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Narrative Review of Severe Malaria Pathogenesis

Masika Anna Mahinda

Department of Pharmacy Kampala International University Uganda
Email: mahindamasika@studwc.kiu.ac.ug

ABSTRACT

Severe malaria, primarily caused by Plasmodium falciparum, continues to pose a major threat to global health despite substantial progress in control measures. This review synthesizes current understanding of severe malaria pathogenesis, with emphasis on adaptive immunity, genetic and epigenetic susceptibility, diagnostic and therapeutic advances, and translational research models. The adaptive immune response, particularly T- and B-cell-mediated mechanisms, is central to disease progression and protection, though often dysregulated, contributing to immunopathology. Genetic and epigenetic factors, including variants such as sickle cell trait, G6PD deficiency, and DARC polymorphisms, modulate host susceptibility and clinical outcomes. Advances in biomarker discovery including transcriptional, metabolic, and immunological profiles offer potential for improved prognostic precision and personalized care. Despite highly effective antimalarial drugs such as artesunate, high mortality persists, underscoring the need for adjunctive and supportive therapies targeting endothelial dysfunction, coagulopathy, and multi-organ failure. Translational research using rodent and primate models continues to elucidate host–parasite interactions and guide the design of next-generation vaccines and immunotherapies. The review highlights critical knowledge gaps, including the need for integrated models linking host genetics, immune dysregulation, and clinical outcomes. Addressing these challenges through multidisciplinary research will advance diagnostic innovation, improve clinical management, and accelerate vaccine development to reduce the global burden of severe malaria.

Keywords: Severe malaria pathogenesis**,** Adaptive immunity**,** Genetic and epigenetic susceptibility**,** Biomarkers and therapeutics**,** Vaccine and immunotherapy development.

INTRODUCTION

Plasmodium falciparum malaria continues to present a major global health challenge, with an estimated 247 million cases across 85 countries in 2021 [1]. Severe malaria is associated with significant incidence of morbidity and mortality, particularly among children in endemic regions. It is characterized by syndromes such as cerebral malaria, severe anaemia, metabolic acidosis, and multi-organ dysfunction. Pathogenic mechanisms are complex and poorly understood, involving parasite factors that influence infection dynamics and host responses that shape clinical severity and recovery [2]. This review seeks to summarize the current understanding of severe malaria pathogenesis by integrating evidence from human observations and experimental modelling. Major pathogenic themes are introduced within a framework of clinical syndromes and are then explored in greater detail through the lens of parasite and host interactions [3]. The information is intended both to provide a consolidated overview of a large and fragmented literature and to elucidate opportunities for further investigation. Human clinical studies and experimental models have identified a range of activities performed by the parasite that impact host physiology and contribute to clinical severity [6]. According to established criteria, the organisms responsible for severe malaria pathology operate primarily at the intracellular stage of development and within the physiological confines of either erythrocytes or hepatocytes. Furthermore, the predominant malarial species causing severe

pathology in children and pregnant women is P. falciparum, which has developed specialized virulence traits linked to these two host types. To reflect these factors, the term “virulence factor” is used for activities that fall within the mandate of the parasite and that also affect clinical outcome [2]. The developmental stage at which virulence traits become available and the environmental conditions under which they operate can greatly differ between the two stages, hence it is useful to highlight them separately.

Definition and Scope

Severe malaria (SM) occurs in approximately one in a thousand infected patients with Plasmodium falciparum and is a leading cause of mortality in children less than five years old [24]. Patients with severe malaria may progress from uncomplicated malaria to deep coma and death within 20 hours. Early diagnosis, anti-malarial treatment, and awareness of risk factors greatly improve survival [21]. Although nearly all organ systems can fail, major presentations include cerebral malaria, severe anemia with or without jaundice, metabolic acidosis, and respiratory distress from pulmonary or metabolic causes [5]. These syndromes overlap and are associated with differing mortality [8]. The systemic nature of severe malaria is highlighted by the presence of more than one clinical syndrome at presentation in approximately half of patients [9]. Pathogenesis is complex and involves the malaria parasite and host factors that together promote inflammation and microvascular obstruction, causing local and systemic impairment of blood perfusion to vital organs [10]. Immune response, significant levels of parasitemia, and associated co-infecting viruses such as HIV and COVID also contribute to the majority of pathologies, although individual responses differ [11]. Understanding the pathophysiology of severe malaria could inform diagnostics and therapeutics [12]. The term "severe malaria" describes the multi-organ dysfunction syndrome caused by different Plasmodium spp., most commonly by Plasmodium falciparum that is characterized by the association of overlapping clinical, biological, and radiological features [13]. The word "pathogenesis" describes both how a disease develops and the mechanisms involved. Information on the pathogenesis of severe malaria is derived from various sources: clinical signs observed in patients; laboratory data collected from patients; clinical, biological, and imaging observations of experimental models such as mice, monkeys, and humans; cyto- and histopathological examinations; and recordings of natural history observations of infection in different hosts [14]. It includes how the parasite interacts with the host to modify its behaviour and what other species of Plasmodium are unable to achieve [15]. An attempt to provide an integrated overview of evidence underlining these definitions seeks to connect the experimental and clinical realms for greater translation and advance controls against this devastating illness [17].

