



Mini Review

Zoonotic babesiosis: Overview of the disease and novel aspects of pathogen identity

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ABSTRACT

Babesiosis is a zoonosis caused by tick-transmitted intraerythrocytic protozoa of the Phylum Apicomplexa. The disease mostly occurs in the USA, but cases have also been reported in several European countries, in Egypt, India, Japan, Korea, Taiwan, and South Africa. The main pathological event is lysis of erythrocytes resulting in haemolytic anaemia, which in severe cases may lead to organ failure and death, particularly in immunocompromised patients. The 2 groups of parasites involved, *Babesia microti*-like and *Babesia sensu stricto* (s.s.) species, differ in their life cycle characteristics and susceptibility to antibabesial drugs. Molecular taxonomy is now making a major contribution to the identification of novel pathogens within both groups. Effective treatment of severe cases was initially hampered by the lack of specific antibabesial drugs for human use, but increased use of supportive measures and of the recently developed antimalarial, atovaquone, particularly in combination with azithromycin, has improved the prospects for management of acute disease especially when caused by *Babesia* s.s. species. Prevention should be based primarily on increasing the awareness of physicians and the public to the risks, but infection from blood transfusions is particularly difficult to prevent. Expanding deer populations, resulting in wider distribution and greater abundance of ticks, heightened medical awareness, and growing numbers of immunocompromised patients are likely to result in a continuing rise of reported cases.

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Introduction

Although best known as an animal disease, human babesiosis is attracting increased attention as a worldwide emerging zoonosis. More than 30 cases, most likely caused by the cattle parasite *Babesia divergens* or by closely related species, have been reported in Europe (Yugoslavia [modern Croatia], France, Great Britain, Ireland, Portugal, Spain, Sweden, Switzerland), almost all in splenectomised patients, often with additional immunocompromising conditions, and usually characterised by acute fulminant infections (Zintl et al., 2003). Recently a related though quite distinct babesia, *B. venatorum* (EU1), was incriminated in similar, though generally milder cases in Austria, Italy, and Germany (Herwaldt et al., 2003a; Häselbarth et al., 2007). In the USA, *B. divergens*-like parasites have caused acute disease in 3 asplenic patients (Herwaldt et al., 1996, 2004; Beattie et al., 2002).

A much more common form of babesiosis in the USA is caused by *B. microti*, a natural parasite of microtine rodents. Several hundred cases have been reported on the eastern seaboard and upper mid-west in both spleen-intact and asplenic patients. This disease usually occurs as relatively mild infections, except in immunocompromised or elderly patients. Many cases have been reported from New England and more recently from Wisconsin and Minnesota (Gray and Weiss, 2008). In Washington State and California, at least 9 cases of another form of babesiosis have occurred in spleen-intact and asplenic patients, caused by parasites (WA1 et seq. and CA1 et seq., respectively) that are morphologically similar to *B. microti* but taxonomically distinct (Kjemtrup and Conrad, 2000). Some of these isolates have been characterised and named *B. duncani* (Conrad et al., 2006).

Isolated cases of human babesiosis caused by *B. microti*-like parasites have been reported in Germany, Japan, and Taiwan (reviewed by Hunfeld et al., 2008), and uncharacterized babesias have also been detected in patients from South Africa, Brazil, India, and Egypt (Bush et al., 1990; Humiczewska and Kuźna-Grygiel, 1997; Marathe et al., 2005; El-Bahnasawy and Morsy, 2008). Kim et al. (2007) reported that a parasite in a Korean case

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Table 1
Summary of human babesiosis species, geographical distribution, vectors, vertebrate reservoirs, relative susceptibility, and pathogenicity (type isolates indicated by GenBank accession numbers).

