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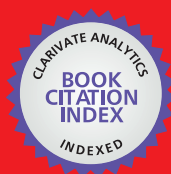
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# Bovine Tropical Theileriosis: An Update

*Arvind Kumar Tripathi and Manu Jaiswal*

## Abstract

Tick-borne diseases (TBDs) cause major economic losses and affect many domestic animals, mainly cattle and sheep, in tropical and subtropical regions. Tropical theileriosis is a TBD caused by a protozoon called *Theileria annulata* transmitted by several tick species of the genus *Hyalomma*. Clinical manifestations of theileriosis are expressed mainly as anorexia, febrile generalized lymphadenitis and anemia followed by lethargy, lacrimation, nasal discharge and exophthalmia. Anemia is a feature point in tropical bovine theileriosis and severity was positively related to parasitaemia rates. Fatality due to infection is greatly dependent on the overproduction of cytokines, such as TNF- $\alpha$  produced by the schizont-infected monocytes/macrophages and uninfected macrophages. Buparvaquone gave 86.66% clinical efficacy against *Theileria annulata*, but 97.1% and 95.2% efficacy against *Theileria parva*. In Theileriosis, hemolysis occurs due to isoantibody to RBC. To prevent this isoantibody lysis, immunosuppressive dose of steroid such as Dexamethasone@2.2 mg/kg.b.wt could be used.

**Keywords:** anorexia, exophthalmia, TNF-A, buparvaquone, macrophages

## 1. Introduction

Tick-borne diseases (TBDs) are major economic concern to livestock, affects many domestic animals, mainly cattle and sheep in the tropical and subtropical regions of the world. Tropical theileriosis, one of the most important TBD caused by a protozoon parasite known as *Theileria annulata*, transmitted by several tick species of the genus *Hyalomma* [1]. Bovine theileriosis, considered as serious problem for livestock in tropical countries affecting millions of animals, especially crossbreed and exotic cattle. In India only *Theileria annulata* is responsible for the majority of theileriosis cases, as there are no reports of *T. parva* till now from the country [2]. *T. Annulata*, a bovine-specific pathogen, causes tropical theileriosis in tropical and subtropical countries of Asia (India, China), Africa (Egypt, Sudan), Middle East, Europe (Portugal) [3, 4]. It leads to high mortality, decreased productivity and draught power in infected animals and hence considered a serious challenge to the livestock improvement programme in these countries. In India economic losses due to blood parasitic diseases in livestock causes estimated losses of USD 498.7 million per annum, among it bovine tropical theileriosis alone caused the loss of USD 384.3 million per annum [5].

## 2. Etio-pathogenesis

*T. annulata* sporozoites transmitted by tick *Hyalomma anatolicum* in the host and causes a lymphoproliferation in the adjacent lymph nodes and causes a disease similar to cancer [6, 7]. Due to an intracellular parasite changes biochemical signaling pathways of the affected cells to ensure its presence in the host cell and transforming lymphoblast and monoblast cells after infecting B-cells and other monocytes cells. After the transformation of the cells by *Theileria* parasite they act like cancer cells and consume a lot of glucose [8]. Anorexia is associated with other symptoms such as hyperthermia, lymph node enlargement, anemia, icterus and haemoglobinuria during subsequent evolution of the disease in cows [9].

Haemolytic anemia syndrome is a specific clinical sign of tropical theileriosis. Icterus is seen in the early stages of tropical theileriosis and haemoglobinuria appears towards the final phases of the disease. *T. annulata* merozoites causes haemolysis, so excretion of hemoglobin in urines [10]. Some non-specific symptoms are frequently reported like hyperthermia and lymph node enlargement, because reinfection with a new genotype of the parasite causes relapse of tropical theileriosis or induces a transient superficial lymph node enlargement.

