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Ehrlichiosis: Tick-borne Malady

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INTRODUCTION

Ehrlichiosis or especially canine ehrlichiosis is an important tick-borne disease with worldwide distribution ranging from Brazil to the United States of America (Dumler et al. 2001; Dumler et al. 2007; Heitman et al. 2016). *Ehrlichia canis* was first identified in Algeria in 1935 by Donatien and Lestoquard (Harrus et al. 1998). It was discovered upon examination of dogs showing signs of anemia and fever. Formerly, it was called Tropical Canine Pancytopenia, but later more appropriately renamed to Canine Monocytic Ehrlichiosis (Huxsoll et al. 1970). Commonly ehrlichiosis is associated with signs including fever, fatigue and myalgia (Buller et al. 1999; Dumler and Walker 2014). In this chapter, various aspects of Ehrlichia like its history, life cycle, transmission, pathogenesis, clinical signs, symptoms, treatment, control, and prevention of ehrlichiosis are discussed in the following sections.

An Ehrlichia infection affecting platelets was first identified in the US in 1978. Its causative agent was identified to be *Ehrlichia platys* which was later renamed *Anaplasma platys.* It caused a clinical syndrome of cyclic infectious thrombocytopenia in canines (Harvey et al. 1978).

Several species of *E. canis* were discovered in dogs over the span of the 1980s to 1990s. However, improvement in molecular genetics later proved that these were species of *Anaplasma* or *Neorickettsia* (Dumler et al. 2001). That is why to date only *E. canis* is the single species that has been isolated from dogs in Europe (Keysary et al. 1996; Aguirre et al. 2004). Many other species of Ehrlichia including *E. chaffeensis, E. ewingii, E. muris,* and *E. ruminatum* out of which only *E. muris* was found in *Ixodes* ticks in Russia and Slovakia (Shpynov et al. 2006; Spitalska et al. 2008).

E. chaffeensis is a major etiologic agent that causes ehrlichiosis in humans (CDC, 2010). It has been identified as the most-wide spread tick-borne disease of humans in the Southern United States (Beall et al. 2012). A few cases of *E. ewingii* infection are also reported infrequently and most of them were discovered in patients already having a history of immune incompetence (Buller et al. 1999; Chapman et al. 2006; Thomas et al. 2007; Allen et al. 2014; Dumler and Walker 2014).

The life cycle of Ehrlichia has been outlined in Fig. 1 & 2. Briefly, Ehrlichia is not transmitted from adult female ticks to the eggs. The newly laid eggs of the ticks are uninfected. These eggs grow into uninfected larvae. When these larvae grow on infected reservoir hosts they become infected after a blood meal. Infected nymphs are formed from these uninfected larvae. These nymphs have the ability to infect a new host and they can accidentally affect human hosts too. After infecting new hosts, the infected nymphs grow into infected adults. These adults can transmit infections to new hosts. When residing on a host the adult female ticks lay uninfected eggs on the hosts nullifying the expression of vertical transmission of Ehrlichia in ticks.

The Ehrlichia are taken up by ticks through blood meal as elementary bodies (Fig. 2). These elementary bodies reside in the gut and then migrate to the salivary glands of the tick. When this tick bites a healthy person the Ehrlichia are transmitted to the host as elementary bodies. These elementary bodies are phagocytosed by neutrophils. Inside neutrophils, these elementary bodies are developed in morulae with reticulate bodies. The reticulate bodies keep developing until the cell bursts releasing elementary bodies into the blood of the host from where it is once again taken by the ticks (Ganguly and Mukhopadhayay 2009).

Disease in Animals

Ehrlichia canis can cause disease in dogs of all breeds irrespective of their sex, age or breed. However, German Shepherds and Siberian Huskies are found to be more prone to ehrlichiosis. These breeds also show poor prognoses for recovery (Nyindo et al. 1980; Harrus et al. 1997). Different strains of ehrlichia cause disease in both animals and humans as shown in Table 1.

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Table 1: Etiological agents of different types of Ehrlichiosis in different hosts.

