Chapter 7

Malaria, Schistosomiasis, and Related Anemia

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Additional information is available at the end of the chapter

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Abstract

Parasitic infections (e.g., malaria and helminthiases) have a huge impact on public health in endemic areas. Moreover, parasitic infestations are prominent causes of anemia in the tropics and subtropics, further perpetuated by malnutrition, inflammatory, and genetic diseases. Anemia-associating parasitic infections vary depending on the requirements and pathophysiology of the parasites. There is an interplay between different factors that can be segregated as host and parasite factors, resulting in severe anemia accompanying these parasitic infestations. The pathophysiological mechanisms leading to anemia associated with the different parasites vary greatly, including hemolysis, anemia of inflammation, bone marrow suppression, and micronutrients deficiency. The major means to deal with this anemia include prevention and treatment of such infestations.

Keywords: malaria, schistosomiasis, anemia, pathogenesis, parasite

1. Overview

Parasitic infestations (e.g., malaria and helminthiases) have an enormous impact on public health in endemic areas. Moreover, parasitic infections are leading causes of anemia in the tropics and subtropics, worsened by malnutrition, inflammatory, and genetic diseases. Anemia-associating parasitic infections vary depending on the requirements and pathophysiology of the parasites. It sounds reasonable that the closer the parasite's association with the red blood cells (RBCs), the more severe the expected anemia. On speaking about blood parasites, malaria is the most important and well-known infection worldwide. Anemia is a clinical condition where the values of hemoglobin, hematocrit, or RBCs counts are more than two standard deviations below the mean for a particular age and sex, with severe anemia characterized by hemoglobin of less than 5 g/dL. Anemia develops as a consequence of blood

loss, when red cells are destructed prematurely, or when the normal erythroid production of red cells is disturbed. These mechanisms often overlap with a number of factors contributing to anemia. Among the important causes of increased cell destruction leading to acquired hemolytic anemia is malaria. Hypersplenism and splenomegaly as in hyper-reactive malaria also play an important role in hemolysis. Another blood parasite of importance is schistosomiasis which is caused by a blood fluke that undergoes a complex life cycle using a species of freshwater snail. Adult flukes pair post maturation inside a human host, for life and begets thousands of eggs that brings harm to organs and are excreted in urine and feces. The larvae hatching from the eggs manage their way into the snails that in turn begets vast numbers of larvae capable of penetrating the human skin. The fluke lives in the veins, urinary bladder, and large intestine of their human hosts and borrow molecules from their hosts to put on their surfaces so that the hosts' immune system would not recognize them as strange.

2. Malaria and anemia

Malaria is an ancient febrile illness that continues to jeopardize human existence. It is one of the major killers, particularly among the tropical countries in Africa, Southeast Asia, and Latin America which is a mosquito-borne disease the characteristic symptoms of which are cyclical bouts of fever with muscle stiffness, shivering, and sweating whose periodicity reflects the intraerythrocytic cycle. Malaria is a disease resulting from the parasitic infestation by *Plasmodium* species, such as *Plasmodium falciparum, P. malariae, P. ovale, P. vivax*, and *P. knowlesi* with *P. falciparum* being the most virulent. Malaria is estimated to be a burden for over 200 million people, leading to more than one million fatalities annually. The main vector for this *Plasmodium* is *Anopheline* species, which are most common tropical inhabitants [1]. Malaria is dependent on the vector-human cycle, and it affects impoverished people in the suburbanized endemic areas with economic and social consequences. Despite decades of efforts on the battle against malaria, it remains to be an important health threat in tropical areas [2]. Malaria can manifest a vast clinical spectrum from silent carrier to fatal shock.

