

Pathogenesis of anaemia and its relationship with hepato-splenomegaly in African animal trypanosomosis: A review

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ABSTRACT: Anaemia is a consistent finding in acute and chronic trypanosomosis and a major contributor to morbidity and mortality in African animal trypanosomosis (AAT). The pathogenesis of anaemia in AAT is both complex, multifaceted and not completely delineated. Some possible patho-mechanisms are popular, including an increase in erythrocyte fragility occasioned by TNF- α from activated macrophages, haemolysis caused by free radicals, and parasite-derived products that cause alterations of red blood cells, predisposing them to erythrophagocytosis. Beyond these, the acquisition of iron from the host by trypanosomes, iron sequestration in the host's liver and spleen, and RBC sequestration in the enlarged liver and spleen were found to possibly contribute to lowered haematocrit in AAT. The review made special reference to *Trypanosoma brucei brucei* and *Trypanosoma congolense*. While the various aetiologies of anaemia are well explained, the beneficial effects of iron sequestration in the liver and spleen and in other cells of the mononuclear phagocytic system require further studies.

Keywords: Erythrophagocytosis, haemolysis, haemosiderosis, parasitaemia, *Trypanosoma brucei*, *Trypanosoma congolense*.

INTRODUCTION

African animal trypanosomosis is a disease primarily caused by the protozoan parasites *Trypanosoma congolense*, *T. vivax*, and *T. brucei brucei* (Kuriakose et al., 2019; Anyogu et al., 2020). The disease is endemic in sub-Saharan Africa, where it has a severe economic impact on livestock production and farming. The disease presents as a mild condition in wild animals but can be fatal in domestic animals if left untreated (Shemsia, 2019). *Trypanosoma brucei brucei* is known to be tissue-invasive, causing inflammatory reactions in the interstitium of various visceral organs with degeneration and necrosis of affected organs (Anyogu et al., 2022; 2023; Obi et al., 2023b). *Trypanosoma congolense*, on the other hand, is the most important African trypanosome and causes

debilitating acute and chronic disease in cattle and other domestic animals (Kuriakose et al., 2019; Obi et al., 2023a). The parasites are extracellular but intravascular, constantly exposed to the host's immune system (Kuriakose et al., 2019).

Trypanosomosis has a significant impact on African agriculture, reducing milk output, live animal output, and the efficiency of animals used for cultivation. In susceptible cattle breeds, the disease can reduce calving by up to 20%, leading to the death of young stock, and reduce meat and milk outputs by at least 50% (Wada et al., 2020). In sheep, the disease causes anaemia, emaciation, and reduced reproductive performance (Malatji, 2022).

Anaemia is regarded as the most significant clinicopatho-

logic finding in AAT and contributes immensely to morbidity and mortality in trypanosomosis (Anyogu *et al.*, 2022; Obi *et al.*, 2023b; Bello *et al.*, 2025). The mechanism or pathophysiology of anaemia in trypanosomosis is complex and multifactorial in origin (Naessens *et al.*, 2005; Bello *et al.*, 2025). Anaemia of trypanosomosis occurs in three phases: phase I (acute), phase II (chronic) and phase III (recovery) (Anosa 1988). The acute phase begins with the initial appearance of trypanosomes in peripheral circulation with parasitaemia usually high, fluctuating and evident on most days (Anosa, 1988; Abenga and Anosa, 2006; Mbaya *et al.*, 2009a, b; 2010; Mbaya *et al.*, 2011). This phase is seen in all hosts, and it is characterised by a sharp drop in erythrocyte count, which also coincides with the activation of myeloid cells (Stijlemans *et al.*, 2018). During this phase, the anaemia is morphologically classified as macrocytic and normochromic (Mbaya *et al.*, 2012). Mortality at this acute phase commonly occurs due to severe pancytopenia and other associated pathologies (Anosa, 1988). Sub-acute cases have been produced experimentally in rodents infected with *T. congolense* (Isoun and Esuroso, 1972) and with *T. brucei* (Mbaya *et al.*, 2010; 2011). The chronic phase follows the acute phase and is characterised by low levels of parasitaemia (Mbaya *et al.*, 2012). With the *T. brucei* infection, which mostly involves tissue invasion, there is aparasitaemia as the parasites establish extravascularly and are less numerous in peripheral circulations (Rabo, 1995) or absent (Mbaya *et al.*, 2007; 2009a). The morphological classification of the anaemia in this chronic phase is normocytic and normochromic (Sadique *et al.* 2001; Takeet and Fagbemi, 2009). The recovery phase is characterised by low, infrequent or absent parasitaemia. At this point, declined erythrocyte values begin to return towards pre-infection values, and other pathological changes undergo resolution (Anosa, 1988), leading to self-recovery as commonly encountered in trypanotolerant wildlife (Mbaya *et al.*, 2009a). In a trypanosusceptible host, after the initial attempt to recover, anaemia becomes progressive until death. In the trypanotolerant hosts, however, the decline in erythrocyte count is milder, but eventually progresses to the level of the initial sharp drop (Stijlemans *et al.*, 2018).