American human babesiosis						
Species	<i>B. microti</i>	<i>B. duncani</i>	CA1–CA4	<i>B. divergens</i> -like	<i>B. divergens</i> -like	<i>B. divergens</i> -like
Type isolate	AF231348	AF158700	AF158704	AY274114	AY887131	AY048113
Distribution	Northeast, upper midwest USA	Washington State, California	Washington State, California	Washington State	Kentucky	Missouri
Vector	<i>Ixodes scapularis</i>	Unknown	Unknown	Unknown	<i>Ixodes dentatus?</i>	<i>Ixodes dentatus?</i>
Reservoir host	Rodents, shrews	Unknown	Unknown	Unknown	Cottontail rabbit?	Cottontail rabbit?
Human susceptibility	Spleen-intact/asplenic	Spleen-intact	Asplenic	Asplenic	Asplenic	Asplenic
Human cases (severity)	Several 100 (subclinical–fatal)	5 (subclinical–severe)	4 (severe, fatal)	1 (severe)	1 (fatal)	1 (fatal)
European human babesiosis						
Species	<i>B. microti</i>	<i>B. divergens</i>	<i>B. venatorum</i> (EU1–3)	<i>B. divergens</i> -like		
Type isolate	EF413181	U16370	AY046575	AJ439713		
Distribution	Germany	Europe	Austria, Italy, Germany	Portugal		
Vector	<i>Ixodes ricinus?</i>	<i>Ixodes ricinus</i>	<i>Ixodes ricinus</i>	Unknown		
Reservoir host	Meadow vole?	Cattle	Deer	Unknown		
Human susceptibility	Spleen-intact, immunosuppressed	Asplenic	Asplenic	Asplenic		
Human cases (severity)	1 (moderate)	> 30 (severe–fatal)	3 (moderate–severe)	1 (fatal)		
Worldwide human babesiosis excluding USA and Europe						
Species	<i>B. microti</i>	<i>B. microti</i>	Ovine babesia-like (KO1)	<i>B. divergens</i> -like		
Type isolate	AB032434	a,b	DQ346955	AF435415 ^c		
Distribution	Japan	Taiwan	Korea	Canary Islands		
Vector	<i>Ixodes ovatus?</i>	Unknown	Unknown	<i>Ixodes ventralloi?</i>		
Reservoir host	Japanese field mouse?	Spinous country-rat?	Ruminants (sheep)?	Unknown		
Human susceptibility	Spleen-intact	Asplenic	Asplenic	Asplenic		
Human cases (severity)	2 (subclinical–moderate)	1 (mild)	1 (severe)	1 (fatal)		

Cases have also been reported from Brazil, Egypt, India, and South Africa.

^a No sequence data available.

^b Shih et al., 1997.

^c insufficient sequence data for Fig.1.

involving a splenectomised woman is unrelated to any of the previously recorded zoonotic species.

The different forms of human babesiosis reported so far are summarised in Table 1.

Disease characteristics

Clinical features

In heavy infections, particularly those caused by *B. divergens*-like parasites occurring in immunocompromised patients, acute illness appears suddenly, usually with haemoglobinuria as a presenting symptom. The clinical presentation also includes persistent non-periodic high fever (40–41 °C), shaking chills, intense sweats, headaches, myalgia, and lumbar and abdominal pain. Jaundice may develop as a result of the high level of haemolysis; vomiting and diarrhoea may be present, and the toxins and anoxia, resulting from the haemolysis and the host immunological response, may cause respiratory, cardiac, renal, or hepatic failure (Zintl et al., 2003; Telford III and Maguire, 2006; Hunfeld et al., 2008). The few known infections with *B. venatorum* have shown similar though generally milder manifestations (Hunfeld et al., 2008). In one case involving a highly immunocompromised patient, the disease was prolonged (Häselbarth et al., 2007), but otherwise there is no reliable evidence that *B. divergens*-like parasites cause chronic disease.

Patients infected by *B. microti* show a wider range of signs and symptoms. A study on Block Island, Rhode Island, USA, concluded that about 25% of adults and 50% of children are asymptomatic or only show very mild 'flu-like' symptoms in cases that may not result in medical consultation and are therefore rarely diagnosed (Krause, 2002). At the other end of the spectrum, very severe manifestations, similar to those seen in *B. divergens* infections, may occur in patients who have been splenectomised, are receiving immunosuppressive therapy, or are elderly. These cases typically show high fever, chills, night sweats, myalgia, haemolytic anaemia, and haemoglobinuria (less marked than in *B. divergens* infections) (White et al., 1998). Life-threatening complications include acute respiratory failure, disseminated intravascular coagulation, congestive heart failure, coma, and renal failure (Hatcher et al., 2001). Immunocompromised individuals are also likely to develop persistent relapsing disease despite treatment (Krause et al., 2008). The symptoms caused by *B. duncani* and related parasites (CA1–4) closely resemble those of *B. microti* infections (Kjemtrup and Conrad, 2000).

Pathogenesis

The primary pathological event in heavy infection is haemolysis, resulting in haemolytic anaemia and jaundice. In the absence of aggressive intervention, the anoxia and toxic effects that follow often lead to organ failure and death. Parasitaemias do

not always relate directly to the degree of anaemia, suggesting that erythrocyte destruction is due not only to lysis of infected cells or their removal by splenic and liver macrophages. Some symptoms, such as fever, myalgia, renal insufficiency, coagulopathy, and hypotension, that occur in *B. microti* infections with parasitaemias of less than 1%, may be caused by excessive production of pro-inflammatory cytokines, as in malaria (Clark and Jacobson, 1998; Krause et al., 2007).