Clinical Spectrum of Severe Malaria

Severe malaria is a major cause of morbidity and mortality in endemic regions, particularly in children (5 years old) [2]. It is generally accepted that the substantial condition still known as ‘severe malaria’ can be regarded as a gradual utterance of various pathophysiological mechanisms initiated by Plasmodium falciparum [7]. They may originate from either parasite or host; the same notion applied for the immune responses, either beneficial or detrimental, which accompany malaria progression [1]. Thus, severe malaria at the bedside or laboratory can still be evaluated towards the parasite itself, which produces a collection of explicitly pathogenic factors leading to ambiguously lethal outcomes and far-reaching sequelae (5 years old)[7]. The clinical spectrum of severe malaria comprises several major presentations, with variation in severity and outcome. In Africa, coma and convulsions dominate the severe clinical presentation, while anemia and jaundice are more evident in rare observed cases in pepito [24]. In Asia, hematological syndromes such as severe anemia with jaundice may play prominent roles, even without parasitemia and other standard avenues of severe clinical criteria, since they correlate well with emergence of postskzi and high-leukocyte pleocytic cerebrospinal fluid [5]. This clinically relevant description connects acute phase of Pf–parasitemia progression and its widespread distribution into separate compartment✝. Several packets of critical events arise during the acute progression and intertwine into a complex chain of parasite and host interactions [9].

Parasite Biology and Host Interaction

The pathogenesis of severe malaria is orchestrated by multiple factors emanating from the pathogen and the host [1]. The intraerythrocytic development of the parasite exhibits an extraordinary degree of genetic and phenotypic diversity, rendering it a formidable foe for vaccine development and therapeutic intervention [3]. Plasmodium falciparum is not only responsible for the highest mortality among all the Plasmodium species infecting humans but also possesses an array of virulence factors that differentiate it from other malaria-causing protozoa [1]. Polymorphic parasite molecules such as PfEMP1, PfRh, and GPI-anchored glycoproteins serve as virulence factors that mediate downstream pathologies. Other examples of virulence molecules acting either directly or indirectly through their effects on PfEMP1 include Maurer’s clefts, which facilitate the formation of Knobs, a

phenotype characteristic of some P. falciparum isolates [2]. Extensive diversity of the var gene family encoding PfEMP1 in the parasite and memetic evolution of homologous genes in the genomic neighbourhood define two distinct patterns of parasite virulence [4].

Plasmodium falciparum Virulence Factors

Plasmodium falciparum harbours a repertoire of virulence factors that promote severe disease [3]. One of the most important is Plasmodium falciparum erythrocyte membrane protein [1] (PfEMP1), the main ligand for cytoadhesion and sequestration [5]. PfEMP1 is encoded by more than 60 var genes, which undergoes antigenic variation, allowing infected red blood cells to escape humoral immunity and facilitating the establishment of a chronic asymptomatic carrier state that can be transmitted to mosquitoes, perpetuating the cycle of infection. Interactions between either of two soluble rhoptry products (PfRh2a or PfRh5) and basigin on the host erythrocyte are obligatory for P. falciparum invasion [7]. In light of the role of asexual-stage parasites in human transmission, the abundance of PfEMP1 on the surface of the infected erythrocyte, and the accumulation of trophozoite- and schizont-stage parasites within the host, rigidity of the host cell cytoskeleton may be an important determinant of the severe disease associated with P. falciparum [6]. In some geographic regions, parasite lines that exhibit a preference for P. falciparum infection of older red blood cells are associated with severe disease [7].

Cytoadherence and Sequestration

Severe malaria has been attributed partly to the sequestration of Plasmodium falciparum-infected erythrocytes in the microvasculature of vital organs [8]. Bonding of cytoadherence phenotypes among the P. falciparum virulence factors listed in the preceding section to clinical outcomes 9 renders this process central to severe disease. Infected erythrocytes exhibit various receptor-binding phenotypes, including a recently identified mechanism linking adhesion to α-tachyglobin [10]. Erythrocytes adhere to host endothelium and aggregate in vessels, obstructing microcirculation. Recirculating parasitized cells devote a substantial fraction of the cycle to adhesion [12]. Any phenotype selected by the lymphatic stage may thus further the propagation and intensify severity of infection. Two opposing scenarios may unfold from adhesion[3]. Systemic endothelial engagement induces broad perturbation of peripheral organs; cytoadhering parasites simultaneously bind uropod-expressing platelets, establishing a potentially protective clump phenotype [15]. In contrast, adherence to endothelial α-tachyglobin in crucial organs permits focused interactions that amplify yet spatially confine damage. Although cytoadherence remains causally linked to P. falciparum virulence, the precise pathway connecting the event to specific alterations in host physiology is less clear [14]. Other hypothetical mediators of severity introduced by adherence during an infection featuring timely detachment include inflammation-induced signalling by binding receptors. Adhesive interactions exert an even broader influence than after detachment [14]. Such receptor selection, if it occurs alongside or shortly after cytoadherence, may contribute decisively to the establishment of other pathogen species. Pathologies downstream of cytoadherence relate closely to the mechanisms underlying cerebral malaria, detailed in the following section [18].