The pathomechanism of anaemia development in trypanosomosis is both parasite-and host-dependent, and generally leads to haemolysis, haemodilution and dyserythropoiesis (Katunguka-Rwakishaya *et al.* 1992). It has also been observed that following the acute stage of anaemia, there is an attempt to recover by the host through reduction in pro-inflammatory response mediated by interleukin IL-10 as well as an increase in extramedullary erythropoiesis, and this coincides with the occurrence of hepatosplenomegaly (Anosa and Kaneko 1984; Stijlemans *et al.* 2010; Stijlemans *et al.* 2018).

The development of anaemia in AAT involves immune system activation and inflammatory responses to the parasites. However, there may be additional contributors

that might have been overlooked, yet are significant in either undermining erythropoiesis or promoting haemolysis of the red blood cells during trypanosome infections. Hence, the present review is aimed at elucidating the pathogenesis of anaemia in AAT and to properly connect the lines between anaemia and hepatosplenomegaly in *T. brucei* and *T. congolense* infections.

MATERIALS AND METHODS

Literature search

The study was based on the data obtained from our previous research, published and unpublished, as well as from a systematic search of “Google Scholar”, “PubMed”, “ResearchGate” and “African Journal Online.” The databases were diligently searched to avoid replication of identical review articles. The Subject Headings and Boolean Searching Operators used were tailored to specifically cover pathogenesis of anaemia, trypanosomosis or trypanosomiasis, oxidative stress, splenomegaly and hepatomegaly, and the information extracted were as they related to African animal trypanosomosis, either in the natural hosts or rodent models of the disease. Articles were eligible for review when they: (i) contained data on the haematology focusing on anaemia in African animal trypanosomosis with special reference to anaemia in AAT or rodent models and lines of connection between anaemia and hepatosplenomegaly in *T. brucei* and *T. congolense* infections, (ii) were published between 1972 and 2025.

Data extraction

Data such as the first author, year of publication, animal species used as research model, species of Trypanosome used and haematological procedures employed were collated in the selected articles. Articles for which the haematology, with special emphasis on the mechanism of anaemia, was not properly discussed were excluded (Figure 1).

RESULTS AND DISCUSSION

Increased osmotic fragility of red blood cells

It was demonstrated that, in comparison to RBCs from non-infected mice, RBCs from infected mice by day 6 post-infection displayed increased osmotic fragility and an altered fatty acid membrane composition (Cnops *et al.*, 2015). The increased RBC fragility was reported to have arisen from host-derived factors like TNF- α generated by activated (M1) macrophages rather than IFN- γ (Nok and Balogun 2003; Coustou *et al.*, 2012; Balogun *et al.*, 2014;

Identification of studies on pathogenesis of anaemia in African animal trypanosomosis via databases

