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Rickettsial diseases in animals and humans:Indian scenario

R. SAHU[1*], N. CHAUDHARY[2], S.R. HOTA[3], S. NAYAK[1], J.K. SAHOO[1] AND A.R. SAHU[4]

[1]ICAR-Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh, India
[2] Tata Trust, Mumbai, India
[3]College of Veterinary Science and Animal Husbandry, OUAT, Bhubaneswar, Odisha, India
[4]ICAR-National Research Centre on Pig, Guwahati, Assam, India

**rkvet09@gmail.com*

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ABSTRACT

Rickettsia are obligate intracellular organisms, associated with number of diseases in humans and animals. Although Rickettsial diseases are highly prevalent in India, they are grossly under-reported. These diseases are showing an upward trend in India, with increased reports in the last decade, especially Canine Rickettsiosis and Bovine anaplasmosis in animals, while scrub typhus, endemic typhus, and epidemic typhus are important emerging or re-emerging zoonoses in human being. Regardless of the emerging scenario of Rickettsial diseases, there are a very few systematic studies on epidemiology of these pathogens.

Key words: Anaplasma, Ehrlichia, endemic typhus, epidemic typhus, Rickettsia, scrub typhus

INTRODUCTION

Rickettsia as prokaryotes, are obligate intracellular organisms, classified under Phylum – *Proteobacteria*, Class - *Alphaproteobacteria* and Family - *Rickettsiaceae*. These are included under unculturables as cannot be grown on artificial media. However, these organisms can be grown in embryonated eggs through yolk sac or artificially grown cell culture (Cox 1938; Cicuttin et al., 2015). In size, they are smaller than bacteria, while larger than virus. They contain both DNA and RNA as genetic material and multiply by binary fission. Some important genus under this family, which are important for animals and humans, are *Ehrlichia, Anaplasma, Neorickettsia, Orientia, Rickettsia* (typhus and spotted fever groups).

Coxiella and *Bartonella* were previously placed among Rickettsial pathogens are now placed under separate family. Unlike Rickettsials which require vectors for transmission, *Coxiella* is transmitted principally through aerosol route, although can be maintained and transmitted through tick vectors (Van den Brom et al., 2015). Both *Coxiella* and *Bartonella*, were previously being isolated as other Rickettsials, while can now be isolated by direct inoculation into suitable artificial media (Omsland et al., 2009; Chaudhry et al., 2012). The present study includes important rickettsial diseases of animals and human in India.

RICKETTSIAL DISEASES OF HUMAN AND ANIMALS

Some of the important Rickettsial pathogens causing disease in human and animals are mentioned below:

Ehrlichia

Important species of *Ehrlichia* causing disease in animals and human are *E. canis* (canine rickettsiosis), *E. ewingii* (canine granulocytic ehrlichiosis), *E. ruminatum* (heart water disease in cattle), *E. chaffensis* (human monocytic ehrlichiosis) and *E. muris*. Recently a new species of *Ehrlichia* was reported from haemolymph of Brazilian *Rhipicephalus (Boophilus) microplus* ticks known as *E. mineirensis* (Cabezas-Cruz et al., 2013).

Canine rickettsiosis

This disease is known by several synonyms, viz. canine ehrlichiosis, canine haemorrhagic fever, canine typhus, tropical canine pancytopaenia, canine monocytic ehrlichiosis, etc. Dogs and cats are the two principal hosts to be infected. German shepherd shows a greater susceptibility to this infection. The agent is mainly transmitted by brown dog tick (*Rhipicephalus sanguineus*) (Ferrolho et al., 2016). Besides that, iatrogenic transmission has also been observed, where the agent is reported to be transmitted through blood transfusion from infected canine to healthy ones (CFSPH, 2013). Most of the cases occur during spring and summer period of the year and the disease is widely prevalent in tropical and sub-tropical countries (Dantas-Torres et al., 2018). Based on clinical symptoms, the disease may be classified as acute, chronic or sub-clinical disease (Buhles et al., 1974). The pathogen infects monocytes in peripheral blood and subsequently throughout body (Rikihisa et al., 1992). Thrombocytopenia occurs due to consumption of platelet, immune mediate destruction of platelets, sequestering of platelets, decrease bone marrow production (Sosa-Gutierrez et al., 2013). The pathogen is having zoonotic potential and main cause of Venezuelan human ehrlichiosis (Unver et al., 2001).