Exophthalmia is one of the emerging clinical manifestation of tropical theileriosis in cow calves and it may be considered a clinical diagnostic marker [11]. Cells infected with *Theileria annulata* produce high levels of inflammatory cytokines, especially TNF- $\alpha$  [12]. The cytokines are potent inducer of majority of clinical symptoms of acute tropical theileriosis such as pyrexia, anemia, anorexia, muscle wasting and necrosis [13]. The activated lymphocytes secretes several cytokines including TNF- $\alpha$ , interleukin-1 and interferon-gamma (IFN- $\gamma$ ) [14]. The clinical manifestation of exophthalmia is hypothesized that there is systemic overproduction of TNF- $\alpha$  or overproduction of TNF- $\alpha$  in the extra-ocular muscle by the parasitized lymphocytes may be accountable for and the increase in intraocular pressure which results into the clinical manifestation of exophthalmia is also possible in diseased calves. *Theileria annulata* schizont infected cells play a direct role in the failure of protective immune responses as infected cells possess a powerful method of immune evasion [15]. However, the role of anti-inflammatory/immunosuppressive cytokines (IL-10 and TGF- $\beta$ ) in the pathology of tropical calf theileriosis and the host-parasite interplay is not well explored.

Due to an immune-mediated erythrophagocytosis, anemia occurs in the later stages of disease following parasitaemia and also responsible for the erythrocyte destruction [16]. The piroplasm infected erythrocytes are removal of by the macrophages in the organs of the reticulo-endothelial system also have the cause of anemia [17].

In addition, TNF- $\alpha$ , a pro-inflammatory cytokines have been implicated in mediating anemia in tropical Theileriosis [13]. Erythrocytes may be destroyed by erythrophagocytosis, oxygen radicals may also be involved in the pathogenesis of the anemia [18].

Schizont-infected cells disseminate through the lymphoid tissues into pituitary and thyroid glands and cause injury [19]. The cattle suffering from theileriosis had significantly lower concentrations of zinc and selenium as compared to healthy controls and additionally. The cattle suffering from theileriosis possess lower concentrations of serum T3 and T4 [20, 21].

### 3. Diagnosis

In acute cases of theileriosis, diagnosis is mainly relied upon clinical symptoms and microscopic examination of thin blood smears. But only a few number of RBC infected, that causing difficulty in the demonstration of parasite in blood smear, so the affected cattle becomes long standing carriers [22]. Such long standing carriers act as the major contributors of infection through the ticks and when these carrier cattles are transported to non-endemic areas these causes a disease outbreak [23]. Hence, detection of piroplasms in carrier animals becomes more challenging. False negative results and has low sensitivity of blood smear method is also associated with in detecting the carrier cattle [22].

So, molecular diagnostic tests like polymerase chain reaction (PCR) has paved way to efficient diagnosis than the conventional techniques [24]. On the basis of various studies performed on a wide range of parasites it has been concluded that PCR is more sensitive than the conventional techniques [25].

For effective detection of Theileria infections in carrier animals, few molecular diagnosis-based assays have also been developed with proven efficacy. A reverse line blotting (RLB) assay based on the amplification of the hyper-variable V4 region of the 18S rDNA gene of Theileria (and of closely-related Babesia parasites) and reverse hybridization of the products with species-specific oligonucleotide probes is most sensitive test for detecting *T. annulata* [26]. Nevertheless, since RLB is a relatively cumbersome assay, it is not entirely suitable for use in the routine diagnosis of Theileria infections. Some PCR-based assays have also been described for detecting *T. annulata* [27].

### 4. Clinical pathology

Along which destruct of the RBC, lower hemoglobin, PCV, and TEC values observed in animals infected with Theileria due to the toxic metabolites of *Theileria spp.* [28]. Continuous loss of blood by blood-sucking ticks is also an important factor. Due to leukocytosis, the higher values of total leucocyte counts occurs [29]. Destruction of lymphocytes in lymphoid organs and the infiltration of these cells into various organs causes lymphocytopenia [30]. Neutrophilia observed in theileriosis-infected cattle due to the release of endogenous corticosteroid in acute disease or stress or inflammation [31]. Due to macrocytic hypochromic anemia in theileriosis infected cattle, value of MCV, MCH, becomes higher.