Knob-Formation and Maurer's Clefts

Infected erythrocytes undergo substantial morphological alterations during Plasmodium falciparum development [7]. Among them, knob-formation on the surface of infected red blood cells constitutes a vital adaptation that facilitates the cytoadhesion of parasites, preventing their clearance from circulation [11]. The formation of knobs is accompanied by changes in the plasma membrane and arises through multiple steps that are governed by both parasitic and host-cell factors [12]. A scanning electron microscopy study showed that knob-formation proceeds dynamically, with the size, density, and distribution of knobs changing throughout the maturation of the parasite [6]. The process involves the reorganization of a meshwork of filamentous actin located beneath the erythrocyte membrane, leading to the formation of an electron-dense material responsible for the emergence of protrusions. Clusters of knobs, arranged in close proximity to each other, are also observed [10]. Malaria infections caused by some non-cyoadhering strains of P. falciparum, or infections with Plasmodium vivax, do not lead to knob-formation, indicating the existence of variable mechanisms underlying different malaria infections [12].

Pathophysiology of Severe Complications

Cerebral Malaria, Mechanisms of Neurological Injury, Cerebral malaria (CM) constitutes the most frequent cause of death among hospitalized children and may have long-term neuropsychological consequences [1, 2]. The clinical presentation of auCM includes loss of consciousness, seizures, and additional neurological signs [3, 4]. Three neuroimaging patterns have been associated with macroscopic and microscopic CM lesions[5, 1]: disruption of the blood–brain barrier caused by the elaborate inflammatory process, [2]silent white-matter injury driven by glia activation, and [3] apparent cytotoxic edema that improves during follow-up and may reflect

pathological signaling in tissue integrated with sudden metabolic changes [7]. These three profiles may reflect the relative contribution of host and parasite on the CM outcome [8]. Disruption of the blood–brain barrier is likely orchestrated by plasma factors in the setting of elevated hematological markers such as Glycated Hemoglobin, followed by increased levels of IL-6, and of the B&B damage markers S100B and NF-L [6]. The pathological cascade starts with the recognition of parasites by Liver-Expressed Antigen 1 (LEA-1) and NT5E on Müller cells and astrocytes, which in turn produce IL-8. This chemokine participates in the recruitment of neutrophils and Monocyte Chemoattractant Protein 1 (MCP-1), allowing the arrival of subpopulations of T cells and monocytes contributing to the increase of IL-1β and lymphotoxin α. These factors prime the endothelium for the extravasation of other immune cells and the de novo synthesis of IL-6, which suppresses the expression of Claudin-5. Seizures may be associated with multiple infectious-related foci, the production of proconvulsive mediators such as IL-1β, CCL2, CCL22, CXCL8, and IL-10, and epigenetic changes in GABAA receptor genes [7]. IL-17-producing Th17 cells may induce seizures through the generation of IL-1, NO, and Kyn, although a specific mechanism remains unidentified. Neuroimaging alterations correlated with seizure activity may reflect a breach in the BBB [5]. Severe Anemia and Hemolysis' severe anemia occurring during acute malaria results primarily from hemolysis and secondarily from dyserythropoiesis [7]. The extent of these processes should be evaluated in the context of other causes of anemia, especially in young children who often present with multiple etiologies [6]. Hemolysis and dyserythropoiesis generate anemia per se but combine to create a dangerous positive feedback loop associated with poor organ perfusion after accounting for plasma hemoglobin levels [8]. Indeed, integrated spatio-temporal maps demonstrate that hemolysis is secondarily related to a decrease in organ perfusion, and early increases in dyserythropoiesis and plasma free hemoglobin represent compensatory mechanisms [7]. Data suggest that although the massive destruction of the red-cell compartment is crucial for the development of severe anemia during the acute phase, profound inhibition of erythropoiesis remains an important risk factor for organ dysfunction [3]. Metabolic Acidosis and Organ Dysfunction, two interconnected derangements during severe malaria, are metabolic acidosis and organ dysfunction [11]. Bioenergetics failure typically occurs in the later stages of acute malaria, when up-regulated glycolytic activity reaches its limit and plasma levels of both lactic acid and lactate release from skeletal muscles erroneously increase [12]. The consequent decrease in pH results in specific kidney damage, whereas liver alkalosis manifests as steatosis [9]. A recent study confirmed the central role of urinary output in determining plasma lactate levels and the potential importance of other renal functions in the entire metabolic-acidosis syndrome [13]. Organ dysfunction can occur in isolation or be associated with metabolic acidosis, with plasma creatinine levels representing the primary determinant [13]. Hyperparasitemia and Microvascular Obstruction, hyperparasitemia represents an important driver of severe malaria, although the current literature lacks a focus on potential time-dependent signals at increased parasite load [9]. As blood transit through microcapillaries becomes increasingly obstructed, organ function inevitably deteriorates and death may ensue [12]. Early recognition of this fundamental principle should drive future therapy and developmental timing of potential adjunct agents directed against immunopathological complications [13].