Immunity

The spleen and cell-mediated immune responses have an essential role in resisting both primary and challenge infections of *Babesia* species (Zwart and Brocklesby, 1979), and the protective effect of transferring splenocytes from immune to naive animals has been demonstrated several times (Homer et al., 2000). However, the spleen is not essential for the development of immunity and its main function is the removal of infected cells from circulation through a combination of the spleen micro-circulation and stimulated phagocytic cell activity (de Vos et al., 1987). In laboratory animals, the specific immune response to babesia infections is primarily cell-mediated, and antibodies appear to have little direct role in immunity, though invading sporozoites are probably vulnerable to antibodies for a short period before they invade erythrocytes (Kjemtrup and Conrad, 2000; Gray and Weiss, 2008). However, observations on the persistence of babesiosis human cases in which depletion of B-cells had occurred as a result of rituximab administration suggest that antibodies have a role in the clearance of the parasites (Krause et al., 2008). *Babesia* spp. employ efficient immunoevasion mechanisms and can survive for long periods in their natural hosts (Allred, 2003). Immunoevasion may also apply to *B. microti* infections in humans since persistence has been demonstrated to occur following acute disease (Krause et al., 1998), but there is little evidence for persistence of *B. divergens*-like parasites in humans except in one case involving *B. venatorum* in a severely immunocompromised patient (Häselbarth et al., 2007).

Pathogen identity

Traditionally, babesias have been divided into 'large' and 'small' forms such as *B. bigemina* and *B. microti*, respectively (Fig. 1). The large babesias, also referred to as *Babesia sensu stricto* (s.s.), can be further differentiated from small babesias by their relative susceptibility to antibabesial drugs (Gray and Pudney, 1999) and by details of their life cycles, particularly the presence of transovarial transmission (Uilenberg, 2006). Transovarial transmission appears to be absent in small babesias such as *B. microti*, a characteristic they share with *Theileria* spp. The advent of molecular taxonomy has clarified the classification of babesias considerably and phylogenetic trees based on the 18S rRNA gene sequence confirm the separation of *Babesia* s.s. species from *B. microti*-like species (Criado-Fornelio et al., 2003). Phylogenetic analyses also highlight the already known close relationship between *B. microti*-like parasites and *Theileria* spp.

At least 4 different groups of *Babesia* spp. cause human babesiosis (Fig. 1). Firstly, *B. microti*, the zoonotic forms of which are all apparently associated with rodents (Goethert and Telford III, 2003); secondly, a group typified by the newly-named *B. duncani* (Conrad et al., 2006), which although morphologically similar to *B. microti* is clearly separate phylogenetically; thirdly, a group comprising *B. divergens*, *B. divergens*-like parasites, and *B. venatorum* (originally designated EU1), which belong to the *Babesia* s.s. group referred to above; and fourthly, a group currently represented by a single species from Korea that seems

most closely related to certain *Babesia* spp. of sheep and according to phylogenetic analysis belongs to the *Babesia* s.s. group, though separate from the clade that includes *B. divergens* (Kim et al., 2007).

Molecular taxonomy has also demonstrated subtle differences between apparently conspecific species. Bovine isolates of *B. divergens* seem only to occur naturally in Europe and according to unpublished work (Slemenda et al., cited by Herwaldt et al., 2003a) show 100% homology for the 18S rRNA gene. If this is the case, the isolates from humans (Olmeda et al., 1997; Beattie et al., 2002; Centeno-Lima et al., 2003) and deer (Duh et al., 2005; Langton et al., 2003; Hilpertshauser et al., 2006) that have been shown to differ by more than 2 bases in the 18S rRNA gene from the reference *B. divergens* bovine strain (GenBank accession no. U16370) should not be considered conspecific with cattle isolates of these parasites. This view is supported by Holman (2006) who found that the *Babesia* spp. that caused the human case reported by Beattie et al. (2002) was not infective for splenectomised calves or for bovine erythrocytes in vitro, despite differing from *B. divergens* in the 18S rRNA gene by only 3 base pairs. However, more recent 18S rRNA gene sequence depositions in GenBank (Vogl, S.J., and Zahler-Rinder, M.M., unpublished, accession nos. EF458219–EF458229) suggest that bovine isolates may differ by one or 2 base pairs. Interestingly, these GenBank data show that an isolate from a human case differed from the majority of bovine isolates by one base pair, but was nevertheless infective for Mongolian gerbils (*Meriones unguiculatus*), which are highly susceptible to bovine isolates of *B. divergens* (Zintl et al., 2003).