Total protein and albumin becomes lower due to the harmful effect of toxic metabolites of Theileria which might be, aggravated due to hepatic insufficiency [32]. Hypoglycemia observed may be due to the utilization of glucose by Theileria spp. present in the blood [33].

### 5. Therapeutic aspect

Early treatment is highly effective in the elimination of both piroplasmic and lymphocytic stages of the protozoan parasites from both blood and lymph nodes within 3–4 days post-treatment with a clinical improvement and an eventual 100% cure

rate [34]. However, late stage treatment did eliminate the protozoal parasites from the blood and lymph nodes, it failed to improve the clinical condition of the affected animals, possibly due to irreversible damage to the lungs. Gharbi et al. [35] reported that buparvaquone produces 86.66% clinical efficacy against *Theileria annulata*, but 97.1% and 95.2% efficacy against *Theileria parva* [36]. Bilgic et al. [36] reported that the late treated cases failed to control by the drug buparvaquone due to the production of pulmonary edema.

*T. annulata* hijacks the host immune response to invade and transform leukocytes [37, 38]. Knowledge of the pathogenic mechanisms that underlie tropical theileriosis is scanty but there is evidence that *T. annulata* schizont-infected cells causes failure of a protective immune response.

The failure to achieve the protective immune response by the host in initial stage of infection are due to non-specific lymphocyte multiplication and disrupting antigen recognition effector mechanisms [39]. *T. annulata* schizont-infected cells possess a powerful method of the host-immune evasion. So, the use of adjunct therapeutics agents to neutralize the immunological imbalances and eliminate the parasite from the infected animals. Complex inter-relationships exist among certain micronutrients, immune function and disease resistance in cattle. Many micronutrients have been shown to influence the immune response of animals. Trace minerals play an important role in dairy cow immune system [40], fertility [41] and growth [42]. Nockels et al. [43] reported that trace mineral retention ability reduced in stressed calves. Inclusion of minerals in the diet does not ensure intake or absorption. During diseased conditions dry matter intake is also decreased. Dietary mineral supplements may not be absorbed properly due to interactions with other nutrients. Antagonists in drinking water such as iron can also harm trace mineral absorption from the digestive tract. In newborn calves, the therapeutic efficacy of conventional chemotherapeutics against bovine tropical theileriosis is not much encouraging. Therefore, trace minerals that causes immunomodulation in bovine tropical theileriosis could improve the therapeutic efficacy of anti-Theilerial drugs [44].

The important cause of hemolysis in Theileriosis is formation of isoantibody against RBC [45]. To prevent this isoantibody lysis, immunosuppressive dose of steroid such as Dexamethasone@2.2 mg/kg.b.wt could be used. It also has stimulatory action on bone marrow to immediately release of reservoir RBC to circulation to help animal to pass that life-threatening phase of anemia. Usually animal with low hemoglobin and low RBC die due to lung congestion followed by respiratory failure. There was a reduction in vascular permeability in the animals treated with dexamethasone that prevented them from pulmonary oedema and sudden death [46].

## 6. Conclusions

Tropical theileriosis is a TBD caused by a protozoon called *Theileria annulata* transmitted by several tick species of the genus *Hyalomma* and causes significant economic loss to dairy farmers of tropical and subtropical countries. Clinical manifestations expressed mainly as anorexia, febrile generalized lymphadenitis and anemia, lethargy, lacrimation, nasal discharge and exophthalmia. Fatality due to infection is greatly dependent on the overproduction of cytokines, such as TNF- $\alpha$  produced by the schizont-infected monocytes/macrophages and uninfected macrophages. Buparvaquone is considered as most efficacious drug against *Theileria annulata* infection.

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## **Conflict of interest**

No potential conflict of interest by the authors.

## **Notes/thanks/other declarations**

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