No.	Diseases	Host	Pathogen	References
1.	Human Granulocytic Ehrlichiosis	Human	*Ehrlichia chiffeensis, Ehrlichia ewingii*	(Ganguly and Mukhopadhayay 2009)
2.	Human Monocytic Ehrlichiosis	Human	*Ehrlichia chiffeensis, Ehrlichia ewingii*	(Ganguly and Mukhopadhayay 2009)
3.	Canine Monocytic Ehrlichiosis	Dogs	*Ehrlichia canis*	(Harrus et al. 1997)
4.	Heartwater	Ruminants	*Ehrlichia ruminantium*	(Allsopp 2010)

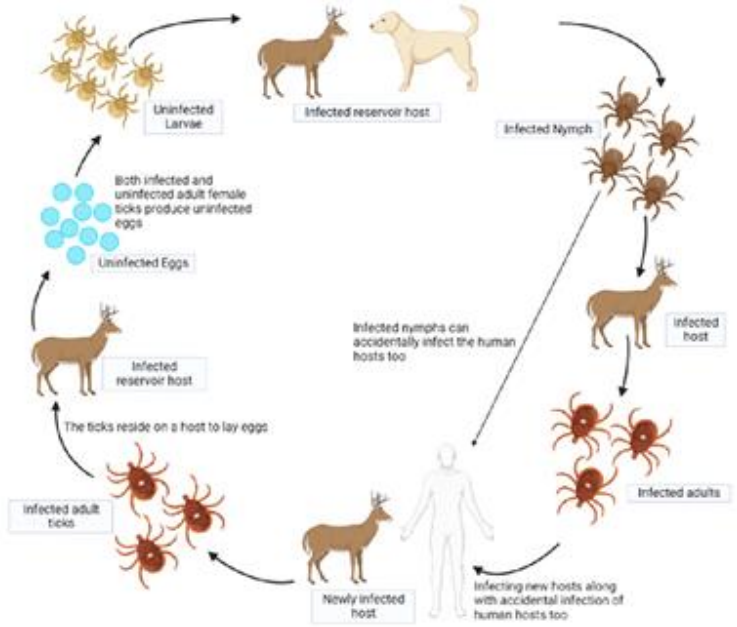

Fig. 1: The infection cycle of Ehrlichia

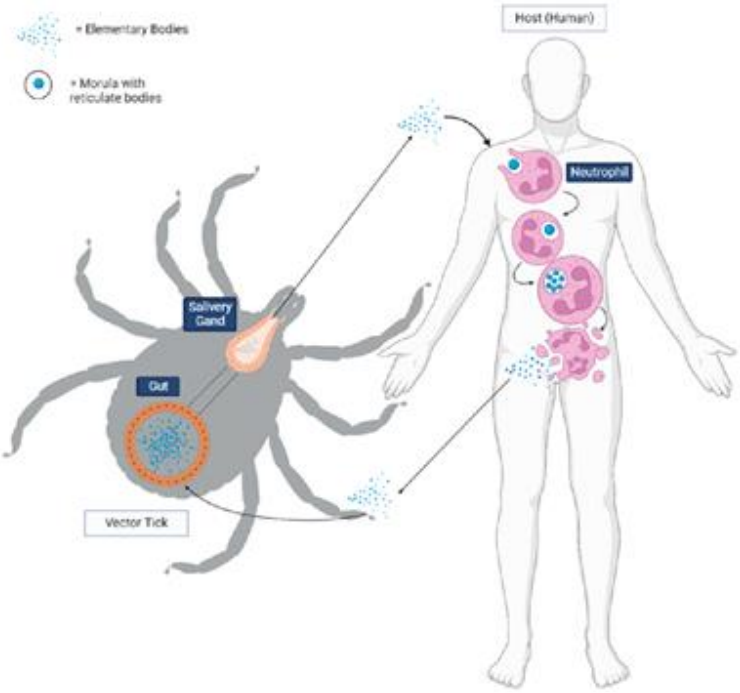

Fig. 2: The life cycle of Ehrlichia

Pathogenesis

The *E. chaffeensis* pathogen mainly affects vertebrates. This pathogen targets the mononuclear phagocytic cells. Mostly, monocytic cells are found to be affected due to an infection but several other cells have also been described by many researchers that are influenced during an Ehrlichia infection. The other cells infected by *E. chaffeensis* include

metamyelocytes, lymphocytes, promyelocytes, atypical lymphocytes, and band and segmented neutrophils (Maeda et al. 1987; Abbott et al. 1991; Dumler et al. 1993; Paddock et al. 1997). The morulae of Ehrlichia are found in the cells of an infected person. There may be 1 or 2 morulae in a cell. This number can go up to 15 morulae in the leucocytes of a person with below-average immune competence (Paddock et al. 1993; Barenfanger et al. 1996; Martin et al. 1999).