European deer appear to harbour several close relatives of *B. divergens* (Duh et al., 2005; Langton et al., 2003; Hilpertshauser et al., 2006; Schmid et al., 2008; Zintl et al., unpublished) with unknown zoonotic potential. It is notable, however, that though *B. capreoli*, a parasite of roe deer (*Capreolus capreolus*), only differs from *B. divergens* bovine isolates by 3 base pairs in the 18S rRNA gene, in vitro studies have convincingly shown that this species is unable to invade human erythrocytes (Malandrin et al., 2009). On the other hand, *B. venatorum*, which is also found in roe deer (Bonnet et al., 2007), differs by 31 base pairs, but is known to be zoonotic (Herwaldt et al., 2003a). It is evident that more studies are required to determine the zoonotic potential of the close relatives of *B. divergens* occurring in deer.

B. microti, long considered on morphological grounds to be a single species found only in rodents, is now thought to consist of a complex of closely related subspecies, many of which are found in non-rodent hosts. Goethert and Telford III (2003) identified 3 clades based on analysis of the 18S rRNA and beta-tubulin genes, with one (Clade 1) containing the majority of strains thought to be zoonotic. This clade includes the American zoonotic strains that have caused most babesiosis cases worldwide, but there are also separate zoonotic strains occurring in Japan ('Kobe' and 'Hobetsu') and Taiwan (Shih et al., 1997). Strains of unknown zoonotic potential but closely related to the zoonotic American strains, according to 18S rRNA or beta-tubulin gene analysis, have been isolated in Germany (Hannover), central Russia (Mis, near Berezniiki, Perm region), Japan and South Korea, eastern Russia (Vladivostok), and north-east China (Xinjiang) (Goethert and Telford III, 2003; Zamoto et al., 2004a, 2004b; Gray, 2006). The German zoonotic strain from Jena (Hildebrandt et al., 2007) probably also belongs to this group. Strains from rodents and ticks in Germany (Munich) and Poland (Pieniasek et al., 2006; Sinski et al., 2006) are closely related to each other but distantly related to the 'US' types. Recent analysis of a third gene, CCT-eta, in 21 *B. microti* isolates concluded that there are at least 4 distinct species; the 'US' type group, a second group ('Munich type') containing the Munich and Polish isolates together with 2 UK isolates, a third containing a single isolate from Japan ('Kobe type'), and a fourth