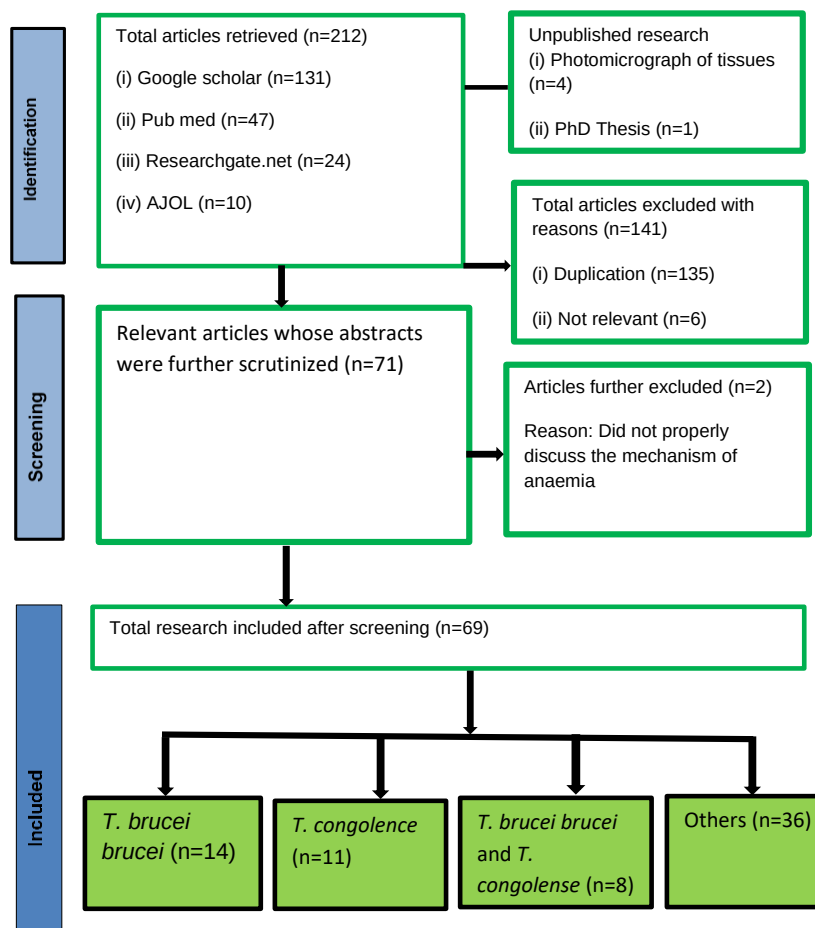


Figure 1. Flow diagram summarising the process of literature search and article selection. Others: Other Trypanosome species and studies on anaemia.

Szempruch *et al.*, 2016). TNF- α may therefore be the cause of the observed alterations in RBC fragility because it has been demonstrated to shorten the half-life of RBCs, which in turn promotes RBC senescence and elimination (Moldawer *et al.*, 1989). Furthermore, in TNF- α knock-off mice infected with *Trypanosoma brucei*, acute anaemia was greatly reduced compared to TNF- α -intact-*Trypanosoma brucei*-infected mice, further substantiating the role of TNF- α in acute anaemia of trypanosomosis (Stijlemans *et al.*, 2018). The erythrocyte count in the TNF- α -deficient mice remained progressively elevated. However, *Trypanosoma congolense* infected mice, which were also TNF- α -deficient, did not experience any beneficial effect on acute anaemia; instead, both acute and chronic anaemia were observed (Naessens *et al.*, 2005; Magez *et al.*, 2007). This suggests that although *T. brucei brucei* and *T. congolense* cause both acute and chronic anaemia in AAT, depending on the hosts' susceptibility, the patho-mechanisms of anaemia development and its severity are different.

Free radicals-induced haemolysis

The mechanism of anaemia in trypanosomosis is greatly associated with the generation of free radicals and superoxides following lipid peroxidation (Mbaya *et al.*, 2012). Infection with trypanosome has been reported to result in increased production of reactive oxygen species (ROS), which act as cytotoxic agents, playing a significant role in the pathophysiology of trypanosomosis (Paiva *et al.*, 2018; Banwo *et al.*, 2024). Generally, these oxidative products attack the cellular integrity of erythrocytes in trypanosomosis (Anosa and Kaneko, 1983; Igbokwe *et al.*, 1994; Umar *et al.*, 2007). They particularly attack erythrocyte membrane proteins and polyunsaturated fatty acids (Slater, 1984) or red blood cells directly, leading to oxidative haemolysis (Ameh, 1984; Igbokwe *et al.*, 1988; Umar *et al.*, 2007).