Histopathologically, bone marrow is the most researched tissue for checking the pathogenic effects of Ehrlichia but no consistent pathogenic patterns have been seen in this disease until now. However, researchers have found the bone marrow in a normocellular or hypercellular state along with myeloid hyperplasia or megakaryocytes, both may also occur together sometimes (Standaert et al. 1998; Dumler et al. 1993; Grant et al. 1997).

In human monocytic ehrlichiosis (HME), the cytopenia associated with diseases is not a direct result of infection. The disturbed cell count is rather attributed to peripheral events like sequestration, cellular destruction mostly by phagocytosis of infected and some non-infected cells too and consumption of the cells (Harkess et al. 1989; Dumler et al. 1993).

Pathological signs seen in Ehrlichia are often found in patients suffering from some immune-compromising disorders along with Ehrlichia. These signs include edema of the lungs, diffuse alveolar damage, interstitial alveolar hemorrhage, and intra-alveolar hemorrhage (Dumler et al. 1991; Paddock et al. 1993; Marty et al. 1995; Paddock et al. 1997; Fordham et al. 1998). Perivascular infiltrates may also be found in several organs including meninges without any evidence of endothelial damage or thrombosis. Lymphohistiocytic infiltrates are the dominant type of infiltrates often found in organs (Marty et al. 1995; Paddock et al. 1997; Walker and Dumler 1997).

Focal necrosis may also be seen in the liver, spleen, and lymph nodes in the bodies of patients suffering from *Ehrlichia chaffeensis* (Dumler et al. 1991; Paddock et al. 1993). Diffuse hemorrhages may also be discovered in visceral organs including the urinary bladder, kidneys, meninges, and diaphragm (Marty et al. 1995; Paddock et al. 1997).

Signs

E. canis infection can produce a variety of clinical signs in dogs after infection depending upon the strain that has infected the animal. The signs may also vary according to the immune response produced by the host's body. Infestation with ticks and other flea-borne pathogens can also cause the signs to deviate from the typical ones or may affect the severity of the infection. Even sometimes it happens that sometimes dogs do not show any clinical signs or laboratory findings related to the diagnosis of Ehrlichia infection despite being carriers of *E. canis* (Harvey et al. 1978; Greig et al. 1996; Egenvall et al. 1997; Harrus et al. 1997; Varela et al. 1997 Breitschwerdt et al. 1998; Egenvall et al. 1998; Goldman et al. 1998; Lilliehöök et al. 1998; Neer 1998; Breitschwerdt 2005; Leiva et al. 2005; Komnenou et al. 2007; Diniz et al. 2008; Tabar et al. 2009; Little 2010).

Diagnosis

Ehrlichia canis aggregates or morulae are rarely detected through blood smear microscopy. Only 4- 6% of clinical cases of ehrlichiosis were found to have blood smear morulae discovered by microscopy. However, the likelihood of detecting morulae increases if microscopy of the buffy coat is performed instead of whole blood (Mylonakis et al. 2003). Further confirmation techniques like PCR must be used for surefire identification of Ehrlichia. An expert cytologist may also be able to identify Ehrlichia morulae by microscopy of lymph node aspirates under oil immersion field views. This technique is also not very effective for diagnosis and has only a 50% chance of success (Mylonakis et al. 2003; Mylonakis et al. 2011). Different diagnostic tools for Ehrlichia are whole blood smear microscopy, buffy coat smear microscopy, cytology of lymph nodes, and PCR technique (Fig. 3).

Transmission

Many of the ticks found in homes, gardens, and pastures are also responsible for Ehrlichia transmission. Out of many examples of such agents involved, *Rhipicephalus sanguine* complex of ticks is the top suspect. It is one of the ticks mostly found indoors. It may also be common in many other places. Other ticks may also be involved in Ehrlichia transmission in other places like gardens and grassy areas. This suggests that the dogs can become infected with Ehrlichia being transmitted through these ticks at any time and in any place. Even in the backyard, gardens, and grassy places found near houses, there is a risk that there might be a population of ticks there that can transmit Ehrlichia. So, whenever a dog is involved in any activity that demands going to or being near a grassy area, it is at risk of getting in contact with ticks and hence becomes a target of Ehrlichia infection (Bremer et al. 2005).