3. Common clinical features of malaria

Fever

Chills

Headache

Myalgia

Malaise

Anemia

Petechie

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4. Manifestations of severe disease

Seizures

Jaundice

Mental confusion

Renal failure

Acute respiratory disease syndrome (ARDS)

Coma

Thrombocytopenia

Severe anemia

Hypoglycemia

Hyperparasitemia

Hypotension

Bleeding

Blackwater fever

5. Genetic basis of malaria-associated anemia

Malaria is a polygenic disease, and the genetic basis of malaria-related anemia is under study. Variable genes have been shown to be involved in host predisposition to the severe forms of malaria, part of which is malaria-related anemia; nevertheless, it is likely that there are undetected malaria-susceptibility genes. It has been found that severe malaria-related anemia is associated with a number of genes, such as FcγRIIA-131H/FcγRIIIB-NA2 haplotype, interleukin-13 promoter polymorphisms (-7402 T/G and -4729G/A), and TNF-238 A allele [3–5]. The host-parasite interaction is complex and not fully understood. Such an interaction leads to a release of a number of cytokines, resulting in the so-called "cytokine storm" in the setting of severe malaria, where injurious cytokines and small molecules become dysregulated and results in a systemic inflammatory response syndrome (SIRS)-like state characterized by high circulating levels of tumor necrosis factor (TNF) and nitric oxide. However, evidence of direct correlation between severe malaria and the activity of these markers is limited [6]. Elevated serum levels of the different cytokines such as TNF, lymphotoxin, interleukins 6, 10, 12, and 18, and macrophage inflammatory protein (MIP)-1 are seen in the setting of malaria. Nevertheless, more studies are needed to clarify whether these predate or follow clinical markers of severe infection [6]. It is proposed that interferon-regulated gene transcripts influence the inflammatory response to cytokines, and these results demonstrated previously undiscovered transcriptional changes in the host that might govern the development of malaria-associated syndromes, such as anemia and metabolic dysregulation [7]. On the other

hand, a number of genes were found to be protecting against malarial anemia such as SCGF, also called C-type lectin domain family member 11A [CLEC11A]), IL12Bpro-2/3′ UTR-T haplotype, FcγRIIA-131H/FcγRIIIB-NA1 haplotype, and NOS2 promoter polymorphisms, along with HLA class II allele DQB1*0501 [3, 8, 9]. In addition, specific genes for commonly inherited diseases found in the tropics are also known for their role in resistance to malaria-related anemia. Such effects imposed by these genes are thought to reflect good examples in the natural selection process in the tropical area. Upon discussing the genetic basis of anemia, it is prudent to speak about the different hemoglobinopathies and their genes such as sickle cell anemia. The most commonly mentioned of such genes are Hb S, hemoglobin E, glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency hereditary elliptocytosis (HE), and thalassemia genes where several studies have found an inhibitory effect of thalassemic gene on malaria-related anemia [10].

6. Pathophysiology of malaria-associated anemia

Anemia is one of the primary pathophysiological events contributing to fatal malaria [11]. Severe and refractory anemia causes hypoxia and leads to heart failure in malaria patients [12]. A number of mechanisms contribute to the pathogenesis of malaria-related anemia, such as erythrocyte destruction and phagocytosis, sequestration of infected RBCs, dyserythropoiesis, and bone marrow suppression. Erythrocyte lysis could be due to hemolysis of either parasitized red cells or non-parasitized cells. Red cells of malaria patients suffering from severe anemia have been found to display abnormal distribution of the different membrane phospholipids, for example, (phosphatidylserine (PS), phosphatidylcholine, and phosphatidyl ethanolamine) non-parasitized, along with membrane damage induced by heme released from the digestion of hemoglobin by the parasite which underwent lipid peroxidation [6]. Expression of specific antibodies directed against the variant parasite antigens (PfEMP-1) surface of the red cells that results in opsonization of the infected red cells [13]. Interestingly, lysis of cells is not confined to parasitized RBCs only where it has been found that non-parasitized erythrocytes inside the parasite culture showed a significant increase in the lipid peroxide genesis and vulnerability to lysis [14]. Moreover, a direct correlation between membrane lipid peroxidation and peroxide hemolysis exists, both before and after monocyte exposure, implying a primary role of membrane peroxidation in red cell lysis. Children with malaria showed low levels of the antioxidant α-tocopherol in the membrane of red cells, a finding that might support the hypothesis that local antioxidant consumption may contribute to erythrocyte loss. It is also suggested that parasite products forming part of the immunoglobulin-antigen complexes retained on non-parasitized erythrocytes include the *P. falciparum* ring surface protein 2 (RSP-2), which results in opsonization of these non-parasitized RBCs and thus provides a mechanism of removing non-parasitized RBCs [6]. A steady decline in the hemoglobin level accompanied by an inappropriate reticulocyte response occurs following an acute malarial infection, where this sort of anemia is explained by sequestration of iron in the spleen and other reticuloendothelial system organs together with a shortened red cell survival. It is considered to be very rare in malaria despite the presence of some