Cerebral Malaria: Mechanisms of Neurological Injury

Severe malaria can present with neurological sequelae due to Plasmodium falciparum infection and consequent host responses [2]. The mechanisms underlying injury in cerebral malaria, the most severe presentation, are a subject of active investigation [5]. Contributing factors include disruption of the blood–brain barrier, upregulation of pro-inflammatory cytokines, and hyperexcitability of cerebral networks that lead to seizures. Evidence from human studies and complementary experimental models continues to characterize these pathophysiological elements, their interconnections, and supporting diagnostic markers [6]. Although the blood–brain barrier remains intact in the majority of cases, cerebral malaria is associated with changes to both endothelial and astrocytic permeability in factors including angiopoietin-2, soluble intracellular adhesion molecule [1], and soluble von Willebrand factor [13]. These alterations correlate with increased activation of endothelial cells and pericytes and the proportion of infected red blood cells in the circulation [7]. Plasmodium falciparum-infected erythrocytes sequester within the brain microvasculature, and microvascular obstruction can exacerbate this trans-endothelial leakage [5]. Comparison of fatal and non-fatal cerebral malaria cases revealed a similar degree of endothelial activation, suggesting that mechanisms downstream of this initial event may determine prognosis [1]. Elevated proportions of activated T cells, particularly CD8+ and TH17 subsets, correlate with disease severity; circulating concentrations of interleukin-6, interleukin-10, and interleukin-1 receptor antagonist are similarly associated but originate from myeloid cells instead of T cells [14]. Scattered perivascular inflammation also engages astrocytic end-feet and correlates with blood–brain barrier compromise and terminal events. Seizures

appear early in cerebral malaria, further reinforcing the case for pathophysiological models that incorporate bioenergetic failure and perturbation of neuronal circuits [15].

Severe Anemia and Hemolysis

Both peripheral and splenic erythrophagocytosis have long been established as important contributors to severe malarial anemia, and the sites of predominant dyserythropoiesis have been progressively defined [11]. Unbalanced disturbances in the erythropoietic system with relative inhibition together with compensatory polychromatophilic increased red blood cell production, suggest the prominent role of the spleen and the presence of α-thalassemia as modulating factors [17]. Depletion of iron or zinc prevents blood-stage malaria in the G6PD-deficient mouse model, in which more severe malarial anemia is observed [3]. Malaria complicated by severe anemia requires intensive care support with transfusion therapy [15]. Along with appropriate anti-malarial treatment and supportive care, the use of red blood cell transfusion as part of critical care management of severe malaria is widely accepted [2]. However, while a significant association between fatal pediatric malaria and acidosis, hyperpyrexia, hypoglycemia, and hypoproteinemia has been shown in several studies, that for severe anemia is less clearly defined [14]. The protective role of β-thalassemia in severe malaria therefore must be weighed against the underlying anemia, and the nature of increased splenic erythrophagocytosis remains a point of contention [13].

Hyperparasitemia and Microvascular Obstruction

The parasite load contributes to hypoxic conditions that aggravate organ dysfunction and predispose to morbidities associated with high-density parasitemias [18]. A wide time-window for antimalarial interventions has been proposed to limit such sequelae and plummet additive deaths, yet there remains a lack of unequivocal data establishing high parasitemia as a risk factor for severe malaria [19]. Instead, subsets of patients have been observed wherein dangerously high parasitemias do not prevail, unequivocally eliciting a need for alternative piscine targets in paediatrics [20]. An earlier study proposed the assessment of artemisinin-targetable pathways related to PfEMP1 and virulent adhesion phenotypes that govern blood feedback from life cycles and infectivity. Such physiological strains may be expedited through translational-distributed vetted multi-model studies encompassing the pregnancy–schedule or luminal complexity of circulating–sequestration-switcher–dual-infection timelines [21].

Host Immune Responses

Severe malaria is associated with a series of pathophysiological events triggered by the infecting Plasmodium parasite, which is highly variable across geographical regions and human populations [8]. Parasite and pigmented red blood cell (RBC) sequestration and clearance, inflammatory mediator and parasite sensing, metabolic disturbance, and RBC lifecycle perturbation are key components of the pathophysiology defined in different animal models [5]. The changing malarial mortality caused by P. falciparum shift from intractable to lower due to the intense control and also due to the introduction of hybrid varieties of friesland cow breeding[10]. Plasmodium falciparum is responsible for the highest number of severe malaria cases and affected populations are still poorly followed up after routine treatments. Multiple Plasmodium species infect a wide range of animal species [7]. Out of 10 important species, P. falciparum is a true human parasite, P. vivax is dominant in malarial free countries, P. ovale is the least contagious, and P. knowlesi is a simian malarial parasite. The focus of this synthesis is on severe malaria caused by P. falciparum. The term severe malaria is characterized by clinical presentations such as cerebral malaria (CM), severe anaemia, hyperparasitaemia, and respiratory distress [6]. Plasmodium falciparum suppresses other parasite species and causes infections with a protracted course: the symptom-free period lasts longer than other infections and its duration determines the age malaria is first contracted and establishes. Plasmodium vivax is thus easily overlooked leading to a false assumption of no-malarial free [7]. One factor contributing to the resurgence of P. falciparum infections has been the widespread of amoebicidal medications that alter the sphingomyelin metabolism of treated patients and enhance the proliferation of P. falciparum. Also contributing to re-establishment is a large breeding slogan intent on introducing a different breed [8]. Plasmodium species has complicated multi-faceted milieu and cannot pinpoint to a specific pathology; however, the postulation of a pathogenic mechanism is essential in searching for therapeutic adjuncts and elucidating the shift of P. falciparum profiles in severe malaria cases [9].