E. canis can be also transmitted among dogs through the bite of brown dog ticks *R. sanguineus* (Bremer et al. 2005).

Treatment

The tetracycline group of antibiotics shows promising results when used for treating ehrlichiosis in dogs or canine monocytic ehrlichiosis. The drug of choice from this to be used against Ehrlichia is doxycycline. Two dosing methods can be used to administer doxycycline to the dogs. The first method is a once-a-day dosing system. A single dose of 10 mg/kg should be given to the dog orally once a day. The second method is a twice-a-day dosing system. In this system, the per day 10 mg/kg dose of doxycycline for the dog is divided into two parts of 5 mg/kg. This dose is then two times a day with an interval of 12 hours between two doses instead

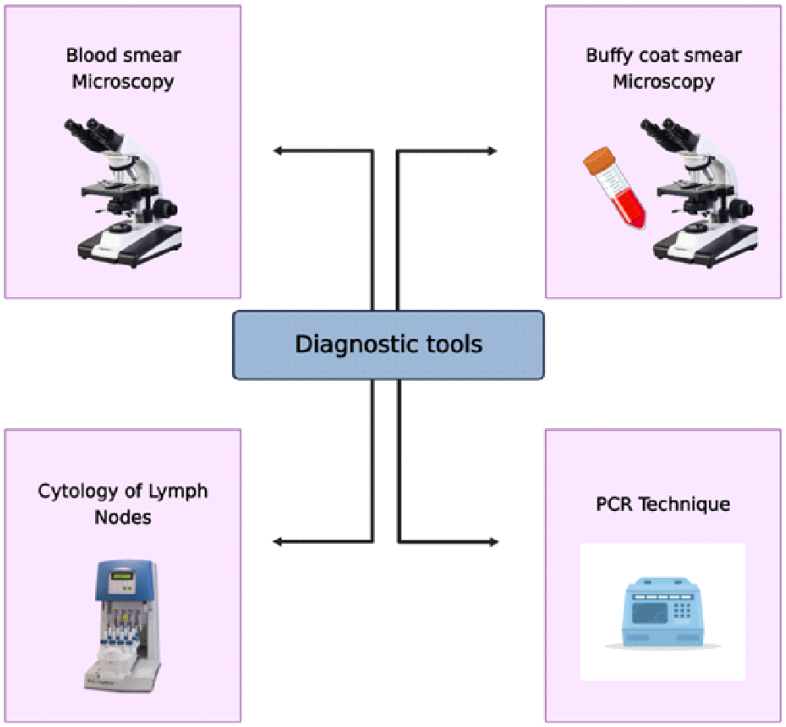

Fig. 3: Different diagnostic tools for Ehrlichia

of giving one single dose for 24 hours. These doses either as a single per day dose or twice per day doses should be continued for at least 4 weeks for complete recovery of dogs from Ehrlichia. This treatment regime for Ehrlichia promises a good prognosis. Hence, effective response can be seen in Ehrlichia sick dogs once this treatment protocol is implemented (Harrus et al. 1998; Harrus et al. 2004; McClure et al. 2010).

The prolonged treatment time of 4 weeks is strictly recommended to completely cure the dog from ehrlichiosis. During experimental investigations, it was proved that shortening this treatment period causes unforeseen circumstances in terms of prognosis and recovery. Several dogs that were experimentally infected with Ehrlichia and given doxycycline for a shorter period even at recommended doses, did not recover completely. Instead of recovering completely, these dogs became subclinical carriers of Ehrlichia (Wen et al. 1997; Breitschwerdt et al. 1998; McClure et al. 2010).

Prevention

Until the present time, researchers have been unable to create a definitive vaccine against Ehrlichia in dogs for its sure-fire prevention in felines. Especially the topic of prevention of *E. canis* infection has seen a lot of debate but chances of a vaccine coming up against infection of this pathogen are still slim. However, recent studies have shown some hope. A certain strain of *E. canis* has shown promising results as a vaccine when in attenuated form. It is expected that in near future a vaccine will be made from this strain for commercial use (Rudoler et al. 2012).