Besides TNF- α production by activated myeloid cells, nitric oxide (NO), which is a free radical, was also found to be an important factor in the development of *T. brucei*-

associated acute anaemia. Because red blood cells (RBCs) contain significant levels of oxygen and haemoglobin, as well as polyunsaturated fatty acids (in the membrane), they are especially vulnerable to oxidative damage (Aguirre *et al.*, 1998). These factors may contribute to haemolysis and consequent anaemia in animals (Harvey, 1997). Rats with acute trypanosomosis caused by *T. brucei* have demonstrated that lipid peroxidation in the erythrocyte membrane plays a significant role in the pathophysiology of anaemia in parasite infections (Igbokwe *et al.*, 1994). Acute anaemia was also relieved in mice treated with nitric oxide inhibitors, and this coincided with a reduction in parasitaemia as well as increased erythropoiesis, shown by an elevated number of immature red blood cells in the circulation (Mabbott and Sternberg, 1995; Mabbott *et al.*, 1998). In another study, treatment of mice with corticosteroids, which inhibit nitric oxide synthesis, was reported to alleviate the development of acute anaemia (Balber 1974).

It appears trypanosomes majorly target macrophages (Grosskinsky *et al.*, 1983). In *T. brucei*-infected mice, it was shown that tumour necrosis factor alpha (TNF- α), gamma interferon (IFN- γ), interleukin-1beta (IL-1B) and IL-6 from activated macrophages mediate the production of free radicals such as nitric oxide (NO), superoxide anion (O₂⁻) and O₂⁻-derived hydrogen peroxide (H₂O₂) in response to parasite antigens (Grosskinsky *et al.*, 1983; Gobert *et al.*, 1998; Paulnock and Collier, 2001; Nyakundi *et al.*, 2002).

Free radicals have been reported to act as cytotoxic agents (Gutteridge, 1995). The erythrocyte, due to its role as an O₂ and CO₂ transporter, is under constant exposure to free radicals (Harvey, 1997). However, red cells have a potent antioxidant protection that modifies free radicals into substantially less reactive intermediates (Çimen, 2008). The RBC antioxidant system primarily consists of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), GSH-peroxidase, and the antioxidant vitamins A, E and C (Kurata *et al.*, 1993). Disturbed antioxidant defences were reported in tissues of rats and sheep experimentally infected with *T. brucei* or *T. congolense* (Ameh, 1984; Igbokwe *et al.*, 1998; Anyogu *et al.*, 2023), and the combined administration of antioxidant vitamins ameliorates anaemia and organ damage during *T. brucei* infection of rats (Umar *et al.*, 2007).

Parasite-derived factors that promote erythrophagocytosis

Parasite-derived factors such as sialidases in the case of *T. congolense* or extracellular vesicles (EVs) in the case of *T. brucei* infections could contribute to modifications of RBCs and thereby promote their elimination (Nok and Balogun 2003; Coustou *et al.*, 2012; Balogun *et al.*, 2014; Szempruch *et al.*, 2016). In addition, in both mouse and

bovine models, *T. congolense*, congopain and sialidases may either directly or indirectly contribute to the development of anaemia by causing damage to red blood cells, which exposes phosphatidylserine on the RBC membrane, a target that promotes erythrophagocytosis. (Bratosin *et al.*, 1998; Authié *et al.*, 2001; Coustou *et al.*, 2012). The occurrence of anaemia in trypanosomosis due to erythrophagocytosis associated with the formation of antigen-antibody complexes with sialic acids had also been reported (Audu *et al.*, 1999; Mbaya *et al.*, 2012).

Dyshaemopoiesis as a mechanism of anaemia development

Dyshaematopoiesis -specifically dyserythropoiesis which refers to the defective development of erythrocytes causes anaemia through two main mechanisms, viz: (i) ineffective erythropoiesis where the red blood cell precursors produced by the bone marrow are defective and are destroyed before they can even leave the bone marrow, and (ii) morphological abnormalities where the red blood cells that manage to enter the bloodstream are often mishappen, fragile, or lysed. The role of dyshaemopoiesis in the pathogenesis of anaemia has been reported in *T. congolense* infection in cattle (Valli *et al.*, 1978); *T. vivax* infection in calves (Logan *et al.*, 1991); *T. congolense* infection in sheep (Katunguka-Rwakishaya *et al.*, 1992); in *T. congolense* infection in multimammate rats (Ojok and Kaeufer-Weiss, 2001) and in goats challenged with *T. brucei* (Biryomumaisho and Katunguka-Rwakishaya, 2007).