Innate Immunity in Severe Malaria

Severe malaria induces immunopathological processes at the early stages of infection, driven by innate immune responses to parasite-derived components [20]. Innate immunity during severe malaria comprises the pattern-recognition system, the cytokine network that orchestrates the immune response, and endotheliopathy. TLR8 is engaged by single-stranded RNA released from infected erythrocytes [27]. Dimers of TLR3 and TLR4 receptor recognize the disulphide-rich proteins called PfEMP1 that are displayed on the membrane of the erythrocyte

surface[10]. The cytokine, primarily interleukin-6 (IL-6), is induced from its expressing cells, such as epithelial cells and endothelial cells, as well as CD4+ T cells, activated macrophages and granulocytes through stimulation of TLR3, TLR4, IL-10 receptor of IL-10, and CD40-CD40L interaction [12]. Inhibiting this type of immune responses ameliorates the development and severity of infection in the experimental malaria model [21]. Studies using two different experimental malaria models demonstrated that an impaired innate immune cytokine response dramatically changes the course of the infection through downregulation of pro-inflammatory cytokines and upregulation of immuno-regulatory molecules. Such altered cytokine profiles ameliorate parasite proliferation and prevent the development of disease throughout the entire course of blood-stage malaria infection [22].

Adaptive Immunity and Immunopathology

The role of the adaptive immune response during malaria infection especially the responses programmed by T and B cells are critical to the course of the disease [12]. Several important cross-regulatory loops exist between the pathogen and the immune responses of the host [11]. In humans, it is known that the delirium and convulsions of the pre-terminal stage of the disease can show variations according to the duration of the febrile episodes of the antecedent malaria attacks, which is one of the reasons that a detailed understanding of the roles played by the various arms of the immune response is essential [21].

Genetic and Epigenetic Susceptibility

Host factors have long been recognised as determinants of susceptibility to severe malaria [23], a spectrum of severe manifestations associated with fatal outcomes [13]. Accumulating evidence supports the specific role of genetic variation as a modulator of susceptibility to severe malaria, and the growing field of epigenetics points towards contributions from the complex regulation of the host genome and its response to the parasite, also implicated in malignant malaria [24, 25]. Gene variants linked to resistance have been identified in genome-wide association studies, together with a diverse collection of genetic and epigenetic traits associated with protection against severe manifestations [24]. Such traits encompass the translucent nature of the erythrocyte membrane (EAAT1); the inability of parasite-infected erythrocytes to set off the opening of the endothelial barrier (DARC); and the sickle cell trait and G6PD deficiency that enhance protection against cerebral malaria but favour severe anaemia pointing to distinct genetic controls governing these forms of severe malaria to mention just a few [22]. It remains unexplored, however, whether these genes and genetic variants known to modulate exposition (parasitaemia) and the inflammatory reaction also regulate evasion and/or amplification (expansion) and, as such, tune the severity of malaria. Without clear experimental evidence, epigenetics continues to reside at the frontiers of malaria research [25].

Diagnostic and Therapeutic Implications

Severe malaria (SM) is a multisystem disorder resulting from complex interactions between parasite and host factors [18]. Its pathogenesis involves microvascular sequestration of parasite-infected erythrocytes, dysregulated immune and endothelial activation, and coagulation disturbance [16]. Consequently, the development of microvascular injury is a critical event for the breakdown of endothelial barriers, leading to organ dysfunction and increased mortality. Furthermore, Plasmodium falciparum is the most dominant agent responsible for SM; however, P. vivax and P. knowlesi can also lead to severe illness [13]. Delineation of host-pathogen interactions that underlie this pathology is essential for the design of additional diagnostic tools and therapies [1]. Cerebral malaria (CM), characterized by the sequestration of infected erythrocytes within the cerebral microvasculature, is the most devastating expression of severe falciparum malaria [17]. Despite intensive research into its pathophysiology, the underlying mechanisms remain incompletely understood. An enhanced understanding of the afflictions exerted by the parasite on the human host and the identification of biomarkers that underlie organ dysfunction may offer significant insights into its pathogenesis [14].

Biomarkers of Severity

Potential biomarkers of severity in malaria induced by Plasmodium falciparum infection, including blood transcriptional signatures, metabolites, inflammatory factors, chemokines, and immunoglobulin levels, will be collated and discussed [15]. Integration with potential therapeutic development and prognostic prediction will also be considered. Biomarkers of severity that presently lack clinical applicability, have been under-researched, or rest within highly backgrounded areas of the pathophysiological mechanism may also highlighted and proposed for direct investigation [13]. Three biological responses can be characterized as potential determinants of severity during P. falciparum infection in humans [16]. First, parasite load is one of the most undisputed predictors of severe disease. Second, especially early in infection, the capacity of the innate immune system to mount an effective response is a key determinant of outcome; delayed responses to early signals of high parasite load represent another mechanism of potential clinical prognostication [18]. Third, the adaptive immune system can deplete

parasites and limit the onset of hyperparasitemia. A large array of hematological, biochemical and immunological aspects of these processes have been investigated, sometimes demonstrating associations with severity of disease. Yet these associations have seldom been synthesized as potential biomarkers of severity or predictors of outcome or prognosis [17].