The first case was reported at Punjab in India during 1992 (Juyal et al., 1992). Then subsequent cases were reported from Tamil Nadu (Lakshmanan et al., 2007), Punjab (Singla et al., 2011), Haryana and Delhi (Dhankar et al., 2011), Mumabi (Rani et al., 2011), Punjab (Wise and Tarlinton, 2012), West Bengal (Das and Konar, 2013), Assam, Nagaland, Jammu and Kashmir and Uttar Pradesh (Mittal et al., 2017), and Gujarat (Bhadesiya and Rayal, 2015).

Most of the studies conducted in India were performed using microscopic detection of pathogen in blood or buffy coat smears (Lakshmanan et al., 2007; Dhankar et al., 2011; Das and Konar, 2013; Milanjeet et al., 2014), serologic detection using ELISA (Singla et al., 2011; Wise and Tarlinton, 2012; Bhadesiya and Raval, 2017), PCR based assay targeting 16s rRNA gene (Lakshmanan et al., 2007; Milanjeet et al., 2014) or combination of these assays (Lakshmanan et al. 2007; Milanjeet et al., 2014; Mittal et al., 2017). Indirect florescent antibody test (IFAT) is considered as the gold standard for detection of antibodies against *E. canis* (Waner et al., 2000). A number of studies have been conducted in India. But most of the study pertains to a limited geographical area, resulting under-reporting of the disease in India. However, an extensive study has been conducted in dog covering different agro-climatic zone in India (Mittal et al., 2017).

Canine granulocytic ehrlichiosis

Canine granulocytic ehrlichiosis (CGE) is caused by *E. ewingii*, transmitted by vector lone star ticks (*Amblyomma americanum*). As the name mentioned, the agent is observed in the granulocytes especially in neutrophills, whereas canine monocytic ehrlichisos is observed in monocytes. In dog it is associated with polyarthritis, along with non-specific symptoms like fever, vomiting, lethargy, etc. The pathogen is having zoonotic potential and causes similar infection to that of human monocytic ehrlichiosis, especially in immunocompromised individuals (Weese and Fulford, 2010). Scanty reports are available on the pathogen in India (Das and Konar, 2013).

Heart water disease

Heart water disease is also known as Cowdriosis or Nintas. It is caused by *Ehrlichia ruminatum*.The agent was previously known as *Cowdria ruminatum*. The pathogen is transmitted by vector bont long tick (*Ambylomma*) through saliva or regurgitated gut content. It commonly affects cattle, sheep, goat, antelopes, buffalo and more commonly seen in young animals. The disease is more commonly found in exotic breeds while indigenous cattle are highly resistant.

The disease is characterised by accumulation of fluid around heart and lungs of animals due to increased vascular permeability which results in muffled heart sound. On post-mortem examination presence of straw coloured fluid around heart which clots on exposure to air due to high fibrinogen

content. Neurological signs like tremors and head pressing are also observed along with respiratory signs like coughing and nasal discharge. Other clinical signs such as fever and petechiae on mucous membrane may be there. This disease is mainly found in Sub-Saharan Africa and West-Indian Island (Zanzibar, Madagascar, Saotome, Mauritius and Reunion) (OIE, 2009). However, the disease is not reported from India (OIE, 2005).

