malaria early, and evaluate presence of bacterial infections in severe malaria to improve outcomes [15]. The markers like Procalcitonin, IL-1 β , CRP, Angiopoietin 2, angiopoietin-2/1 ratio, histidine-rich protein 2, help in identifying patients having severe malaria early and help in evaluation of

secondary bacterial infections early with other modalities and treat [16-17].

Discussion

Pre-referral settings or Primary Health Care: Severe malaria often presents in endemic areas of rural setups mostly far from the health centers. Most of the Indian primary health centers choose to treat fever with empirical therapy and evaluation of malaria with microscopy and Rapid diagnostic tests. Referral for medical care can take hours, or sometimes days. As there is delay in identifying the severe malaria with new diagnostic tests due to unavailability or cost issues.

In African countries after identifying severe malaria where parental drug facilities not available, with pre-referral of severe malaria with rectal artesunate, initial studies showed that it reduces mortality by about 25% in children [18]. However recently a large sequential observational study (CARAMAL) done in Nigeria, Uganda and the Democratic Republic of the Congo, Mortality reportedly increased after rectal artesunate was deployed, attributed to delays in the referral of severely ill children to hospital. This can also be attributed to lack of tertiary care, evaluation and treatment of secondary infections in Severe Malaria. However there were multiple contributing factors like non availability of pre-referral rectal antibiotic formulations unfortunately [19].

Currently, WHO recommends that if intravenous treatment for severe malaria is not feasible but injections are available, both adults and children should receive a single intramuscular dose of artesunate. It is recommended to transfer the patient to tertiary care as early as possible.

It is recommended to use RCAM score as a screening tool to detect patients at high risk for mortality (Table-2) [20-21]. Hence in a case of suspected or confirmed severe malaria, if RCAM score is 2 > it is always recommended to start I.v Artesunate therapy + Empirical therapy of i.v antibiotics prior to referral as mortality is higher in patients with RCAM score >2 [20-21].

Table-2: RCAM score			
RCAM SCORE- Respiration, Consciousness, Malaria	Score		
Variable	0	1	2
GCS	15	11-14	<10
Respiratory rate	<20	20 to 39	>40
SCORES > 2 – Mortality – 13 to 40%			

Tertiary Health Care or hospital: At the level of the tertiary center or hospital in an area of higher malaria transmission, the difficulty in distinguishing malaria from sepsis in means that both parenteral anti-malarials (i.v Artesunate) and broad-spectrum antibiotics should be given together as soon as the diagnosis is suspected.

The disease spectrum or burden among local population and pattern of disease presentations are identified and treated based on symptoms, risk factors of the populations as well as based on Organ involvement.

Initiation of anti-malarials initially does not harm if the infection turns out to be bacterial or viral, and administration of antibiotics does no harm if the infection is severe malaria only. Immediate administration of parenteral artesunate and broad-spectrum antibiotics to a suspected of having severe malaria is *the single most significant life-saving intervention* in saving these patients.

The recommended empirical antibiotic therapy is mentioned in table-3.

Table-3: Recommended empirical antibiotic therapy		
Malaria with organ involvement	Suspicion and common organism	Empirical antibiotics
Pneumonia	Streptococcal, H-influenza	Ceftriaxone AND Macrolides or Fluroquinolones
BRAIN- Altered Mentation or Seizures	Bacterial with Tuberculosis	Ceftriaxone, Vancomycin ± Ampicillin ± Antitubercular Drugs
Shock and Multiorgan Dysfunction	Gram- negative infections > Gram positive	Based on local burden and presentation – Carbapenems and Polymyxin group of Antibiotics
Evaluate for concomittent viral and parasitic infections	Dengue, Chikungunya leptospirosis, Scrubs typhus Leishmaniasis Filariasis, trypanosomiasis, babesiosis HIV, COVID Tuberculosis	Treat empirically or definitive therapy – Depending on Local disease burden

In patients with clinical spectrum of malaria, early identification of possibility of severe malaria evaluation with diagnostic tests like CRP, Procalcitonin, Angiopoietin 2, angiopoietin-2/1 ratio, histidine-rich protein 2. There should be aggressive evaluation for secondary infections in severe malaria with the use of Blood culture or PCR based diagnostic modalities. Based of the identified organism and organ involvement antibiotics should be tailored to treat the specific infections [15-17]. If the workup is negative, if the patients shows signs of improvement, de-escalation of empirical therapy should be considered after 48 to 72 hours of duration.