In the experimental *T. congolense* TREU 112 infection in Holstein calves reported by Valli *et al.* (1978), the anaemia was of moderate severity, haemolytic and as was shown by a sharply decreased myeloid: erythroid ratio, regenerative, macrocytic and normochromic in the acute phase, changing to normocytic normochromic with chronicity. Logan *et al.* (1991) reported observation of erythroid hyperplasia, evidenced by a decrease in the myeloid: erythroid (M:E) ratio, in *T. vivax* infection of calves. In the sheep infected with *T. congolense*, erythropoiesis was enhanced but did not sufficiently compensate for the accelerated destruction of erythrocytes, and the anaemia could be attributed to increased destruction of erythrocytes since there was no evidence of dyshaemopoiesis (Katunguka-Rwakishaya *et al.*, 1992). Ojok and Kaeufer-Weiss (2001), in addition to reporting regenerative anaemia, observed a reduced erythropoietic activity and increased intra and extravascular erythrophagocytic activity in the chronic stages of *T. congolense* infection in multimammate rats. In goats challenged with *T. brucei*, haemolytic and regenerative anaemia with decreased M:E ratio was observed (Biryomumaisho and Katunguka-Rwakishaya, 2007).

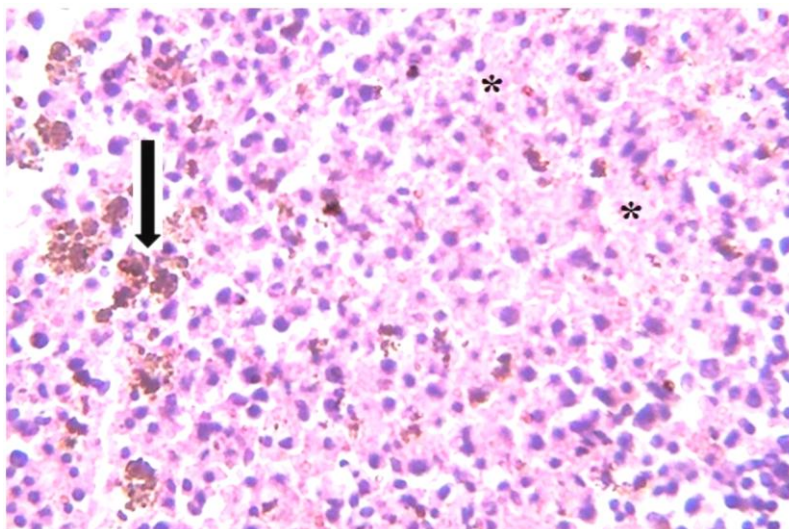


Figure 2. Splenic tissue of West African dwarf ram chronically infected with *Trypanosoma brucei brucei*. Note massive deposits of hemosiderin pigment (arrow) in the red pulp with moderate sequestration of red blood cells (asterisks). H & E stains, x400 (Anyogu, 2021).

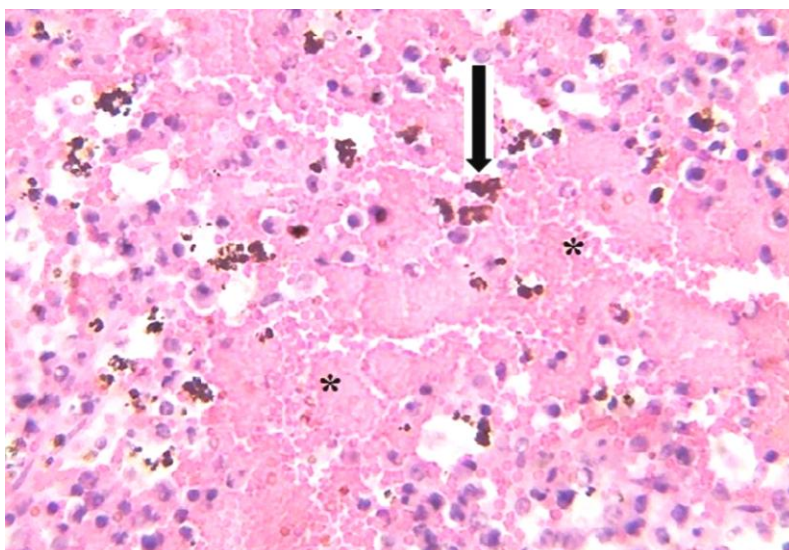


Figure 3. Splenic tissue of West African dwarf ram chronically infected with *Trypanosoma congolense*. Note massive sequestration of red blood cells (asterisks) and large deposits of hemosiderin pigment (arrow). H & E stains, x400 (Anyogu, 2021).