Human monocytic ehrlichiosis

Human monocytic ehrlichiosis (HME) is caused by *E. chaffensis*, which primarily infects monocytes and macrophages. First human case was reported in 1986 (Maeda et al., 1987). The disease is characterised by non-specific symptoms like fever, headache and myalgia. The agent is principally transmitted by lone star tick (*Amblyomma americanum*). Alternatively, *Ixodes pacificus* and *Dermacentor variabilis* have also been incriminated as vector (Steiert and Gilfoy, 2002; Paddock and Childs, 2003). White tailed deer and dogs are considered as most important reservoir. Besides, the agent has also been reported in opposums, foxes, wolves, raccoons, voles, coyotes, and goats (Dawson et al., 1994a,b; Paddock and Childs, 2003).

As reported by CDC, incidence of HME is increasing since the year of first reporting. Number of cases reported in 2016 was 1377 as compared to 200 in 2000. Most of the cases are reported during summer months due to increased activity of lone star ticks during the period. The disease is mostly prevalent in south-eastern and south-central United States, followed by Eastern Coast extending westward to Texas, and the prevalence rate corresponds to distribution of vector (CDC, 2018). The agent is not reported from India.

E. muris

E. muris has been implicated to cause severe infection in wild mice, most commonly associated with hepatomegaly and splenomegaly. *Haemaphysalis flava* has been implicated as vector associated with transmission of the agent. Although human infections has not been reported so far, the human infections associated with *E. muris* like pathogen has been reported (Castillo et al., 2015; Johnson et al., 2015).

Anaplasma

The important species of *Anaplasma* are *Anaplasma marginale* (bovine anaplasmosis), *A. phagocytophilum* (canine ehrlichiosis), *A. platys* (canine ehrlichiosis), *A. centrale* (cattle), *A. ovis* (Sheep, deer, goat), and *A. caudatum* (cattle). The Anaplasmosis in different species are described here under:

Bovine anaplasmosis

Bovine anaplasmosis is also known as *Gall Sickness* as the organ gall bladder is most commonly affected. *Anaplasma marginale, A. centrale*, and *A. caudatum* are the common agents associated with bovine anaplasmosis. Among cattle, *Bos indicus* is less likely to be infected, due to innate resistance and low tick infestation as compared to *Bos taurus* (Bock et al., 1997; Jonsson et al., 2008). Tropical cattle tick (*Boophilus microplus) is most commonly associated with transmission of the agent, as high prevalence has been reported from the geographical regions, which are endemic to the tick.* Besides, at least 20 different species of tick has been involved in transmission of the agent (Futse et al., 2003; Aubry and Geale, 2011). *A. marginale* is distributed in wide geographical area in tropical and subtropical regions of the New World, Europe, Africa, Asia and Australia (Aubry and Geale, 2011).

Inverse age resistance phenomenon is observed in bovine anaplasmosis, where calves and adults are equally prone to infection, but calves are more resistant to disease as compared to adults. Calves less than one year usually exhibit sub-clinical form, while in 1-2 year aged group the disease is moderately severe, while in older cattle the disease is severe and fatal (Aubry and Geale, 2011). The disease is commonly observed as per-acute or acute form. In per-acute form death occurs within a few hours of appearance of clinical sign. While in acute condition, common clinical manifestations are anaemia, decreased milk production, in-appetence, rapid breathing, brown colouration of urine,

and pale and yellow discolouration of mucous membrane. Abortion is observed in case of pregnant animals. Macrocytic normo-chromic anaemia is one of the persistent clinical features observed, which occurs due to destruction of infected and non-infected erythrocytes due to immune mediated phagocytosis. Indigenous breeds are reported to be resistant compared to exotic breeds (Sharma et al., 2013).

Anaplasmosis is reported to be hyper-endemic in developing countries (Rodríguez et al., 2009; Kumar et al., 2015), especially in tropical and sub-tropical countries (CABI, 2018). In India, bovine anaplasmosis has been reported from several states viz. Karnataka (Muraleedharan et al., 2005), Tamil Nadu (Arunkumar et al., 2013; Velusamy et al., 2014), Kerala (Nair et al., 2013), Haryana (Kumar et al., 2015), Punjab (Sharma et al., 2015). In the recent past, there is increase in reports of bovine anaplasmosis, and the disease is considered to be emerging in India (Kumar et al., 2015). In field settings most of the cases are diagnosed on the basis of microscopy. However due to poor sensitivity of microscopy (~30%), may result in non-detection of clinical cases.