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evidences in support of the nature of the normocytic normochromic anemia with evidence of malaria-related anemia due to hemolysis; however, recent data indicate that these mechanisms (singly or in combination) do not fully explain the severity of this anemia. Dyserythropoiesis is proposed to play a role in malaria-related anemia, although malaria-related anemia might partially be attributed to sequestration of parasitized cells, the continuous reduction in hemoglobin level for several weeks after the acute episode should raise the possibility of involvement of other factors. Hematologic studies have shown that bone marrow suppression and inefficient erythropoiesis have an important share in the severe anemia of malaria infection [15]. Host mechanisms in control of suppression of erythropoiesis might involve an exaggerated and steady innate immune response or a pathologic alteration of the T-cell differentiation response along with the concomitant production of certain proinflammatory cytokines. We are not to over-look the erythrocytes destructed by the spleen and reticuloendothelial hyperactivity, where large numbers of both parasitized and non-parasitized red cells are destructed. Dyserythropoiesis and severe anemia attributed to malaria are closely associated with excess release of interferon (IFN)-γ and TNF-α, along with nitrous oxide, which promote enhanced malarial anemia pathogenesis also resulting in bone marrow suppression and erythrophagocytosis. Other cytokines like interleukin (IL)-12 and 18 have also been implicated in dyserythropoiesis. Hemozoin, which is a malarial pigment resulting from incomplete hemoglobin digestion by the parasite, has also been incriminated in the impaired erythroid development through its direct effects on human monocyte function and/or erythroid precursors [16]. Other contributing factors to malarial anemia are coinfection with other organisms such as bacteria, viruses (e.g., human immunodeficiency virus), and helminthiasis. In summary, the pathogenesis of malaria-related anemia seems to be very complex. It is indicated that there is a cardinal defect in erythroid maturation with existence of a significant degree of erythrophagocytosis. Nevertheless, more elaboration on the subject of pathophysiology of malaria-related anemia is needed. Concerning non-falciparum malaria, although not common, but it can be seen in the non-falciparum malarial patients, particularly in cases where hemolysis due to G-6-PD deficiency is encountered and those receiving some drugs inducing hemolysis. The most important drug to be considered on speaking about hemolysis due to G-6-PD deficiency is primaquine, which is an effective antimalarial drug recommended for the dormant hypnozoites of vivax malaria.

7. Mechanisms of anemia in malaria

Increased destruction	Inadequate response to anemia
1. Destruction and lysis of parasitized erythrocytes	Dyserythropoiesis due to:
2. Destruction and lysis of un parasitized erythrocytes	**1.** Excess IFN-γ
3. Drug-induced hemolysis	**2.** Excess TNF-α
	3. Deficient interleukin-12 production

Increased destruction		Inadequate response to anemia	
4.	Destruction by the spleen and reticuloendothelial system	**4.**	Effect of hemozoin leading to impaired erythroid development

Table 1. Mechanisms of anemia in malaria.