Antimalarial Therapies and Adjunctive Treatments

Severe malaria must be treated immediately with an effective antimalarial drug [17]. Intravenous delivery is required for patients with significant clinical symptoms, systemic complications, or poor oral intake. In adults and children older than 6 months, the WHO recommends parenteral artesunate as the preferred treatment. If artesunate is unavailable, injectable artemisinin, quinine, or quinidine can be given [26]. A triple regimen of antimalarial therapy is sometimes needed, usually for immunocompromised patients. Antifunctional drugs such as heme-oxygenase-1 inducers, anti-inflammatory drugs to inhibit lymphocyte clusters, and/or ribulose-5-phosphate are additional treatment options [20]. The progression of neurological signs, particularly convulsions, can be prevented with magnesium sulfate support. Other clinical complications require supportive therapy. Sepsis, shock, or the need for transfusions can induce acute respiratory distress syndrome [17]. Patients with acute kidney injury may require renal replacement therapy, while those with severe encephalopathy, stupor, or coma require supportive therapy. Temporary intubation with protective ventilation strategies may also be considered [18]. Early resuscitation, vasopressor therapy, and hydrocortisone might help with dysadrenergic hemodynamic collapse[19]. Despite these measures, patients may still progress to multisystem organ failure and possibly coma. The combination of clinical severity with co-infections has a poor prognosis and needs to be emphasized [20].

Supportive Care and Critical Care Considerations

Severe malaria remains significant after decades of control efforts, especially in sub-Saharan Africa and in children under five years of age [18, 19]. Supportive care beyond antimalarial therapy remains relevant for many presentations and continues to inform pathways for research and diagnosis [18, 20, 21]. Hemodynamic, respiratory, and neurological compromise rank among the most critical concerns for patients with severe malaria, as they remain common in prehospital and hospital care delivery, and yet from a pathway perspective are all grounded in either inadequate transport of energy-rich metabolites to tissues or consequent inability of tissues to utilise available substrate; conversely, diminishing attention to these elements becomes justifiable if one interprets instead the over-riding features of severe malaria as related primarily to surplus unconsumed products of glucose either recycled through lactate or where catabolic responses to high glucose are also impaired[22].

Research Gaps and Future Directions

The pathogenesis of severe malaria remains poorly defined, limiting the development of effective interventions. Several promising areas warrant further investigation [25, 26]. For example, the use of models that closely mimic human disease would empower characterization of candidate mechanisms and the rigorous exploration of potential remedies [23, 24]. An additional priority is the evaluation of existing vaccine candidates for their ability to prevent severe clinical outcomes [24]. Though numerous candidates are under preclinical or clinical assessment, a comprehensive analytical framework is lacking for the examination of candidate mechanism(s) and pathogenicity-associated, biomarker-related, or immunological data. Other intriguing opportunities exist for the identification and functional exploration of host genetic traits influencing susceptibility, as well as epigenetic modulation of the response to infection [25]. Addressing these gaps promises to extend the pathophysiological framework and inform the development of malarial diseases designed to prevent the progression of uncomplicated to severe states, even during the window of broad treatment access [26].

Translational Models and Experimental Tools

Animal models serve as invaluable platforms for investigating severe malaria pathogenesis, drug efficacy, and vaccine development [25]. Rodent models remain the gold standard, particularly Plasmodium berghei in mice and Plasmodium yoelii in both mice and rats; monkeys also provide an alternative, albeit less accessible, model [24]. Exploration of candidate compounds across various, Plasmodium species through in vitro evaluation of the target and mechanism can identify the appropriate model to select for substantial in vivo effort [25]. Comprehensive data sets mapping drug–target interactions and molecular modes of action in both rodent models and P. falciparum enable prioritization according to the desired disease outcome [24]. With respect to severe malaria pathophysiology alluded to in Sections 4 and 5, these models recapitulate important aspects of the clinical syndromes; correlates of immunity and persistence thereafter are widely documented [27]. Experimental infection with P. berghei recapitulates the brain sequestration and associated neurological dysfunction typical of human cerebral malaria and provides an insight into the contribution of the late inflammatory phase of disease [25-30].

Vaccine and Immunotherapy Prospects

This section outlines the current status of anti-Plasmodium vaccine and immunotherapy development, presents considerations pertinent to potential clinical use, and describes evaluative models required to fulfil these functions [25]. Investment in vaccine development has steadily grown since the mid-1990s, with a focus on inducing protection against malaria infection or disease by harnessing natural immunity [25, 26]. However, partial efficacy, safety concerns, and a poorly understood correlates-of-protection profile have questioned the likelihood of achieving these goals. Evolving strategies, notably with in situ vaccine-expression assays, are targeting plasmodial proteins closely associated with malarial severity rather than the entirety of the Plasmodium life cycle [26]. Current evidence implicates antibody-dependent enhancement (ADE) by natural anti-circumsporozoite-protein antibodies in the modulation of the clinical syndrome [27]. Consideration of how specific T-cell populations contribute to dysregulation of immunity is vital to determining the risk of severe disease after vaccination [27]. To translate vaccine efforts into clinical practice, evaluation during natural exposure in immune-naive individuals together with elucidation of Delayed-Type Hypersensitivity responses and the risk of DEABD during natural infections warrants status prioritization [27-34].