Canine anaplasmosis

Causative agents associated with canine anaplasmosis are *Anaplasma phagocytophillus* and *A. platys*. *Anaplasma phagocytophillus* is associated with canine granulocytic anaplasmosis lameness, which is many times confused with Lyme disease (Dumler et al., 2001). The pathogen is having zoonotic significance, and in humans it is associated with human granulocytic anaplasmosis. Common clinical symptoms are fever, headache, myalgia, chills, loss of appetite, cough, and diarrhoea (Bakken and Dumler, 2008). *Ixodes ricinus* is the vector usually involved in transmission of this disease (Stuen et al., 2013).

Anaplasma platys is associated with infectious canine cyclic thrombocytopenia, where the clinical signs are fever, lethargy, anorexia, pale mucous membranes, petechiae and lymphadenomegaly (Matei et al., 2016; Huber et al., 2017).

There are scanty reports, though the pathogen is prevalent in India. In North-Eastern part of India, 4.71% of infection has been detected in dogs due to *A. phagocytophilum*. Rate of infection was higher in case of pet dogs (6.09%) as compared to stray dogs (Borthakur et. al., 2014). Twenty seven cases of *A. platys* have been reported at Indian Veterinary Research Institute poly clinics. The cases reported were in co-infection with *E. canis*, *Babesia gibsoni and B. canis* (Kumar and Varshney, 2007). Besides that *A. platys has* also been reported from Delhi, Maharashtra and Goa (Rani et al., 2011; Wise and Tarlinton, 2012).

Neorickettsia

Important species included under the genus *Neorickettsia* are *N. risticii* (Potomac horse fever), *N. helminthoeca* (Salmon poisoning) and *N. elokominica* (Elokomin fluke fever). The different diseases due to Neorickettsia are described here under:

Potomac horse fever

Potomac Horse Fever is caused by *Neorickettsia risticii*, otherwise known as *Ehrlichia risticii*. The disease is also known as Shasta fever or Equine monocytic ehrlichiosis. As the name indicates, the disease was first recognised in the horses at Potomac River, Washington in 1980 (Whitlock et al., 1984). Freshwater snails act as vector for the pathogen. While, trematodes, *Acanthatrium oregonense* released from the snails are also involved in transmission of disease. Globally the disease is being reported from North and South America, Europe and India (Rikihisa et al., 2005). The disease is mainly observed during July to Septembers and associated with pastures bordering creeks or rivers (Baird and Arroyo, 2013).

The pathogen is often associated with infection of enterocytes of the small and large intestine resulting in acute enterocolitis syndrome, characterised by mild colic, fever and diarrhoea, along with leucopenia and thrombocytopenia. In pregnant mares, the pathogen is often associated with abortion. Rikihisa et al. (2005) reported the disease condition in India however, there is no

literature regarding presence of the pathogen in the country.

Salmon poisoning

Salmon poisoning is caused by *N. helminthoeca* and the principal susceptible host is dog. A classical life cycle of *N. helminthoeca* involves "snail-fish-dog" cycle. Fluke *Nanophyetus salmincola* is the vector involved in this transmission is (Headley et al., 2011). Ingestion of uncooked food acts as source of disease (Millemann and Knapp, 1970). Clinical signs appear 5–7 days after eating infected fish and persist for 7–10 days. In untreated animals case fatality rate can go up to 90%. The pathogen mainly affects the lymphoid tissues and intestines resulting in enlargement of the G.I. lymph follicles, lymph nodes, tonsils, thymus and spleen. Salmon poisoning is endemic in United States of America, British Columbia and Canada (Booth et al., 1984; Rikihisa et al., 2005; Gorham and Foreyt, 2006). So far, there is no report of this disease from India.