Quick action upon discovering that a dog has become infested with ticks can also help in saving the dog from getting infected with Ehrlichia. Under normal conditions, it is a general consideration that the infectious agents take 24-48 hours to travel from the salivary gland of ticks to the host's bloodstream. Hence an injection of a preventive drug at that time will save the dog from getting infected with Ehrlichia (Nicholson et al. 2010). However, recent studies have brought us the bad news that some Ehrlichia agents like *E. canis* are transmitted from the tick's salivary glands to the host's bloodstream more rapidly than the other pathogens that follow the general 4-48 hours transmission time rule (Gray et al. 2013). *E. canis* is also a problematic pathogen as it can re-infect dogs even after they have recovered from the infection once. This happens because no persistent immunity is developed against this pathogen in the host's body (Harrus et al. 1997).

Control

To prevent dogs from getting ehrlichiosis the focus must be shifted to control of its transmission agents. So, the control of tick populations that are transmitting Ehrlichia will ultimately control the prevalence of these diseases in dogs.

To save a dog from getting Ehrlichia infection, it is necessary to save them from getting in contact with these Ehrlichia-transmitting ticks. Some measures to be taken for saving dogs from the attacks of these ticks are:

- Keep the dogs away from large fields. Large fields usually have a high chance of having ticks. Once a dog gets infested with even a single tick then this tick will be transmitted to indoor housing areas and its population will grow into large numbers rapidly. This will not only make the infested dog sick, but it will also pose a threat to other dogs living in nearby areas (Sainz et al. 2015).

Table 2: Vectors involved in Ehrlichia transmission.

No.	Common name	Scientific name	Reference(s)
1.	Dog tick	*Dermacentor variabilis*	Anderson et al. 1993; Roland et al. 1998; Kramer et al. 1999
2.	Western Black-legged tick	*Ixodes pacificus*	Kramer et al. 1999
3.	Castor bean tick	*Ixodes ricinus*	Alekseev et al. 2001

- Dogs should be prevented from getting infested by ticks even if they live in an area where the tick population is abundant. This objective is harder to achieve but it can be achieved by regularly treating dogs with acaricidal drugs (Torres 2008; Pereira et al. 2009).
- Registered tick repellents like pyrethroids and several preparations of diazinon can be used to keep the ticks away from dogs (Sainz et al. 2015).

Control of these ticks is also possible by keeping in mind the temperatures at which the ticks are active and keeping the dogs indoors at that time to prevent them from getting infested with the ticks. In the case of *R. sanguineus* ticks, they are active only when the temperature is above 10-12 ℃ but below this temperature, these ticks are mostly inactive. Hence, at lower temperatures dogs are somewhat safe from the infestation of these ticks and in turn from Ehrlichia infection (Sainz et al. 2015).

Similarly, *I. Ricinus* ticks become active when the temperature rises above 6℃. So, these ticks are more active as compared to the *R. sanguines* ticks and hence require more intense measures for saving dogs from being infested with them (Gray et al. 2013).

Disease in Humans

Zoonotic ehrlichiosis in humans is a potentially fatal tick-borne disease. In humans, ehrlichiosis can be caused by infectious agents like *Ehrlichia chaffeensis* or *Ehrlichia ewingii*. The first case of human monocytic ehrlichiosis was diagnosed in 1991 and its etiological agent was discovered to be *E. chaffeensis* (Dawson et al. 1991). Later in the year 1992 cases of granulocytic ehrlichiosis were also diagnosed and reported. These cases of ehrlichiosis were different from the ones reported in the past because the infectious agent involved in causing diseases this time was found to be *E. ewingii* (Dawson et al. 1991; Fishbein et al. 1994; Paddock and Childs 2003; Chapman et al. 2006).

Transmission

Centers for Disease Control and Prevention in 2010 and 2014 reported that in humans, ehrlichiosis is majorly transmitted only through tick bites. The main culprit involved in the transmission of ehrlichiosis in humans is a tick named the lone star tick along with several other species of ticks as shown in (Table 2). The scientific name of this tick is *Amblyomma americanum*. Transmission of Ehrlichia solely happens through bites of this tick and hence Ehrlichia is most prevalent in the regions where the lone star tick population is the highest. This tick is most commonly found in southeastern, south-central, and northeastern parts of the United States (Paddock and Childs 2003; Beall et al. 2012).