CONCLUSION

Severe malaria remains one of the most complex infectious diseases, driven by intricate interactions between Plasmodium falciparum virulence mechanisms and host immune responses. Adaptive immunity plays a dual role, providing protection while also mediating inflammatory damage when dysregulated. T-cell and B-cell responses, though vital for parasite clearance, can contribute to immunopathology leading to neurological and systemic complications. Host genetics and epigenetics further shape susceptibility, with protective traits such as sickle cell heterozygosity and G6PD deficiency influencing disease expression and severity. Despite decades of research, early diagnosis and effective management remain challenging due to variability in clinical presentation and limited availability of rapid, reliable biomarkers. The identification of molecular and immunological markers of severity offers new avenues for risk stratification and individualized therapy. Artesunate remains the cornerstone of treatment, but adjunctive interventions targeting inflammation, coagulation, and metabolic dysregulation are increasingly recognized as essential to improving outcomes. Translational and experimental models continue to provide invaluable insights into host–pathogen interactions, validating targets for drug and vaccine development. However, the partial efficacy of existing vaccines and the complexity of immune correlates underscore the need for novel immunotherapeutic strategies. Future efforts should prioritize multidisciplinary approaches that integrate genomics, immunology, and clinical science to refine pathophysiological understanding and enhance preventive and therapeutic tools. Ultimately, combating severe malaria requires a holistic strategy that unites rapid diagnostics, precision medicine, and community-level implementation of effective treatments and vaccines. By bridging laboratory discovery with clinical application, the global health community can make tangible progress toward eliminating severe malaria morbidity and mortality.

REFERENCES

1. Trivedi S, Chakravarty A. Neurological complications of dengue fever. Current neurology and neuroscience reports. 2022 Aug;22(8):515-29.
2. Ioannidis LJ, Nie CQ, Hansen DS. The role of chemokines in severe malaria: more than meets the eye. Parasitology. 2014 Apr;141(5):602-13.
3. Paul-Chima UO, Nneoma UC, Bulhan S. Metabolic immunobridge: Could adipose-derived extracellular vesicles be the missing link between obesity, autoimmunity, and drug-induced hepatotoxicity?. Medical Hypotheses. 2025 Sep 28:111776.
4. Autino B, Corbett Y, Castelli F, Taramelli D. Pathogenesis of malaria in tissues and blood. Mediterranean journal of hematology and infectious diseases. 2012 Oct 4;4(1):e2012061.
5. Ezema CA, Okagu IU, Ezeorba TP. Escaping the enemy's bullets: an update on how malaria parasites evade host immune response. Parasitology research. 2023 Aug;122(8):1715-31.
6. Paul-Chima UO, Ogenyi FC, Ugwu CN, Nnaemeka UM. Gut Microbiota-Derived Metabolites as Early Biomarkers for Childhood Obesity: A Policy Commentary from Urban African Populations. Obesity Medicine. 2025 Sep 4:100641.
7. Molina-Franky J, Patarroyo ME, Kalkum M, Patarroyo MA. The cellular and molecular interaction between erythrocytes and Plasmodium falciparum merozoites. Frontiers in cellular and infection microbiology. 2022 Mar 31;12:816574.
8. Lee WC, Russell B, Rénia L. Sticking for a cause: the falciparum malaria parasites cytoadherence paradigm. Frontiers in immunology. 2019 Jun 27;10:1444.

