



# Enfermedades Infecciosas y Microbiología Clínica

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## Editorial

### More threats: The increase in tick-borne diseases and their spectrum

### Más amenazas. El aumento de las enfermedades transmitidas por garrapatas y de su espectro

Hard tick-borne diseases (TBD) are in vogue, not only because famous people like Lady Diana, Princess of Wales, the president of the United States George W. Bush, actors such as Alec Baldwin and Richard Gere, or the singer Justin Bieber, among others, have suffered from Lyme borreliosis (LB). Recently, as warned by the European Centre for Disease Prevention and Control (ECDC) and other health agencies, or the renowned Dr. Fauci wrote, rivers of ink flow about the threat and increase of TBD.<sup>1,2</sup> The fact is that, although these “nasty blood-sucking arthropods” had been suspected of transmitting diseases for many centuries, it has only been 131 years since the first implication of hard ticks (*Ixodidae*) in the transmission of an infectious disease<sup>3</sup> and nowadays they are considered the main vectors of infectious diseases in the northern hemisphere, and worldwide after mosquitoes. Ticks have been existed long before humans walked the Earth. Thus, fossils of ticks have been found in 99 million-year-old amber next to a dinosaur feather.<sup>4</sup> There is evidence not only of the circulation of ticks for millions of years, but also of the agents that they transmit today. Two-thirds of the genome of the bacterium *Borrelia burgdorferi sensu stricto* have been found in the iceman mummy Ötzi, a man who lived around 5300 years ago.<sup>5</sup> Even more, some scientists suggest that a rickettsial ancestor may be involved in the origin of the mitochondria, and consequently in the origin of the eukaryotic cell.<sup>6</sup> All this without forgetting that some authors hypothesize that the fifth plague that God sent to the Egyptians (Exodus, 9:1–7), which caused the massive death of livestock, may have been related with the babesiosis.<sup>3</sup>

Focused in Spain, when one of the signatories of this editorial became interested in TBD, following the diagnosis of one of the first cases of LB in 1987, only Mediterranean spotted fever (MSF) or boutonniere fever (BF) (1928) and babesiosis (1984) have been described. Crimean-Congo haemorrhagic fever (CCHF) (1940) and tick-borne encephalitis (TBE) (1948) were also known in Europe, but thanks to clinical observation, to the greater availability of cell culture techniques and above all, to the incorporation of molecular biology techniques in clinical microbiology laboratories, the spectrum of TBD in Spain has expanded, with 16 diseases and/or infectious agents currently involved in human pathology.

Many contributions to the spectrum and aetiology of TBD have been made from Spain: the first report of tick paralysis in European

patients in 1990<sup>7</sup>; the description in 2002 of the rickettsial disease known as DEBONEL (acronym of *Dermacentor*-borne-necrosis-erythema-lymphadenopathy)<sup>8</sup> and the involvement of *Candidatus Rickettsia rioja* in this disease, main agent of this syndrome together with *Rickettsia slovaca*.<sup>9</sup> We also were involved in the current known *Rickettsia raoultii* as agent of DEBONEL, a syndrome that the Hungarians called TIBOLA (tick-borne lymphadenopathy) and a few years ago the group of Marseille included within the acronym SENLAT (scalp-eschar-and-neck-lymphadenopathy-after-tick-bite), although tick-bites frequently are found in the scalp in cases of DEBONEL.<sup>9</sup> Also from Spain, *Rickettsia monacensis* was involved as pathogen in 2007, causing a similar clinical picture as BF<sup>10</sup>; *Rickettsia parkeri* was identified as agent of spotted fever in South America in 2004<sup>11</sup> as well as later, 2010, *Rickettsia massiliae*.<sup>12</sup> From our Centre of Rickettsiosis and Arthropod-Borne Diseases (CRETAV), we have also contributed on the spectrum of other TBD in Spain that had already been described in other European countries, such as anaplasmosis in 1999<sup>13</sup>; the *Rickettsia sibirica mongolitimonae* infection in 2008,<sup>14</sup> or the recent description of the first case of *Neoehrlichia mikurensis* infection in our country.<sup>15</sup>