8. Clinical manifestation of malaria-associated anemia

Malaria-related anemia is a frequent manifestation of *P. falciparum* malaria; nevertheless, it is increasingly being reported as a manifestation of *P. vivax* malaria. The most vulnerable groups of people are those under five years old and pregnant women. Furthermore, micronutrient deficiencies caused stunting and also impaired host immunity, thereby increasing the degree to which malaria is associated with low concentrations of hemoglobin, beside increased inflammation, and with increased need for iron in young erythroblasts where the anemia might be severe enough to require blood transfusion. Generally speaking, the spectrum of presentation is broad and influenced by a number of factors that are host related or parasite related or a mixture of both such as the age at presentation, whether it is acute or chronic malaria, the patient's immune status and if he already lives an endemic area or not and the association with other conditions that might worsen or protect against the anemia. Pallor is the most commonly encountered presentation of malarial anemia that can be detected by physical examination and confirmed by a simple hemoglobin test. Additional symptoms requiring referral and blood transfusion are an ejection systolic murmur, change in the consciousness level, the presence of splenomegaly, or malarial parasitemia. In severe malaria-related anemia, it is proposed that cardiac symptoms could be caused by a cardiomyopathy as an after-effect of malarial chronic anemia. Moreover, severe malarial anemia might present with severe lactic acidosis. Severe malarial anemia has been commonly linked to *P. falciparum*; nevertheless, *P. vivax* has been found to cause severe malarial anemia. It is known that parasite density in *P. vivax* malaria plays a significant role that influences the fragility of the RBCs, Heinz body formation, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC) levels; there for, the RBCs of the patients recurrently infected with *P. vivax* parasite are imposed to structural and functional dysfunction, finally culminating in anemia. However, the anemia is not an uncommon presentation in the patients with *P. vivax* malaria. This is the case that is commonly seen when antimalarial treatment is used in G-6-PD deficient individuals. As in other types of drug induced hemolytic anemia, drug-induced *P. vivax* malaria hemolytic anemia warrants prompt detection and early management. The type of anemia in *P. falciparum* malaria is that of normocytic and normochromic, and absent reticulocytes. Blackwater fever is another type of hemolytic anemia in malarial patients that tends to present with classical features of hemolysis such as hemoglobinuria. This fever is a special clinical entity that presents with features of acute intravascular hemolysis that classically occurs after the reintroduction of quinine in long-term inhabitants in malaria endemic areas and repeatedly inadequately using it. Those patients suffering from G-6-PD deficiency are at particular risk of this syndrome, when being subject-

ed to oxidant drugs even in the absence of malarial infection. The features of this serious complication are bilious vomiting, prostration, intravascular hemolysis, hemoglobinuria, and renal impairment. This is usually a serious and severe complication that should be avoided.

9. Common clinical presentations of malaria-associated anemia

Pallor

Ejection systolic murmur

Change in the consciousness level in association with splenomegaly and parasitemia

Myocardiopathy

Severe lactic acidosis

Blackwater fever

10. Diagnosis of severe malaria-associated anemia

The severe malarial anemia is defined by the World Health Organization (WHO) as:

A hemoglobin less than 5 g/dL or hematocrit less than 15%.

Parasitemia with more than 100,000 parasites/μL of blood.

Normocytic blood film (thus excluding thalassemia as well as iron, B12, and folate deficiencies).

[17, 6].

11. Management of malaria-associated anemia

The fundamentals of management of malaria-related anemia is based on the main principles of dealing with anemia "improvement of RBC genesis, where decreased RBC production is the fundamental pathophysiology along with RBC replacement and decrease RBC lysis in cases that have increase RBC destruction as the culprit pathophysiology" and fundamentals of management for infection "elimination of the source of infection and control of complications from pathogen virulence, host responses and treatment".

11.1. Role of erythropoietin

Despite the fact that ineffective or inadequate erythropoietin production might contribute to malaria-associated anemia in some settings; nevertheless, studies from endemic areas such

as Africa showed that children with malaria have elevated erythropoietin production than expected. Therefore, a plausible explanation is that it is rather the response to erythropoietin which contributes to the pathology rather than synthesis, as seen in the anemia of chronic diseases. And as such, administering erythropoietin is not expected to improve malarial anemia [6]

11.2. Is there any role for blood transfusion?

The blood transfusion for malaria-related anemia is an old practice that has been practiced for a long time, the benefits of which have not been validated. Nevertheless, the use of blood transfusion in management of malaria-related anemia carries a high risk for blood-borne infections, particularly in poor resource settings where screening in the blood bank process is lacking or ineffective.

11.3. Is there any role for iron supplementation?

A group of researchers reported that iron supplementation with antimalarial treatment significantly reduced malaria. Moreover, they refuted the assumption that supplementation during an acute attack of malaria increases the risk for parasitological failure or deaths [18].

11.4. Eliminating source of Infection

Theoretically, the fastest way of getting rid of the source of malarial infection and its products is the blood exchange, where it was thought to decrease the degree of parasitemia, when used as adjunct therapy to quinine; however, since there was no supporting evidence, the CDC is now advising against it [19, 20]. On the other hand, antimalarial drug therapy is considered to be the slower method for getting rid of the source of infection, and is definitely needed to manage malaria-related anemia although some of these drugs are to be used cautiously fearing drug-induced hemolytic anemia.