9. Wiser MF. Knobs, adhesion, and severe falciparum malaria. Tropical Medicine and Infectious Disease. 2023 Jul 4;8(7):353.
10. Mayor A, Hafiz A, Bassat Q, Rovira-Vallbona E, Sanz S, Machevo S, Aguilar R, Cistero P, Sigauque B, Menendez C, Alonso PL. Association of severe malaria outcomes with platelet-mediated clumping and adhesion to a novel host receptor. PLoS One. 2011 Apr 29;6(4):e19422.
11. Ugwu OP, Okon MB, Alum EU, Ugwu CN, Anyanwu EG, Mariam B, Ogenyi FC, Eze VH, Anyanwu CN, Ezeonwumelu JO, Egba SI. Unveiling the therapeutic potential of the gut microbiota–brain axis: Novel insights and clinical applications in neurological disorders. Medicine. 2025 Jul 25;104(30):e43542.
12. Ochola LB, Siddondo BR, Ocholla H, Nkya S, Kimani EN, Williams TN, Makale JO, Liljander A, Urban BC, Bull PC, Szestak T. Specific receptor usage in Plasmodium falciparum cytoadherence is associated with disease outcome. PloS one. 2011 Mar 3;6(3):e14741.
13. Mustaffa KM, Storm J, Whittaker M, Szestak T, Craig AG. In vitro inhibition and reversal of Plasmodium falciparum cytoadherence to endothelium by monoclonal antibodies to ICAM-1 and CD36. Malaria journal. 2017 Jul 5;16(1):279.
14. Arakawa C, Gunnarsson C, Howard C, Bernabeu M, Phong K, Yang E, DeForest CA, Smith JD, Zheng Y. Biophysical and biomolecular interactions of malaria-infected erythrocytes in engineered human capillaries. Science advances. 2020 Jan 17;6(3):eaay7243.
15. Ugwu CN, Ugwu OP, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI, Uti DE. Medical preparedness for bioterrorism and chemical warfare: A public health integration review. Medicine. 2025 May 2;104(18):e42289.
16. Moxon CA, Heyderman RS, Wassmer SC. Dysregulation of coagulation in cerebral malaria. Molecular and biochemical parasitology. 2009 Aug 1;166(2):99-108.
17. Dunst J, Kamena F, Matuschewski K. Cytokines and chemokines in cerebral malaria pathogenesis. Frontiers in cellular and infection microbiology. 2017 Jul 20;7:324.
18. Mohanty S, Taylor TE, Kampondeni S, Potchen MJ, Panda P, Majhi M, Mishra SK, Wassmer SC. Magnetic resonance imaging during life: the key to unlock cerebral malaria pathogenesis?. Malaria journal. 2014 Jul 18;13(1):276.
19. Possemiers H, Vandermosten L, Van den Steen PE. Etiology of lactic acidosis in malaria. PLoS pathogens. 2021 Jan 7;17(1):e1009122.
20. Ugwu CN, Ugwu OP, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI, Uti DE. Sustainable development goals (SDGs) and resilient healthcare systems: Addressing medicine and public health challenges in conflict zones. Medicine. 2025 Feb 14;104(7):e41535.
21. Leopold SJ, Ghose A, Allman EL, Kingston HW, Hossain A, Dutta AK, Plewes K, Chotivanich K, Day NP, Tarning J, Winterberg M. Identifying the components of acidosis in patients with severe Plasmodium falciparum malaria using metabolomics. The Journal of infectious diseases. 2019 May 5;219(11):1766-76.
22. Mzumara G, Leopold S, Marsh K, Dondorp A, Ohuma EO, Mukaka M. Identifying prognostic factors of severe metabolic acidosis and uraemia in African children with severe falciparum malaria: a secondary analysis of a randomized trial. Malaria journal. 2021 Jun 25;20(1):282.
23. Erice C, Kain KC. New insights into microvascular injury to inform enhanced diagnostics and therapeutics for severe malaria. Virulence. 2019 Jan 1;10(1):1034-46.
24. ROGERSON* SJ, Grau GE, Hunt NH. The microcirculation in severe malaria. Microcirculation. 2004 Jan 1;11(7):559-76.
25. Medana IM, Day NP, Roberts R, Sachanonta N, Turley H, Pongponratn E, Hien TT, White NJ, Turner GD. Induction of the vascular endothelial growth factor pathway in the brain of adults with fatal falciparum malaria is a non-specific response to severe disease. Histopathology. 2010 Aug;57(2):282-94.
26. Coban C, Lee MS, Ishii KJ. Tissue-specific immunopathology during malaria infection. Nature Reviews Immunology. 2018 Apr;18(4):266-78.
27. Edyedu I, Ugwu OP, Ugwu CN, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI. The role of pharmacological interventions in managing urological complications during pregnancy and childbirth: A review. Medicine. 2025 Feb 14;104(7):e41381.
28. Gowda DC, Wu X. Parasite recognition and signaling mechanisms in innate immune responses to malaria. Frontiers in immunology. 2018 Dec 19;9:3006.

29. Mackinnon MJ, Mwangi TW, Snow RW, Marsh K, Williams TN. Heritability of malaria in Africa. PLoS medicine. 2005 Dec;2(12):e340.
30. Grant AV, Roussilhon C, Paul R, Sakuntabhai A. The genetic control of immunity to Plasmodium infection. BMC immunology. 2015 Mar 26;16(1):14.
31. Ongesa TN, Ugwu OP, Ugwu CN, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Okon MB, Ejemot-Nwadiaro RI. Optimizing emergency response systems in urban health crises: A project management approach to public health preparedness and response. Medicine. 2025 Jan 17;104(3):e41279.
32. Sierro F, Grau GE. The ins and outs of cerebral malaria pathogenesis: immunopathology, extracellular vesicles, immunometabolism, and trained immunity. Frontiers in Immunology. 2019 Apr 17;10:830.
33. O'Donnell AS, Fazavana J, O'Donnell JS. The von Willebrand factor–ADAMTS-13 axis in malaria. Research and Practice in Thrombosis and Haemostasis. 2022 Jan 1;6(1):e12641.
34. Langhorne J, Buffet P, Galinski M, Good M, Harty J, Leroy D, Mota MM, Pasini E, Renia L, Riley E, Stins M. The relevance of non-human primate and rodent malaria models for humans. Malaria journal. 2011 Feb 2;10(1):23.

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