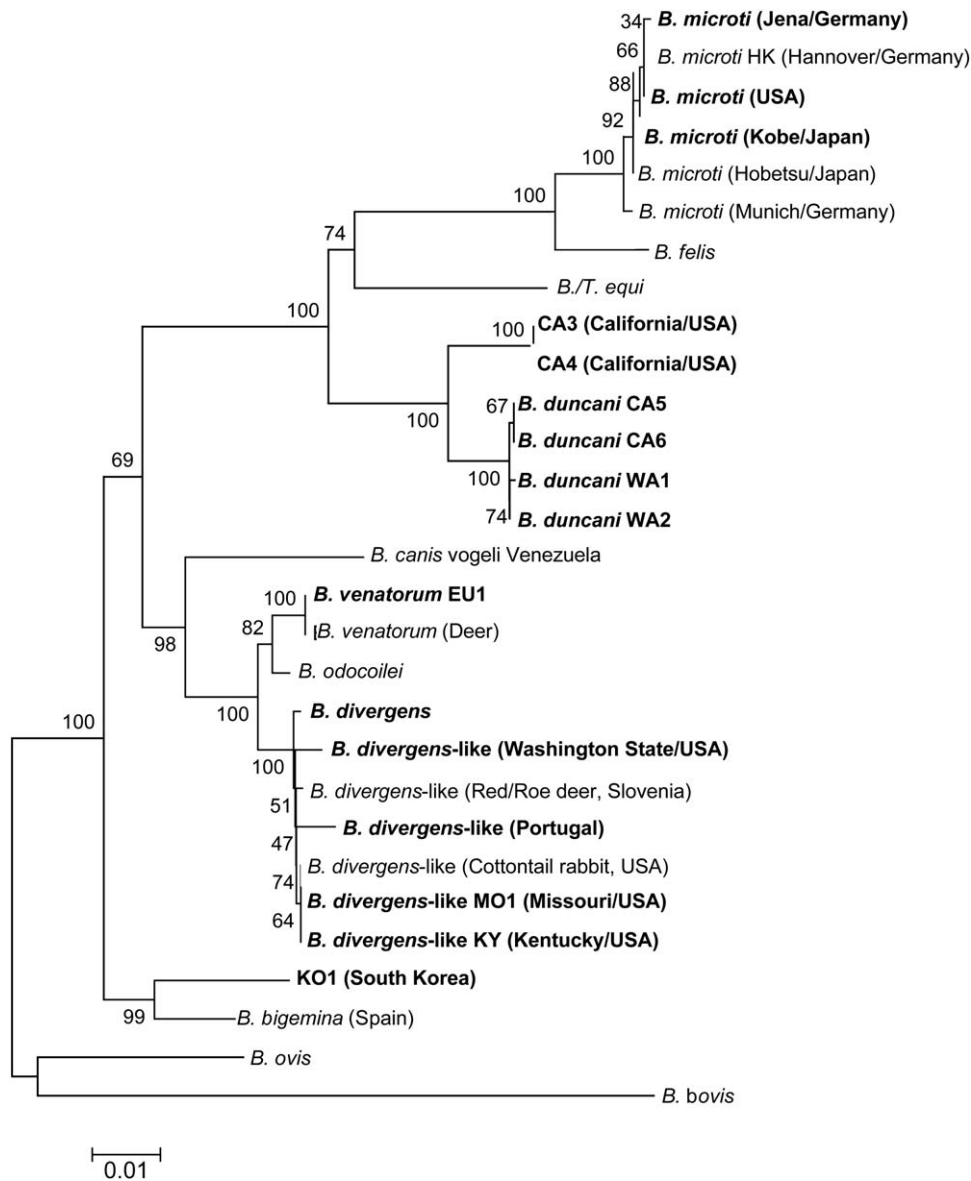


Fig. 1. Phylogenetic relationships of human babesia isolates (in bold) determined by neighbour-joining analysis of 18S rRNA gene sequences.

containing 3 Japanese isolates ('Hobetsu type') (Nakajima et al., 2009). Further genetic analysis may reveal markers for zoonotic capacity, which will help to define the risk posed by these widespread parasites.

Life cycles

Babesia spp. multiply in erythrocytes by asynchronous binary fission, resulting in considerable pleomorphism (Fig. 2). This replication eventually gives rise to gametocytes that are ingested by the vector tick. Conjugation of gametocytes occurs in the tick gut followed by multiplication by multiple fission and migration to various tissues including the salivary glands. Further development occurs in the salivary glands before transmission. In *Babesia* s.s. species, the ovaries are also invaded, which leads to transovarial transmission (Fig. 3).

All the known vectors are ixodid ticks belonging to the genus *Ixodes* (Table 1). Most *Ixodes* spp. are endophilic and inhabit the burrows or nests of small animals or birds where the unfed stages

(larvae, nymphs, and adults) wait for the host, but those involved in transmission to humans are exophilic, the host-seeking stages occurring in the open where they ascend the vegetation to ambush passing hosts. These include the best-known arthropod vectors of human disease in northern temperate regions, *I. ricinus* (Europe) and *I. scapularis* (North America). It is probable that all tick stages – larvae, nymphs, and adults (though not males) – can acquire and transmit *B. divergens*-like species because of transovarial transmission. In *B. microti*, the absence of transovarial transmission (Walter and Weber, 1981; Spielman et al., 1984; Gray et al., 2002) suggests that only nymphs and adults can transmit the parasite, despite some reports of PCR-positive larvae.

The reservoir hosts of *B. divergens* and *B. microti* are well documented as cattle (Zintl et al., 2003) and microtine rodents and shrews (Goethert and Telford III, 2003), respectively. Although deer have been identified as hosts of *B. divergens* in several studies, the babesias involved are probably not conspecific with this cattle parasite as previously discussed (Gray, 2006). However, deer have been incriminated by PCR as hosts of the

related but distinct zoonotic species, *B. venatorum* (Duh et al., 2005). In America, the eastern cottontail rabbit (*Sylvilagus floridanus*) is thought to be the reservoir host of a *B. divergens*-like species isolated from a patient in Kentucky, and this was later found to be identical to a Missouri isolate (Holman, 2006). Another lagomorph may be the vertebrate reservoir of a babesia isolated from a patient in Washington State, because it shows 99.9% 18S rRNA gene homology with an isolate from Texan black-tailed jackrabbits (Yabsley et al., 2006).