11.5. Treating coinfecting organisms

Studies addressing the effect of coinfection on malarial anemia showed variable results with complex outcomes on anemia [21]. Similar outcomes were seen with studies dealing with the issue of treating coinfection or not [22].

11.6. Control of complications

It is of paramount importance to bear in mind the early recognition of malarial anemia as one of the serious complications of malaria, and thus it is recommended to include hemoglobin measurement as part of the management plan of malaria patients at the primary-care

level, especially in determining whether a patient should be referred to an appropriate treatment center or not.

11.7. Prevention

The following measures are to be taken so as to prevent and control complications of malaria-related anemia:

1. Follow-up for the patients to decide on the response to treatment.
2. Control of complications of malaria-related anemia.
3. Close monitoring for the possible complications of malaria related anemia especially for cardiac and respiratory complications.
4. Monitoring for selected treatment methods such as adverse drug reactions in antimalarial therapy.
5. Intermittent prophylactic treatment for pregnant women as per the WHO recommendations [23].

12. Anemia in schistosomiasis

Schistosomiasis is considered to fall just second to malaria upon discussing the prevalence of parasitic infestations in the world, being prevalent in more than 70 countries worldwide, with an infection rate affecting one in each 30 individuals. It is most prevalent in tropical and subtropical areas of South America, Africa, and Asia. World Health Organization (WHO) estimates the disease burden to be more than 240 million people infected worldwide, with 400–600 millions of people at risk [24, 25]. Schistosomiasis tends to involve a number of organs leading to dysfunction of these particular organs, such as renal and bladder dysfunction (*Schistosoma haematobium*) or liver and intestinal disease caused by *Schistosoma* (*mansoni*, *japonicum*, *mekongi*, and *intercalatum*) in endemic areas, and it is also a contributory cause of anemia and stunting of growth. Schistosomiasis is acquired when cercaria breaks through the skin while swimming or bathing in fresh water when the human host comes into contact with the infectious, free-living, cercarial larvae that are released by the parasite's intermediate hosts [25]. Therefore, patterns of water supply, sanitation, and human water use are critical factors in defining the risk of infection [25, 26]. Moreover, the geographic distribution of the different *Schistosoma* species depends solely on the distribution of the particular snail species that serve as intermediate hosts. On the other hand, the distribution of snails depends on climate, water quality, and other ecologic factors [27, 28]. Thanks to animal models of schistosome infection, where they have allowed intensive study of the immunology and molecular biology of schistosomiasis. Analysis of host responses to these complex multicellular parasites has granted considerable awareness about the regulation of cell-mediated and

humoral immunity [29], as well as the resistance pathways available for elimination of macroparasites [30]. Molecular studies of the parasite have granted information on new manners of genetic expression, not only but even the whole genome of the parasite has been sequenced [31, 32], as well as leads for the development of vaccines and new pharmaceuticals for control of this prevalent chronic infection [25].

12.1. Schistosomiasis-related anemia: molecular and genetic basis

The most common presentation of chronic infestation with *S. mansoni* is with the relatively asymptomatic intestinal form of the disease, while a minority develops hepatosplenomegaly characterized by severe hepatic disease complicated by portal hypertension. Such distinct heterogeneity of disease severity is seen among both, humans and experimental mouse model. Severe disease is featured by profound hepatic egg-evoked granulomatous inflammation in a proinflammatory cytokine setting, whereas mild disease conforms with reduced liver inflammation in a Th2 distorted cytokine setting. This distinct variation reflects that genetic differences play a pivotal role in disease development. Smith et al. demonstrated in their study, that severe hepatic pathology in F2 mice 7 wk after infection was significantly associated with a surge in the synthesis of the proinflammatory cytokines IL-17, IFN-γ, and TNF-α by schistosome egg antigen-evoked mesenteric lymph node cells. A quantitative analysis of trait loci revealed a number of genetic intervals governing immunopathology along with IL-17 and IFN-γ production. Egg granuloma size was found to have a significant linkage to the dominantly inherited loci; D4Mit203 and D17Mit82. Moreover, these genetic loci were found to have a decisive effect on the development of immunopathology in murine as evidenced by the significantly reduced hepatic granulomatous inflammation and IL-17 synthesis in interval-specific congenic mice [33]. It is likely due to these genetic differences that a minority of infected persons tends to show the severe form of schistosomiasis with hepatosplenic involvement and hypersplenism.