These lone star ticks are particularly very effective agents of Ehrlichia transmission. Their effectiveness increases because of characteristics like being aggressive non-selective feeders and having the ability to bite and transmit infections throughout all stages of life (Childs and Paddock 2003). Centers for Disease Control and Prevention in 2010 stated that the adult and nymph stages are however the major culprits of Ehrlichia transmission. The feeding seasons of these stages coincide with the peak infection seasons of Ehrlichia. This peak is achieved during hot weather ranging from the month of May to July (Paddock and Childs 2003; Dumler and Walker 2014).

American Academy of Pediatrics in 2015 released a statement claiming that transfusion and transplantation of organs like liver and kidney have also been reported as a medium for transmitting *E. chaffeensis* (Antony et al. 1995; Paddock and Childs 2003; Dumler and Walker 2014; Sachdev et al. 2014). Only one such case of *Ehrlichia ewingii* transmission has been reported to occur when a young boy went through the transfusion of platelets (Regan et al. 2013).

Zoonosis

Many wild and domestic animals serve as reservoirs for Ehrlichia pathogens. These animals then serve as the basis for the zoonotic transmission of Ehrlichia to humans through ticks. An example of such a wild reservoir animal is the white-tailed deer scientifically named *Odocoileus virginianus*. This deer has been found to be naturally infected with *E. chaffeensis* and is thus involved in maintaining its enzootic cycle (Yabsley et al. 2002; Childs and Paddock 2003; Paddock and Yabsley 2007). Similarly, just like the white-tailed deer, domestic dogs are also involved in the zoonotic transmission of Ehrlichia by serving as reservoirs maintaining the enzootic life cycle of the pathogen. Domestic dogs are majorly found to be the reservoirs of *E. ewingii* (Yabsley et al. 2002; Beall et al. 2012). The dogs can also serve as transport carriers. The pet or stray dogs once infected can carry the pathogen closer to human populations making them more prone to being infected with Ehrlichia (Childs and Paddock 2003; Paddock and Childs 2003).

Along with Ehrlichia, some animals can also serve as potential hosts for the lone star ticks making the transmission of Ehrlichia from animals to humans possible. This category includes a large number of animals. Some examples of such animals are domestic dogs, birds, rabbits, goats, wild turkeys, red foxes, opossums, canids, and raccoons (Childs and

Paddock 2003; Paddock and Childs 2003; Paddock and Yabsley 2007).

Signs and Symptoms

In humans, ehrlichiosis has non-specific symptoms that begin to appear after 7 to 14 days of incubation period post-exposure to the infectious agent (Dumler and Walker 2014). In humans, the commonly observed signs of Ehrlichia include fever, headache, chills, nausea, myalgia, and malaise (Buller et al. 1999; Dumler and Walker 2014).

Severe illness in the case of ehrlichiosis is indicated by some characteristic signs. In adults, the signs seen with increasing severity of ehrlichiosis usually included confusion, lymphadenopathy, diarrhea, and cough. However, the signs of severe illness were seen to differ in children as compared to adult patients. In children, the severity of ehrlichiosis was marked by the appearance of edema on the hands and feet. When laboratory diagnostic tests for further studying the pathological effects of Ehrlichia infection were conducted, some new facts were unveiled for the researchers. Ehrlichia also affected the blood profile of its hosts. This disturbance was seen as leukopenia and thrombocytopenia during the blood analysis of the patients. Along with these blood tests, the conduction of serum analysis also revealed increased serum levels of hepatic aminotransferase (Dumler and Walker 2014).

According to reports from the Centers for Disease Control and Prevention 2010, a large number of cases of *E. chaffeensis* infection in children were marked with the appearance of a rash. The rash was seen in less than 1/3rd of the ehrlichiosis cases of adults. The rash seen in ehrlichiosis started as a maculopapular rash in the early stages of infection. However, as the infection progressed the rash also changed its state from maculopapular to petechial (Harkess et al. 1991; Paddock and Childs 2003; Chapman et al. 2006; Dumler and Walker 2014). American Academy of Pediatrics 2015 confirmed in its reports that the rash had some characteristic appearance areas on the human body. The rash was typically seen on the trunk. The rash started to appear 7 days after symptoms developed in the patient. The rash often kept itself limited to the trunk and did not spread to the hands or feet of the patient (Chapman et al. 2006). It was also observed during diagnostic studies that the rash is commonly seen during *E. chaffeensis* infections. Rashes were rather rare to be seen when a person was diagnosed to be infected with *E. ewingii* (Chapman et al. 2006).