Iron sequestration in trypanosomes and in the host's liver and spleen influences erythropoiesis

Heme oxygenase is lacking in trypanosomes, and their iron requirements are satisfied through uptake of heme-containing proteins (Mach and Sutak, 2020). Trypanosomes are also unable to synthesise heme *de novo*, hence, completely dependent on the host (Tripodi *et al.*, 2011). However, iron is a nutrient element that is strictly regulated in the mammalian blood, lymph and secretions

by chelating molecules that limit their bioavailability (Kariuki *et al.*, 2019). This enables the host to minimise parasitaemia, such that immunocompetence in the face of trypanosome infection might be related to better iron regulation (Nairz *et al.*, 2018).

In the spleens of trypanotolerant West African dwarf sheep chronically infected with *Trypanosoma brucei brucei* (Figure 2) or *Trypanosoma congolense* (Figure 3), a massive sequestration of RBCs in the red pulp was found with severe haemosiderosis. While in the spleen of dogs,

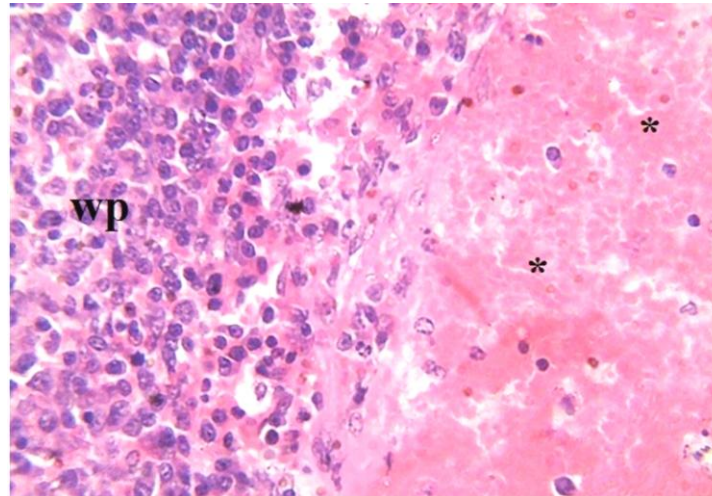


Figure 4. Splenic tissue of dog sub-acutely infected with *Trypanosoma brucei* showing massive sequestration of red blood cells (asterisks) in the red pulp. Wp = white pulp. H&E stain, x400 (Obi, 2021).

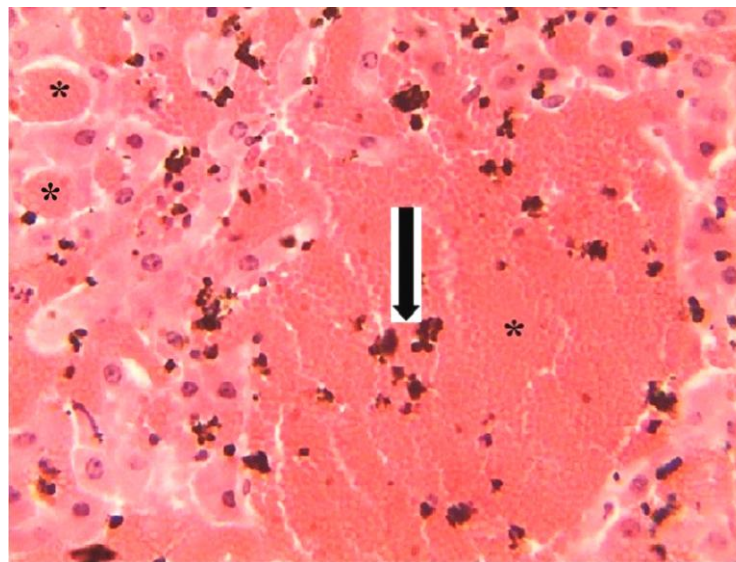


Figure 5. Liver tissue of West African dwarf sheep infected with *Trypanosoma brucei brucei* for 11 months, showing very massive sequestration of red blood cells in the sinusoids (asterisks) and large deposits of hemosiderin pigment (arrow). H&E stain, x400 (Anyogu, 2021).