The most important reservoir host of zoonotic American *B. microti* is the white-footed mouse, *Peromyscus leucopus*. The reservoir hosts of 'US' type European strains may be voles such as *Microtus agrarius* (Walter, 1984), but this species also harbours 'Munich' type parasites that are transmitted by the rodent-tick

I. trianguliceps (Bown et al., 2008), and this tick species does not bite humans. The reservoir hosts of the WA and CA parasites (that include *B. duncani*) are unknown but in view of the taxonomic position of these parasites (Conrad et al., 2006) it is tempting to speculate that they may be wild ruminants. Similarly, the finding that the newly discovered zoonotic species in Korea is closely related to certain sheep parasites (Kim et al., 2007) suggest that small ruminants may be reservoir hosts.

Epidemiology

The reported incidence of approximately 40 human cases due to *B. divergens* and related parasites in Europe (Vannier and

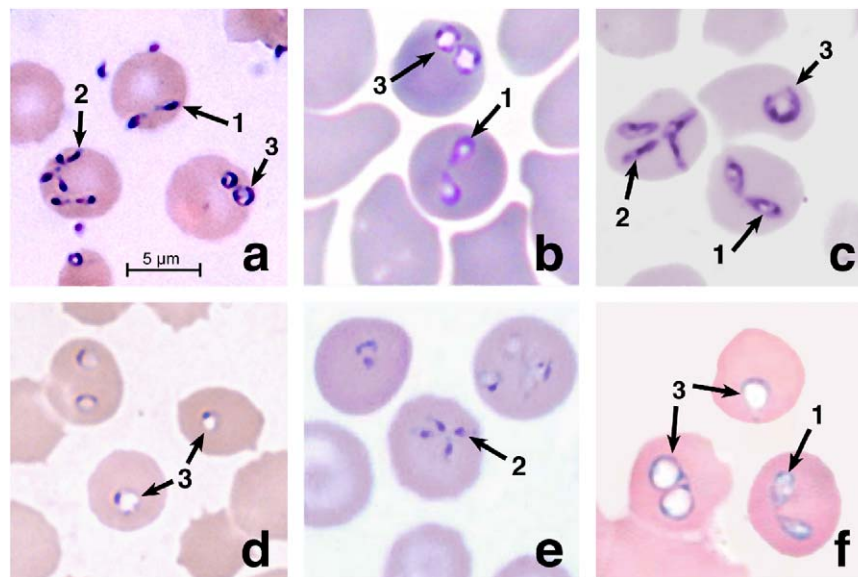


Fig. 2. Babesia parasites in human erythrocytes. a) *B. divergens*, b) *B. venatorum*, c) *B. divergens*-like, Kentucky, d) *B. microti*, e) *B. duncani*, f) KO1, Korea. 1. Paired piriforms; 2. Tetrads; 3. Ring forms. The parasites shown in Fig. 2a, b, c, e, and f were assembled from original photographs (supplied by the authors), first published as follows: a) Hunfeld et al., 2008; b) Häselbarth et al., 2007; c) Beattie et al., 2002; e) Kjemtrup et al., 2002; f) Kim et al., 2007. The parasites in Fig. 2d were photographed on a Giemsa-stained thin blood smear.