E. chaffeensis infections lead to the appearance of severe signs. *E. chaffeensis* infections have been reported to lead to death in 1 to 3% of cases out of all *E. chaffeensis* infections. The death of a patient can occur as early as during the second week of infection by *E. chaffeensis* (Paddock and Childs 2003; Chapman et al. 2006). However, *E. ewingii* infections are much less severe than *E. chaffeensis* infections. *E. ewingii* causes milder signs during infection. There are no deaths reported due to *E. ewingii* infection (Paddock and Childs 2003; Dumler and Walker 2014).

Treatment

Ehrlichiosis usually appears like any other infection and the signs can vary from mild to moderate and severe. Generally, people are hospitalized for treatment of Ehrlichia depending upon the severity of signs. Around 50 to 70 % of the people infected with Ehrlichia are hospitalized for treatment (Fishbein et al. 1994; Paddock and Childs 2003; Chapman et al. 2006).

According to the American Academy of Pediatrics 2015, it is necessary to begin the treatment of Ehrlichia as soon as the signs and symptoms appear. Laboratory confirmation should not be regarded as a reason to delay the treatment (Chapman et al. 2006; Todd et al. 2015). American Academy of Pediatrics 2015 has recommended beginning treatment within 5 days after post appearance of signs of Ehrlichia infection to expect a better prognosis for the recovery of the patient as compared to the situation where treatment is withheld or delayed beyond this time frame (Fishbein et al. 1994).

Unjustified delay in treatment or giving no treatment to an Ehrlichia patient at all can lead to severe consequences as the disease progresses. It can lead to the failure of important organs like kidneys. The nervous may also be affected due to Ehrlichia infection. It can also lead to issues like Adult Respiratory Distress Syndrome (ARDS) and Disseminated Intravascular coagulation-like syndrome (Dahlgren 2011; Dumler and Walker 2014).

Prevention

Since the main agents for Ehrlichia transmission in humans are the ticks, the main efforts of reducing ehrlichiosis depend on the effective control of tick populations and the elimination of its reservoirs (Childs and Paddock 2003). Dogs can also serve as reservoirs for both ticks and *E. ewingii* so it is recommended for pet dog owners to be careful that their dogs should not come in contact with infection or become a reservoir of ticks. This objective can be achieved by using acaricide-containing collars, veterinary ectoparasite control drugs, or by using topical applicants against tick attachment and infestation (Pereira et al. 2009).

The American Academy of Pediatrics has recommended in 2015 that starting treatment of Ehrlichia-infected patients at the earliest opportunity after appearance signs is a good measure to save human lives but prevention is still better than cure. The best option to prevent ehrlichiosis infections in humans is to avoid tick bites. The people and pets visiting Ehrlichia endemic and tick-infested areas should be checked for ticks to prevent the transfer of ticks. Regular checkups of people and pets should be made customary as a preventive measure for reducing Ehrlichia transmission. As there is no

vaccine or prophylactic drug against Ehrlichia, it is necessary for humans to reduce their exposure to ticks to prevent infection. An important measure that people can adopt to prevent tick bites is to wear full-covering clothing impregnated with permethrin. Furthermore, using repellents *n,n-diethyl-m-toluamide* (DEET) is also effective to avoid tick bites (Chapman et al. 2006; Brett et al. 2014).

Conclusion

Ehrlichia might seem a moderate disease but can result in fatality if left untreated. Ehrlichia affects a wide variety of animals. The major impact of Ehrlichia is seen in our beloved pet dogs. This disease can not only kill a dog, but it can also lead to disease in humans too if the dog is affected by an Ehrlichia strain with zoonotic potential.

Such a situation makes it necessary for humans to take special care of preventing Ehrlichia transmission from infected dogs. In absence of a vaccine, the best method for preventing Ehrlichia infection is by preventing tick infestation in dogs. If there is no agent to transmit Ehrlichia then there will be no spread of infection. This prevention is far better than a medicinal cure because even after a dog has fully recovered from Ehrlichia, it still remains a carrier of Ehrlichia. This puts the other dogs, animals, and even humans around it at risk of an Ehrlichia infection.

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