12.2. Epidemiology of schistosomiasis-associated anemia

In addition to hookworm anemia, anemia in schistosomiasis poses an important public health problem, particularly for those tropical countries in Africa where schistosomiasis is endemic and a strong correlation is found between it and anemia.

12.3. Pathophysiology and manifestations of schistosomiasis-associated anemia

Schistosomiasis or bilharziasis is a group of helminthic infestations that are brought about by blood flatworms of the Schistosoma genus. The pathology of schistosomiasis is typically evoked by ova trapped in the tissues, where the activation of CD4 T cell-mediated immunity results in granulomatous inflammation. Three important forms of schistosomiasis have been described: intestinal, urinary, and hepatic. The former two forms of schistosomiasis are the two common forms relating to anemia. It has been noted that there are several negative effects of the mentioned two forms of schistosomiasis on the coming nutritional parameters in humans [25]:

1. Urinary and fecal blood and iron loss
2. Anemia and hemoglobin levels
3. Proteinuria
4. Child growth and adult protein-energy status
5. Physical fitness and physical activity

It is well known that schistosomiasis can cause iron deficiency anemia by direct blood loss in case of urinary and gastrointestinal schistosomiasis through urine and stools [34]. Interestingly, the hemoglobin level and the hematocrit were found to be inversely related to egg count, in contrary to the prevalence of anemia which tends to increase with increasing egg count [35]. There for it is concluded that this negative association between the degree of infection by *S. haematobium* and iron status showed a deleterious consequence of urinary schistosomiasis on nutrition and hematopoietic status, a thing that should be put in consideration when designing nutrition intervention programs [35]. Other explanations for the anemia associated with schistosomiasis are the anemia of inflammation and the presence of coinfection with other parasites such as hook worm [36, 37].

12.4. Schistosomiasis-related anemia: diagnosis and management

The diagnosis of anemia in schistosomiasis needs evidence of coexistence of both anemia validated by the measurement of hemoglobin and blood fluke infestation by stool or urinary examination for detection of blood fluke ova. Nevertheless, great care should be taken because not all cases with both anemia and blood fluke infestation can be attributed to blood fluke infestation as anemia can be a common copresentation with helminthic infestation in tropical countries. Other etiologies for iron deficiency anemia, particularly hookworm infestation, should be evaluated. Undoubtedly, the coinfestation between hookworm and blood fluke is reported to coexist in the tropics. Compared to hookworm anemia, treatment of anemia in schistosomiasis is usually started with an antihelminthic drug. It has been found that a blanket coverage of a single-dose anthelminthic treatment covering the at-risk population like school children in the endemic areas achieved hematological benefits among most of the children with *S. haematobium* infestation [38]. Such a recommendation is yet waiting establishment in the case of pregnant women [39]. The drug of choice for treatment of schistosomiasis infection is praziquantel (40 mg/kg), similar to other fluke infestations. Moreover, the nutritional supplementation therapy should be similar to hookworm anemia. Nevertheless, as praziquantel does not reduce the hookworm intensity of infection, which is another major cause of anemia in the endemic area, alterations in the prevalence of anemia among the population should be due only to the elimination of *Schistosoma* species infestation. Accordingly, in the area with high prevalence of mixed infection of hookworms and blood flukes, combined antihelminthic drugs for both infestations are advised. It has been found by Friis et al. that the combination of multi-micronutrient fortification and anthelminthic treatment independently raised the hemoglobin. The treatment effect was thought to be due to decrement in *S. mansoni* and hookworm load of infection [40]. However, meta-analysis on this issue did not support their findings, but rather suggested further research on the subject [41]. It has

been noted that in areas with schistosomiasis and hookworm infestations, combination treatment with praziquantel and albendazole, plus iron supplementation, is likely to promote good population health and improve hemoglobin levels.

12.5. Schistosomiasis-related anemia: prevention

It is advisable to implement community-level treatment and control of schistosomiasis in endemic areas where protein-energy malnutrition and anemia frequently coexist where such strategies will likely improve child growth, appetite, physical fitness, and activity levels and decrease anemia and symptoms of the infestation [42]. Therefore, screening and early management of identified cases are the best means to prevent schistosomiasis-associated anemia. The development of vaccines will give the solution to this dilemma [43].

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