Elokomin fluke fever

Elokomin fluke fever is caused by *N. elokominica*, a similar disease to Salmon poisoning, but it involves wide range of host species viz. canids, ferrets, bears and raccoons (The Merck Veterinary Manual, 2016).

Orientia

There are two species of genus *Orientia*, viz. *O. tsutsugamushi* and *O. chuto*. *Orientia tsutsugamushi* is classically associated with scrub typhus, whereas *O. chuto* is being recently isolated in Dubai from an Australian tourist exhibiting symptoms of fever, myalgia, rash and eschar (Izzard et al., 2010; Taylor et al., 2015). Scrub typhus is also known as Rural Typhus, Hairy Mite Fever, Keelani Fever, Japanese Fever and Chigger borne typhus. Globally spread of scrub typhus has been described in terms of tsutsugamushi triangle. The triangle, in west extends up to Pakistan and Afghanistan, in east it extends up to Northern Japan and Far eastern Russia, while in south eastern it extends up to Northern part of Australia (Sharma et al., 2010). Globally around 1 billion population are at risk, while annually around 1 million cases are reported across globe (Sharma et al., 2010).

As the name indicates, 'Tsutsuga' means small and dangerous, and 'Mushi' means creature. Larval stages of Trombiculid mites (*Leptotrombidium deliense* and *L. akamushi*) act as vector for scrub typhus (Kelly et al., 2015). Scrub means a type of vegetation like abandoned plantation, rice field, forest clearing and river bank which acts as mite Island and serves as endemic foci for the vector. Wild rodents acts as natural hosts to Scrub Typhus, which acts as asymptomatic reservoir of the pathogen and helps in establishments of diseases in different foci, as they migrate along with pathogen (Kelly et al., 2015). Most of the cases of scrub typhus occur after July and before February i.e. during monsoon and post-monsoon period, which is associated with increased incidence of rain and exposure to rural people occurs due to harvesting in field during this period. While, increase in incidence during post monsoon period, occurs due to increased scrub vegetation (Tshokey et al., 2016).

Most common characteristic sign associated with scrub typhus is eschar, found at the site of bite, but absence of eschar does not rule out absence of infection. Scrub typhus is associated with non-specific clinical signs, which include fever, headache, myalgia, dry cough, and GI disturbance (Devine, 2003; Peter et al., 2015). While scrub typhus is associated with life threatening complications like renal failure, meningitis, myocarditis, pneumonia, multi organ failure etc. (Peter et al., 2015; Taylor et al., 2015).

In India scrub typhus is most common zoonotic Rickettsial infection. The disease has been reported from almost all the states from India. While scrub typhus is mostly prevalent in Shivalik Ranges i.e. from Himalayan foothills of Kashmir to Assam, Vindhya ranges and Satpura in Central India, and Decan Plateau in Southern India. As per recently published studies, it is one of the most common agent associated with pyrexia of unknown origin cases in India (Kumar et al., 2014a; Sinha et al., 2014; Morch et al., 2017; Giri et al., 2018;

Rawat et al., 2018).

Rickettsia

Rickettsia is one of the important genus under family *Rickettsiaceae*, because of its public health importance. Based on the clinical disease, Rickettsials are classically divided into two groups, Typhus group and Spotted fever group. Important species under Typhus group are *R. typhi* (endemic typhus), *R. prowazekii* (epidemic typhus). While, important species of spotted fever group are *R. rickettsii* (Rocky mountain spotted fever), *R. conorii* (Indian tick typhus), *R. africae* (African tick typhus), *R. akari* (Rickattsial pox), *R. australis* (Queensland tick typhus), and *R. felis* (cat flea rickettsiosis). Some of the above mentioned Rickettsial diseases, important in context to India, are discussed below:

Endemic typhus

Endemic typhus is known by several names, viz. Murine typhus, Urban typhus, Shop typhus, Flea Borne Typhus. Rats of the genus *Rattus rattus, R. norvegicus, R. exulans* act as a natural host but don't show any symptoms. Along with rats, shrews and skunks also act as host. Rat flea (*Xenopsylla cheopis*) and rat louse (*Polyplax spinulosa*) involved in transmission of disease. Besides, *Ctenocephalidis felis* (Cat flea) and *Leptopsylla segnis* (mouse flea) may also act as a vector. Source of infection are inhalation of infected flea faeces, contamination with conjunctiva, swatting of flea while feeding or scratching of the site after bite. Life cycle of the pathogen involves rat-flea-rat, and humans get infected due to accidental exposure (Eisen and Gage, 2012).