Of particular interest, due to the implications it has and is likely to have, was the description of the circulation of the Crimean-Congo hemorrhagic fever virus (CCHFV) in ticks collected from deer in Cáceres in 2010.<sup>16</sup> It is worth recalling the facts. For years, we had been observing patients with bites caused by the tick *Hyalomma marginatum* in our practices, and this was unusual. Until then, we mainly observed bites caused by *Ixodes ricinus*, vector in our area of LB, babesiosis, anaplasmosis, *R. monacensis* infection, current neoehrlichiosis, and probably *Rickettsia helvetica* infection, as well as TBE in other areas of Europe. Moreover, although less frequently, we observed tick bites from the complex *Rhipicephalus sanguineus*, vectors of the MSF or BF and the emerging *R. sibirica mongolitimonae* infection, that is widely distributed throughout the Iberian Peninsula and causes a wide spectrum of clinical manifestations.<sup>17</sup> We also observed bites by *Dermacentor marginatus*, vector of DEBONEL and tularemia, in the coldest months of the year. The question was that, if some species of the *Hyalomma* genus were recognized vectors of CCHFV and it was the most geographically widespread tick-borne arbovirosis, why would not be circulating in our area? Convinced of the paradigm “what is not sought is not found”, which had given us such good results with other TBD, and with the support of the Spanish Health

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Research Fund (FIS; PS09/02492), we started looking for the virus. The surprise was the finding of the CCHFV in *H. lusitanicum* instead of *H. marginatum* specimens,<sup>16</sup> the latter being a recognized vector that bite humans more frequently. Our early detection alerted of the risk of disease outbreaks. Could human cases be going unnoticed? At the end of August 2016, Dr. Patricia Muñoz from the “Hospital Universitario Ramón y Cajal” and Dr. José R. Arribas from the “Hospital Universitario La Paz”, shared with us the case of a nurse who had recently cared for a patient who had died of multi-organ failure in whom an overlapping clinical picture was being reproduced. It was not clear, but it was possible that the index case had been bitten by a tick in a rural area of Ávila, rich in livestock.<sup>18</sup> CCHF is primarily a tick-borne condition but can lead to nosocomial cases and outbreaks through contact with CCHFV-infected secretions or tissues. We recommended ruling out this infection, which was confirmed at the National Microbiology Centre, also allowing retrospective diagnosis of the index case.<sup>18</sup> A retrospective case from 2013 was reported in 2021, when the virus was detected in frozen samples, and to date 17 autochthonous cases have been reported in Spain, six of them fatal (RENAVE; <https://cne.isciii.es/es/servicios/enfermedades-transmisibles/protocolos-renave>).

Genetic studies suggested that the virus had been circulating in Spain for several decades, and although the first serological study that we performed, in population at risk from areas close to that in which the virus was detected in ticks and in samples from the sera collection from the CRETAV, gave negative results, subsequent analyses have demonstrated that the infection is more widespread than we previously thought.<sup>19</sup> In the current issue of the “Enfermedades Infecciosas y Microbiología Clínica” journal, Dr. Lorenzo-Juanes et al.<sup>20</sup> have studied during 2023 the seroprevalence of CCHF in 658 patients from the area of Béjar (12,021 inhabitants) without suspected disease, with the detection of antibodies against CCHFV in four of them (0.6%). In their discussion, among other aspects, they review the serological findings from previous studies that have shown IgG seroprevalences of CCHFV of 1.16% in donors and 2.22% in febrile patients in areas where the vector and the virus circulate.<sup>19,20</sup> The area of Béjar can be considered endemic for CCHF since a not inconsiderable percentage of the 17 cases reported to RENAVE have occurred in Salamanca, specifically in that geographical area. The epidemiological characteristics of the individuals in the sample studied could be overlapping those of other areas of Spain exposed to *Hyalomma* spp. We cannot guess the future, and we do not know if there is a real increase in the number of cases of CCHF, and/or some other TBD. To date, the impression of those who subscribe to this editorial is that they are on the rise. Nevertheless, and in support of this view, it should be noted that four out of the 17 cases of CCHF reported from 2013 to date have been occurred this year; it is recognized that several factors facilitate the geographical spread of ticks and the exposition to them; it is also true, as a positive factor, that we are more aware and have more resources for the diagnosis. What will happen? John Lennon said, “tomorrow never knows”. There is no doubt that we are facing an emerging arboviro-sis, which causes from asymptomatic/oligosymptomatic infection to fatal cases (35% of the cases diagnosed in Spain) transmitted for one or more tick species (everything suggests that not only *H. marginatum* is involved, but also *H. lusitanicum*). There is no vaccine available and no antiviral treatment with clearly effective activity against this arboviro-sis. So, remember that “what is not sought is not found” and, at the moment, the best weapon to prevent complications and nosocomial outbreaks is an early diagnosis.<sup>19</sup> What will happen?

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