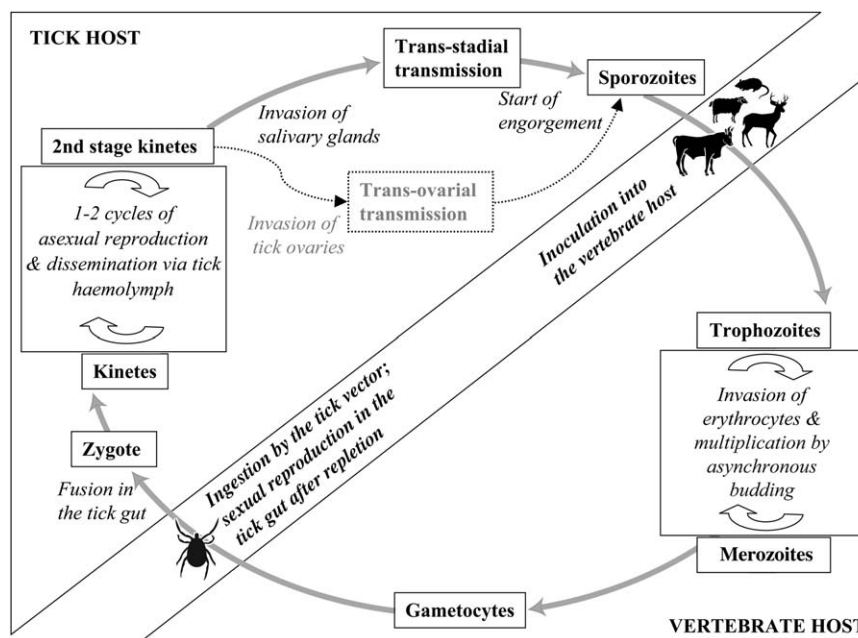


Fig. 3. Generic life-cycle diagram of *Babesia* spp. Transovarial transmission only occurs in *Babesia* sensu stricto species ('large' babesias).

Krause, 2009) is surprisingly low in view of the widespread distribution of infected ticks, cattle (and deer), and the size of the population at risk. Although most cases have occurred in splenectomised individuals, other as yet unidentified risk factors may be involved, since splenectomy is not a particularly rare procedure. The case fatality rate, although very high initially, has been reduced to about 40% by aggressive therapy (Zintl et al., 2003). Chronic disease has never been reported, and the evidence for asymptomatic infection is limited so far, being based on only a few serological studies (Hunfeld et al., 2008). The same general infectivity and disease characteristics apply to the related parasites involved in the American cases, but the vertebrate reservoirs are probably exclusively wildlife species, because as far as is known *B. divergens*-like parasites do not occur in domestic animals in the USA.

The several hundred recorded cases caused by *B. microti* in the USA is probably an underestimate because babesiosis is not reportable nationally, and symptoms may be mild and transient. The case fatality rate in hospitalised cases is about 5% (White et al., 1998), but a large proportion of infections are thought to be asymptomatic, and this is supported by reported seroprevalence studies. For example, a serosurvey during a single transmission season on Shelter Island, New York, showed point prevalence values of 4.4% for June and 6.9% for October (Filstein et al., 1980), and patients seropositive for Lyme disease showed seropositivity for *B. microti* of between 9.2 and 10.2% (Krause et al., 1991). Most babesiosis is caused by tick-bite, but an increasing number of cases are transmitted by blood transfusion (Leiby, 2006). There is good evidence that the geographical distribution of zoonotic *B. microti* is expanding in the USA, along with that of its vector, *I. scapularis* (Herwaldt et al., 2003b). The occurrence of cases in several other parts of the world suggests that zoonotic strains of this species are widespread, and more cases will probably come to light in these regions in the future.

B. duncani has caused few cases so far, but in view of the susceptibility of spleen-intact patients and the occurrence of disease transmitted by blood-transfusion, it is likely that there are many asymptomatic infections (Conrad et al., 2006). Serosurveys, though performed with unvalidated tests, indicated seroprevalences of 3.5–17.8% (Persing et al., 1995; Fritz et al., 1997).

Diagnosis, treatment, and prevention

Preliminary diagnosis of *Babesia* spp. infection can be made from indicative clinical features, especially in acute cases in which haemoglobinuria is evident. However, in chronic and subacute *B. microti* infections, clinical presentations may be further complicated by coinfection with other human pathogens such as *Borrelia burgdorferi* s.l. and *Anaplasma phagocytophilum* both of which are transmitted by the vectors of babesiosis (Swanson et al., 2006). Definitive diagnosis can be made by detection of characteristic intraerythrocytic forms of the parasites in Giemsa-stained thin blood smears (Fig. 2). In the *Babesia* s.s. group, paired piriforms (Fig. 2a1, b1, c1, f1) are diagnostic but may never be seen in the *B. microti/duncani*-like babesias, in which tetrads (Maltese cross forms), although uncommon, are regarded as diagnostic (Fig. 2e2). It should be noted, however, that in abnormal hosts such as humans, most zoonotic babesia species show tetrads, especially in immunocompromised individuals (Fig. 2a2, c2). *Babesia* spp. parasites do not deposit haemozoin in erythrocytes, and this aids the differentiation of single *B. microti* forms (Fig. 2d3) from *Plasmodium* spp. trophozoites.

Diagnostic confirmation can be obtained from serology (IFAT) and/or PCR analysis (preferably followed by sequencing of the PCR product), which are available for several *Babesia* spp. at specialist

laboratories. Both serology and PCR have been used in investigations of blood transfusion-related babesiosis for detection of asymptomatic infections in blood donors (Leiby, 2006).