which are trypanosusceptible, RBCs sequestration was massive in the red pulp, but haemosiderosis was mild (Figure 4). This may be why trypanotolerant hosts are better at controlling parasitaemia, possibly by iron sequestration in the reticuloendothelial tissues. However, the benefits of iron sequestration in the liver and spleen in relation to controlling acute and chronic anaemia in the trypanotolerant hosts are arguable, as iron is essential for erythropoiesis. Nonetheless, the parasites effectively compete against the host's chelates in acquiring iron through trypanosomal transferrin receptors (Wilson and Britigan, 1998).

Hepato-splenomegaly and anaemia

Erythropoiesis primarily takes place in the bone marrow. However, in severe anaemia where the bone marrow alone cannot compensate, extra-medullary haematopoiesis may occur in both the liver and spleen (Kazazian *et al.*, 1974; Cheng and Kazazian, 1976). The possible occurrence of extramedullary erythropoiesis in AAT might contribute to hepatosplenomegaly and RBCs sequestration in the liver and spleen (Figures 2-4). The degradation of red blood cells by activated phagocytes is usually massive in the liver and spleen. In a WAD sheep infected with *T. brucei brucei*

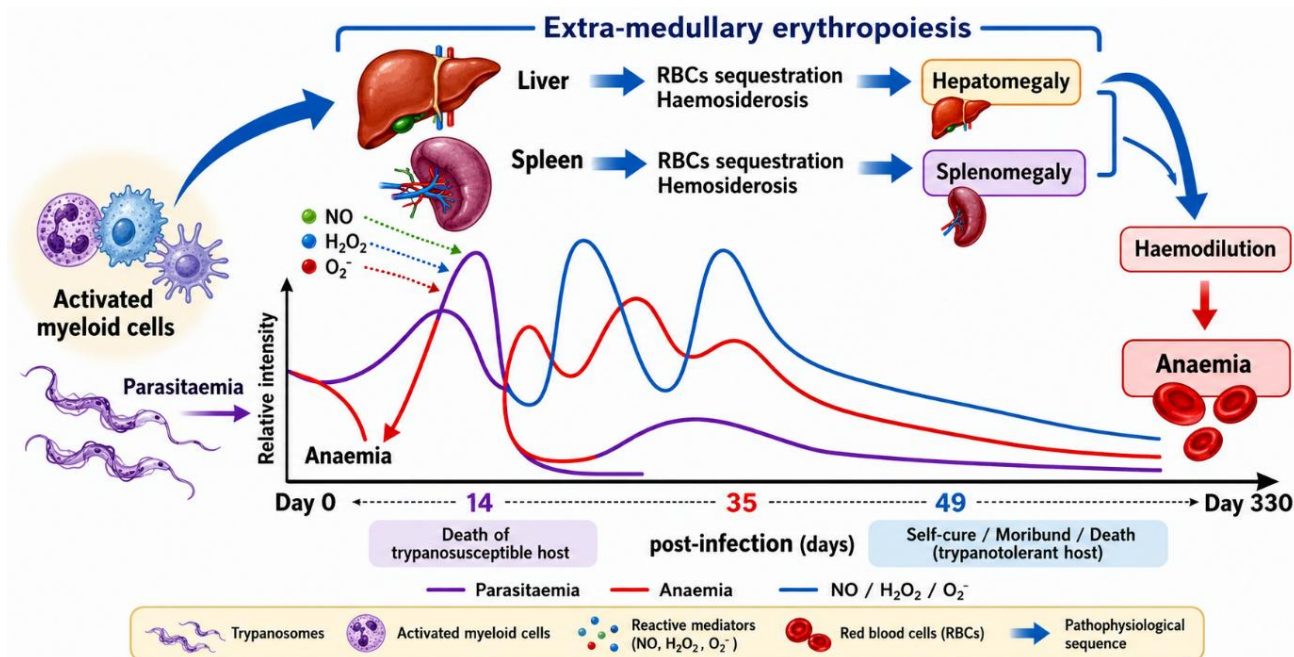


Figure 6. Schematic diagram showing anaemia resulting from parasitaemia and activation of the myeloid cells leading to free radical generation causing haemolysis, erythrophagocytosis, and death of host or an attempt to recover from anaemia through myeloid response to parasitaemia and extramedullary erythropoiesis leading to hepatosplenomegaly, which in turn contributes to haemodilution and chronic anaemia seen in trypanotolerant hosts (Anyogu, 2021).

for 11 months, the liver looked like a bag of blood due to RBCs sequestration in the sinusoids (Figure 5). This extensive destruction of erythrocytes might affect free haemoglobin uptake by haptoglobin and decrease iron export from the liver. There might not be enough ferritin for iron storage; hence, iron is removed from the circulation by deposition in the form of insoluble haemosiderin, as seen in the liver and spleen. This might reduce iron availability for erythropoiesis. It is noteworthy to mention that severe erythrophagocytosis occurs in the bone marrow and might significantly contribute to anaemia in AAT; however, the patho- mechanisms are outside the focus of this review.

Hepatosplenomegaly may contribute to a drop in venous haematocrit (Amole *et al.*, 1982), possibly through haemodilution (Figure 6). Amole *et al.