 

# *Babesia* spp. infections transmitted through blood transfusion[1]

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**ABSTRACT.** Babesiosis in humans is caused by infection with various species of *Babesia* (Apicomplexa, Piroplasmida), mainly transmitted by an arthropod vector – *Ixodes* spp. ticks. This review will focus on blood transfusion as another mode of *Babesia* transmission, especially in endemic areas, as well as the impact of human babesiosis on transfusion medicine.

**Key words**: *Babesia* spp., human babesiosis, zoonosis, tick-transmitted, blood transfusion-transmitted

Babesiosis in humans is a potentially emerging tick-borne zoonotic disease caused by infection of red blood cells (RBCs) with various species of protozoan of the genus *Babesia* (Apicomplexa, Piroplasmida). This disease has been recognized for over 40 years, with the first fatal case reported in 1957 in former Yugoslavia (Croatia) [1], and the first confirmed case in the USA described in 1966 on Nantucket Island of the New England coast [2,3]. To date, nearly all cases of human babesiosis reported in the literature (over 1000) have been attributed to the rodent parasite *Babesia microti*, which is a cause of endemic human disease, especially in the Northeast – including Rhode Island – and upper Midwest of the United States [4–6]. Recently, WA1-, MO1- and CA1-type *Babesia* species have been identified as causing clinical symptoms of babesiosis in the United States, and some of these isolates have been characterized by molecular analysis and described as a new species *B. duncani* [5].

In Europe, babesiosis is a considerably rare disease but more severe than typical infections with *B. microti*. Since 1956, over 30 cases of infection in humans have been attributed to the cattle species *B. divergens*. Recently, two new human cases of babesiosis in Italy and Austria were found to be caused by infection with closely related species (referred to as EU1) that could be clearly differentiated from *B. divergens* by their molecular characteristics [7]. Another report described a case of infection in Germany with a *Babesia* species exhibiting > 99% homology with 18S rDNA sequence of the recently described *Babesia* EU1-type, clustering within the *B. divergens*/*B. odocoilei* complex [8]. The EU1-type *Babesia* have now been described as a new species *B. venatorum* [7]. Interestingly, the rodent species *B. microti* is also present throughout Europe, both in the wild animal reservoir and in its vector, *I. ricinus* ticks [9]. However, there has only been one verified case of human babesiosis due to infection by this parasite – in Germany [10]. The biology and epidemiology of two species of *Babesia* (*B. microti* and *B. divergens*) occurring in Poland have recently been reviewed by Siński and Welc-Falęciak [9].

*Babesia* spp. infections are transmitted primarily through the bite of an infected *Ixodes* spp. tick. Less common routes of transmission are transplacentally or perinatally (congenital babesiosis) and by blood transfusion. Transplacental-perinatal infection was described by Esernio-Jenssen et al. [11] and New et

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Table 1. Number of cases and routes of *Babesia* spp. transmission in neonates

| Number of cases | Route of transmission | References |
|---|---|---|
| 2 | tick-transmitted | Scimeca et al., 1986 [13] |
| 6 | transfusion-transmitted | Fox et al., 2006 [14] |
| 2 | congenital | Esernio-Jenssen et. al., 1987 [11]; New et. al., 1997 [12] |

al. [12] (Table 1). From 1987 to 2009 only three cases of congenital babesiosis were reported in the United States [15]. However, since 1979, between 70 and 100 blood transfusion-related cases with significant associated morbidity and mortality were reported in this country, while the actual number has presumably been much higher [16,17]. In Poland, only seven human cases of babesiosis have been reported, including one imported from Brazil [18], another with strong molecular evidence of infection with EU1-type *Babesia* (*B. venatorum*) [19], as well as five cases of foresters who were anti-*B. microti* IgG positive [20] (Table 2). Besides the cases in the United States and one in Japan, there have been no reports of transfusion-transmitted babesiosis from other countries, and its occurrence in Europe is not well defined [17,6]. The characteristics of *Babesia* species and the numbers of transfusion-transmitted cases of human babesiosis are presented in Table 3.

Human babesiosis, as a zoonotic malaria-like disease can exhibit a spectrum of clinical symptoms, from asymptomatic infection to a severe life-threatening illness [21]. Asymptomatic babesiosis infections, especially with *B. microti*, are frequently undetected. They are generally self-limiting, lasting for 1–6 weeks after infection, although in some cases, low level parasitaemia may persist for over a year [22]. It has been well established that clearance of parasites from the blood is dependent on both the immunological status of the infected person and the *Babesia* species or genotype. Severe disease symptoms, which can appear suddenly after infection, usually in immunosuppressed individuals, include haemolytic anaemia, thrombocytopenia, haematuria and renal failure. Additional complications like disseminated intravascular coagulation and adult respiratory distress syndrome may also occur [23]. In groups at high risk of infection (infants, elderly, asplenic and HIV positive persons) the clinical disease can progress rapidly, sometimes resulting in very high levels of parasitaemia of up to 75%, 1–3 weeks after infection [17]. Infections with *B. microti* are generally mild compared with the more severe and often fulminant life-threatening infections with *B. divergens*.

Suspected *Babesia* infection in symptomatic individuals, whose illness was most likely the result of a tick bite, has to be confirmed by laboratory evidence. This can include direct testing for the parasite by (1) identification of intraerythrocytic *Babesia* in a peripheral blood smear by light microscopy, (2) isolation of the parasite from a blood specimen by intraperitoneal inoculation of hamsters and weekly examination of smears of blood obtained by tail snip, or (3) identification of *B. microti* DNA in a blood specimen by polymerase chain reaction (PCR) analysis. This is supported by indirect testing, i.e. the demonstration of *Babesia* specific antibodies. A total immunoglobulin (Ig) or IgG titer of at least 1:64 in an indirect fluorescent antibody assay (IFA) has been used as a specific cutoff associated with asymptomatic infection, whereas *Babesia* IFA titers of 1:1024 and above are associated with symptomatic infection. However, according to Herwaldt et al. [7], if serological data are the only diagnostic criteria, the case should be considered probable rather than confirmed.