Initially the standard drug treatment for all human babesiosis consisted of a combination of quinine and clindamycin (Hunfeld et al., 2008). The efficacy of these drugs does not approach that of the most effective animal antibabesial drug, imidocarb dipropionate, which was used successfully under special license in 2 patients infected with *B. divergens* but is not approved for general use in humans (Zintl et al., 2003). The more recently developed hydroxy-naphthoquinone, atovaquone, is licensed for human use and has good anti-babesia activity, especially against *B. divergens* (Gray and Pudney, 1999). However, the drug failed to prevent recrudescences of *B. microti* in laboratory animals unless given in combination with azithromycin or clindamycin, and drug resistance may be induced when atovaquone is administered on its own (Wittner et al., 1996; Gray and Pudney, 1999). The atovaquone/azithromycin combination was shown to be effective in humans in a clinical trial against *B. microti* (Krause et al., 2000) and is now the recommended drug therapy for mild cases, though in acute cases the quinine/clindamycin combination is still preferred (Wormser et al., 2006). In view of the excellent experimental efficacy of atovaquone against *B. divergens* (Pudney and Gray, 1997), the atovaquone/azithromycin combination may be the best option for cases caused by this parasite. In immunosuppressed patients, the efficacy of drugs, whatever the combination, is significantly reduced (Häselbarth et al., 2007; Krause et al., 2008), and in such patients prolonged treatment with antibabesial drugs may be required for cure. For all acute cases, exchange transfusion should be considered as an additional emergency measure.

Specific treatments to prevent human babesiosis do not seem practical. Imidocarb dipropionate can be used prophylactically against cattle babesiosis, but no drug is available for such an approach in humans, and considering the relative rarity of the disease it is most unlikely that vaccines will be developed.

The primary risk factor for infection with *Babesia* spp. is a tick bite and in view of the additional zoonotic diseases that the vectors of human babesiosis transmit, general measures to prevent tick bites are the most appropriate. For the vectors of *B. divergens* and *B. microti* (*I. ricinus* and *I. scapularis*, respectively) infectious tick bites are most likely to occur in areas where cattle are maintained on humid and rough pastures (*B. divergens*) and in deciduous woodland and peri-domestic settings (*B. microti*). The risk of *B. divergens* infection can be reduced by controlling ticks on cattle with pour-on acaricides and by pasture improvement (Zintl et al., 2003), though implementation of these measures is often inadequate. In the USA, a variety of methods have been used to suppress the vector of *B. microti* (and of other tick-borne pathogens), including the targeting of wild animals with acaricides, for example baited tubes for rodents and the 4-Poster acaricide-application device for deer (Piesman and Eisen, 2008). A recent study in 5 eastern states found that the 4-Poster device achieved reductions in *I. scapularis* populations of 60–82% over a 2-year period, and it was concluded this host-targeted measure is efficacious, economical and environmentally friendly (Pound et al., 2009).

Total avoidance of tick habitats by the public may not be practical, but increasing public awareness of the threat posed by ticks and of personal protection measures, such as the wearing of appropriate clothing, application of repellents, and prompt removal of attached ticks, are probably the most effective preventive measures currently available (Piesman and Eisen, 2008). Such measures are all the more necessary for asplenic individuals and other immunocompromised patients since such people are at increased risk for severe babesiosis.

Species that cause asymptomatic infections, such as *B. microti* and *B. duncani*, can also be transmitted by blood transfusion, and in view of the subclinical status of many infections and the persistence of the parasite in stored blood, this route of infection is cause for concern. Between 1979 and 2006 more than 70 cases were reported with the actual number probably being much higher (Leiby, 2006). Numbers of cases are difficult to determine because the disease is not reported nationally and furthermore it is likely that new cases are not thought to be sufficiently noteworthy for publication. There are no recognised screening tests or standard procedures to inactivate parasites, and the feasibility of preventing contamination of the blood supply appears uncertain (Leiby, 2006). The current situation was summarised in a recent workshop (Gubernot et al., 2009), in which possible approaches for the screening of the blood supply and inactivation of the pathogen were addressed.

Conclusion

Reports of human babesiosis cases will probably occur more frequently in the future as a result of increased medical and public awareness, and the rising numbers of immunocompromised patients. Advances in molecular taxonomy have helped to detect new pathogens and to elucidate some aspects of their ecology. However, for other species there is still no information on the identity of vertebrate reservoirs or tick vectors. Educating the public on infection risk and personal protection measures, and health providers on the details and pitfalls of diagnosis and treatment, are the most appropriate ways to prevent and control this potentially dangerous disease.

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