In low transmission settings where misdiagnosis is much less likely, it is advisable in adults to treat only for severe malaria unless there is evidence for concomitant bacterial sepsis. However, antibiotics should be given to all adult patients with a very high parasitemia (>20%) as concomitant bacteremia was 5.2% in multiple studies, and should be given immediately if there is any unexplained clinical deterioration as low parasitemia and severe malaria is associated with bacterial infection [3-4].

Outcomes or fate of severe malaria with bacterial infections: Severe malaria causes

considerable illness and death, and similarly, bacterial infections complicated by sepsis and organ dysfunction result in high mortality. Combination of severe malaria and secondary bacterial infections has poor outcomes if not diagnosed and treated early [4-6]. Several studies have shown that it lead long term sequelae of organ dysfunction like stroke, renal failure, epileptic, psychomotor abnormalities [4].

Conclusions

Evidence on severe malaria with secondary bacterial infections is limited due to overlapping

clinical features and nonspecific laboratory tests. Delayed or missed treatment leads to poor outcomes. Screening suspected cases using microscopy (parasitemia), CRP, procalcitonin, and newer markers such as haptoglobin and Lpc-2 can help identify patients at risk of severe malaria or secondary bacterial infections. Early initiation of parenteral artesunate and empirical therapy improves outcomes. Evaluation with blood culture and PCR-based techniques is crucial to guide antibiotic selection, duration, and timely de-escalation.

Financial Support and sponsorship: Nil

Conflicts of interest: There are no conflicts of interest.