Human babesiosis is the most common tick-borne disease transmitted by blood transfusion from

Table 2. Characteristics of human infections with *Babesia* spp. in Poland

| No. of cases | Co-infection | Methods of detection | References |
|---|---|---|---|
| 1 | unknown | microscopy of stained blood smear (not well defined) | Humiczewska and Kuźna-Grygiel [18] |
| 1 | co-infection with *Borrelia burgdorferi* | PCR, sequence analysis of 18S rDNA | Welc-Falęciak et al. [19] |
| 5 | co-infection with *Borrelia burgdorferi* | IFA anti-*B. microti* IgG | Pancewicz et al. [20] |
| Total = 7 | | | |

Table 3. Summary of transfusion-transmitted cases of human babesiosis (after Gray et al. [21] and Leiby [6] with modifications)

| Species | Distribution (genotype) | Vector | Reservoir host | No. of transfusion-transmitted cases |
|---|---|---|---|---|
| *Babesia microti* | USA | *Ixodes scapularis* | Rodents, shrews | 70-100 |
| | Europe | *Ixodes ricinus*<br>*Ixodes trianguliceps* | *Myodes glareolus*<br>*Apodemus* sp.<br>*Microtus arvalis*<br>*Microtus oeconomus* | 1 |
| | Japan | *Ixodes persulcatus* | *Apodemus speciosus* | 1 |
| | Taiwan (TW-1) | unknown | rodents | 0 |
| *Babesia divergens* | Europe USA (MO-1) | *Ixodes ricinus*<br>unknown | cattle<br>unknown | 0 |
| *Babesia venatorum* | Europe (EU-1) | *Ixodes ricinus* | deer | 0 |
| *Babesia duncani* | USA (WA-1-WA-2 and CA-5-CA-6) | unknown | unknown | 2 |
| Other *Babesia* spp. | South Korea (KO-1) | unknown | ruminants (sheep)? | 0 |

individuals with asymptomatic infection and prolonged parasitaemia. These blood donors unknowingly harbour circulating parasites for months to years [24]. The reported incubation period of transfusion-transmitted babesiosis is 4–9 weeks [25], compared with 1–4 weeks for the tick-transmitted disease [26]. The issue of contaminated blood is complicated by the fact that *Babesia* trophozoites remain viable for 35 days during routine storage of red blood cell concentrates at 4°C and can survive in cryopreserved RBCs [27,28]. Using currently available low-sensitivity screening methods, asymptomatic infection is practically undetectable and the only means of screening blood donors is a questionnaire that includes a query regarding a known history of babesiosis. This means that the exclusion of donors with a potentially transmissible *Babesia* spp. infection remains problematic in endemic areas. The important problem of tick-borne diseases in the context of transfusion-transmitted pathogens, including *Babesia* spp. infections, has been the subject of a recent Polish review [29].

The problem of human babesiosis in Poland and across Europe is still not fully appreciated, and the impact of this disease on transfusion medicine is undoubtedly underestimated. Transfusion-transmitted babesiosis might play a role in the emergence of this disease, especially in the northeast of Poland where there are well recognized endemic areas for *Babesia* [20,30,31]. Current methods for screening blood donors (i.e. questions regarding previous infection) and the processing of blood and cryopreservation of RBCs do not completely eliminate the risk of transfusion-transmitted babesiosis. While this risk is real, it is important to maintain a balance between excessively restrictive approach eliminating blood donors and that taking into account actual risk of transfusion transmitted babesiosis. Thus, in European countries including Poland, further studies are required to evaluate the importance of *Babesia* spp. infections due to tick transmission and as a result of transfusion with contaminated blood components.

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## Zakażenie przez *Babesia* spp. drogą transfuzji krwi

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W prezentowanej pracy przedstawiono aktualny stan wiedzy dotyczący zakażenia ludzi pierwotniakami z rodzaju *Babesia* (Apicomplexa, Piroplasmida). Do gatunków inwazyjnych dla człowieka w Europie, w tym również w Polsce, należą: *Babesia divergens*, *B. venatorum* (*Babesia* typ EU1) i *B. microti*. W transmisji zakażenia tymi pasożytami udział biorą głównie kleszcze z rodzaju *Ixodes*. Od kilku lat obserwuje się w Polsce znaczny wzrost liczby kleszczy *I. ricinus* zakażonych tymi pasożytami, jak również coraz częściej stwierdza się zakażenie tymi pasożytami u ludzi. Stąd babeszjoza, jako jedna z chorób odkleszczowych (TBD) u ludzi, może mieć istotne znaczenie dla krwiodawstwa. Transfuzja krwi lub preparatów krwiopochodnych od dawców przebywających na terenach endemicznych dla *Babesia* spp. może stanowić zagrożenie zakażenia biorców, szczególnie dzieci do 2 roku życia, ludzi w podeszłym wieku, chorych po splenektomii, przyjmujących leki immunosupresyjne lub poddanych chemioterapii. Dane dotyczące realnej oceny ryzyka infekcji drogą krwi i preparatów krwiopochodnych jak i właściwej diagnostyki w fazie ostrej (babeszjoza) i przewlekłej infekcji u ludzi, są dyskutowane w świetle najnowszych osiągnięć w tym zakresie w USA.

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