* (1982) also reported that during the acute phase of *T. brucei* infection in mice, IgM sensitisation by immune complexes, together with splenomegaly and hepatomegaly, causes waves of anaemia which coincide with parasitological crises. The mechanism is not well understood, but it is thought to be through an increase in portal venous pressure, an increase in vascular space and a decrease in renal perfusion pressure, triggering the renin-angiotensin-aldosterone system that ultimately leads to increased salt and water retention and expansion of the extravascular fluid and plasma volume (Anderson *et al.*, 1976; Hess *et al.*, 1976). Secondly, it was posited that sequestration of the red cells in the spleen and liver may decrease the number of red cells in circulation, as sequestered red cells exchange slowly with the circulating red cells (Hess *et al.*, 1976).

CONCLUSION

Data from the literature show that both parasite-derived factors and hosts' responses contribute to anaemia in AAT. The pathogenesis of anaemia in trypanosomosis stems mainly from extravascular haemolysis in the expanded active mononuclear phagocytic system (MPS) of the host. The result of the extensive haemolysis is a drastic reduction of all the erythrocytic indices during successive waves of parasitaemia. The complex and multifactorial nature of the mechanism of anaemia in trypanosomosis compromises primarily the cellular integrity of erythrocytes, leading to either haemolytic anaemia or enhanced erythrophagocytosis. Furthermore, Trypanosomes flagella-inflicted injuries on the red blood cell (RBC) membranes, as well as the microtubule-reinforced body of the organisms, greatly enhance the erythrophagocytosis of damaged RBC by the MPS. In the same vein, the RBCs, reticulocytes and platelets that adhered to trypanosomes via sialic acid receptors caused injuries to the membrane of the RBCs at the point of contact. Undulating pyrexia, trypanosome autolysates, oxidative stress, lipid peroxidation, immunochemical reactions, disseminated intravascular coagulation, dyserythropoiesis, tumour necrosis factors (TNF), and bone marrow nitric oxide (NO) activity are among the factors that promote haemolytic anaemia in trypanosomosis. The pattern of anaemia varied, depending on whether the species of trypanosome was "humoral" or "haemic". While various aetiologies of anaemia are well explained, the

beneficial effects of iron sequestration in the liver and spleen and in other cells of the MPS require further studies. There are evidences that iron supplementation may be beneficial in both reducing oxidative stress and relieving anaemia in trypanosome-infected animals. However, this might be very minimal and may vary from host to host and with the species of trypanosomes involved. Hepatosplenomegaly may contribute to a drop in venous haematocrit, possibly through haemodilution, and IgM sensitisation by immune complexes, together with splenomegaly and hepatomegaly, causes waves of anaemia which coincide with parasitological crises.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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