The pathogen affects vascular endothelial cells resulting in obliterative thrombo vasculitis and perivascular nodules. The disease is associated with non-specific clinical symptoms viz. fever, headache, and rash on trunk and extremities. However complications are observed in some cases with involvement of liver, kidney, lung, and brain (Peniche Lara et al., 2012). The disease is reported from almost all the countries except Antarctica. However murine typhus is more prevalent in south-east Asian region (Carr et al., 2014; van der Vaart et al., 2014). In India cases are reported from Uttar Pradesh, Karnataka, West Bengal, Andhra Pradesh, Madhya Pradesh, and Kashmir (Rahi et al., 2016; MoHFW, 2016).

Epidemic typhus

Epidemic Typhus is also known as Jail Fever, Urban Fever, Louse-borne Typhus, etc. As the synonym '*Louse borne Typhus*' indicates, human body louse acts as vector for the pathogen, and in winter season along with overcrowding helps in spreading of the disease (Raoult and Houhamdi, 2007). The only animal reported to be the reservoir for the disease is flying squirrel, *Glaucomys volans volans* (Bozeman et al., 1975).

Clinical signs associated with the disease are characterized by fever, myalgia, headache, arthralagia and appearance of characteristic rash, which begins in trunk region, spreading centrifugally. A recrudescent form of disease is observed in epidemic typhus, known as Brill-Zinsser disease, which is a milder form of disease and observed in case of immune-depressed individuals (Green et al., 1990).

In India, epidemic typhus is endemic in Northern part of the country, across Himalayan hills to Kullu valley (MoHFW, 2016). However a very few case reports are available in India, notably from Karnataka (Vivek et al., 2016).

Indian tick typhus

Indian Tick Typhus which is also known as Boutonesee Fever, Israeli Spotted Fever and Mediterranean Spotted Fever. Vector responsible for transmitting the disease is *Riphicephalus sanguineus*. It has a wide host range which includes wild rodents, sheep and goats, non- human primates. Up to 80% of Dogs are found to be serologically positive. But clinical signs are not evident in case of animals.

Clinical signs are observed in case of humans' starts with small red dish shaped ulcer is observed at the site of bite of tick along with localized lymphadenitis, at the site of bite. Fever persists for 5-7 days. Myalgia and arthralgia are also

commonly observed clinical symptoms (Raoult and Rovery, 2007).Complication may occur in some cases, resulting neurological symptoms and multi-organ failure.

In India, the disease has been reported from Haryana, Himachal Pradesh, Maharastra, and Delhi (Padbidri et al., 1984; Mahajan et al., 2007; Chaudhry et al., 2009; Kumar et al., 2014b; Gupta and Singh, 2014; Nigam et al., 2016).

CONCLUSION

In the present analysis it was observed that Rickettsial diseases are showing an upward trend in India, with increased reports in the recent past, especially Canine Rickettsiosis and Bovine anaplasmosis in animals, while scrub typhus, endemic typhus, and epidemic typhus are important emerging or re-emerging zoonoses in cases of human. However diseases like Canine Granulocytic Ehrilichiosis, Canine Anaplasmosis, Endemic Typhus, and Indian Tick Typhus although prevalent in India, are grossly under reported. Hence, studies should be conducted all over India, for estimating actual burden of the disease in the country. Along with it an epidemiological approach should be adopted in the studies for better assessment of vector dynamics and unknown reservoirs in domestic and wildlife settings especially for zoonotic pathogens,

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