References

1. Tripathi V, Preetha GS, Pandey AK, Vijay P. Tribal malaria in India: An analysis of malaria incidence and mortality over 20-year period (2000–2020). *Vector-Borne and Zoonotic Diseases*. 2023; 23(3):113-118.
2. World Health Organization. Guidelines for malaria. *WHO: Geneva*. 2022.
3. Severe malaria. *Trop Med Int Health*. 2014; 19 Suppl 1:7-131.
4. White NJ. Severe malaria. *Malar J*. 2022; 21(1):284.
5. Wilairatana P, Mala W, Masangkay FR, Kotepui KU, Kotepui M. The prevalence of malaria and bacteremia co-infections among febrile patients: A systematic review and meta-analysis. *Tropical Medicine and Infectious Disease*. 2022; 7(9):243.
6. Wilairatana P, Kotepui KU, Mala W, Wangdi K, Kotepui M. Prevalence, probability, and characteristics of malaria and filariasis co-infections: A systematic review and meta-analysis. *PLOS Neglected Tropical Diseases*. 2022; 16(10): e0010857.
7. Takem EN, Roca A, Cunningham A. The association between malaria and non-typhoid Salmonella bacteraemia in children in sub-Saharan Africa: a literature review. *Malar J*. 2014; 13:400.
8. Hanson J, Nyein PP, Aung NM, Kyi MM. Time for pragmatic, prospective clinical trials to determine the role of empirical antibacterial therapy in critically ill adults hospitalized with malaria. *Int J Inf Dis*. 2021; 102:28-31.
9. Phu NH, Day NPJ, Tuan PQ, Mai NTH, Chau TTH, Van Chuong L et al. Concomitant Bacteremia in adults with severe falciparum malaria. *Clin Infect Dis*. 2020; 71(9):e465-e470.
10. Aung NM, Nyein PP, Htut TY, Htet ZW, Kyi TT, Anstey NM, Kyi MM, Hanson J. Antibiotic Therapy in Adults with Malaria (ANTHEM): High Rate of Clinically Significant Bacteremia in Hospitalized Adults Diagnosed with Falciparum Malaria. *Am J Trop Med Hyg*. 2018; 99(3):688-696.
11. Sandlund J, Naucler P, Dashti S, Shokri A, Eriksson S, Hjertqvist M, Karlsson L, Capraru T, Färnert A. Bacterial coinfections in travelers with malaria: rationale for antibiotic therapy. *J Clin Microbiol*. 2013; 51(1):15-21.
12. Pandey S, Rai P, Guha SK, Maji A, Ghosh S, Halder P, Gupta MK, Halder SN, Modak D. Outcome of Adult Malarial Co-infections in Eastern India. *J Glob Infect Dis*. 2022; 14(2):57-63.
13. Weiland AS. Recent Advances in Imported Malaria Pathogenesis, Diagnosis, and Management. *Curr Emerg Hosp Med Rep*. 2023; 11(2):49-57.
14. Maturana CR, de Oliveira AD, Nadal S, Bilalli B, Serrat FZ, Soley ME, Igual ES, Bosch M, Lluch AV, Abelló A, López-Codina D, Suñé TP, Clols ES, Joseph-Munné J. Advances and challenges in automated malaria diagnosis using digital microscopy imaging with artificial intelligence tools: A review. *Front Microbiol*. 2022; 13:1006659.
15. Foko LPK, Narang G, Tamang S, Hawadak J, Jakhan J, Sharma A, Singh V. The spectrum of clinical biomarkers in severe malaria and new avenues for exploration. *Virulence*. 2022; 13(1):634-653.
16. Mahittikorn A, Kotepui KU, Mala W, Wilairatana P, Kotepui M. Procalcitonin as a Candidate Biomarker for Malarial Infection and Severe Malaria: A Meta-Analysis. *Int J Environ Res Public Health*. 2022; 19(18):11389.
17. Mahittikorn A, Kwankaew P, Rattaprasert P, Kotepui KU, Masangkay FR, Kotepui M. Elevation of serum interleukin-1 β levels as a potential indicator for malarial infection and severe malaria: a meta-analysis. *Malar J*. 2022; 21(1):308.
18. Gomes MF, Faiz MA, Gyapong JO, Warsame M, Agbenyega T et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. *Lancet*. 2009; 373(9663):557-66.
19. Brunner NC, Omoluabi E, Awor P, Okitawutshu J, Tshetu Kitoto A et al. Prereferral rectal artesunate and referral completion among children with suspected severe malaria in the Democratic

- Republic of the Congo, Nigeria and Uganda. *BMJ Glob Health*. 2022; 7(5):e008346.
20. Aggarwal HK, Jain D, Rao A, Kalra R. Role of coma acidosis malaria score in patients with severe malaria among Indian population: A tertiary care center experience. *Eurasian J Med*. 2017; 49:30-35.
21. Kaung M, Kyi TT, Aung NM, Kyaw MP, Min M, Htet ZW, Anstey NM, Kyi MM, Hanson J. The prognostic utility of bedside assessment of adults hospitalized with malaria in Myanmar: a retrospective analysis. *Malar J*. 2015; 14:63.

Cite this article as: Abbas M, Fakruddin M, Tabassum S and Begum F. Integrated diagnostic and therapeutic approaches for bacterial co-infections in severe malaria. *Al Ameen J Med Sci* 2025; 18(4): 319-325.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial (CC BY-NC 4.0) License, which allows others to remix, adapt and build upon this work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

*All correspondences to: Dr. Mohammad Fakruddin, Assistant Professor, Department of General Medicine, Al Ameen Medical College and Hospital, Athani Road, Vijayapura-586108, Karnataka, India. Email: md fakrubm@gmail.com