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WJCID will focus on a broad spectrum of topics on infectious diseases that will cover epidemiology, immune-pathogenesis, genetic factors, host susceptibility to infection, vector control, novel approaches of treatment, molecular diagnostic and vaccines. It will provide a common stage to share the visions, new approaches, most advanced techniques, and to discuss research problems that will help everyone working in the field of various infections to exchange their views and to improve public health. *WJCID* will also focus on broad range of infections like opportunistic infections, zoonotic infections, tropical and neglected tropical diseases, emerging infections, *etc.* and following topics related to these issues: (1) Causative agents discussing various pathogens; (2) Vectors and Mode of transmission; (3) Host-pathogen interaction and immune-pathogenesis of the disease; (4) Epidemiology of the infection and vector control strategies; (5) Genetic factors covering both host and pathogen; (6) Molecular diagnostic techniques vaccines; and (7) Recent advances in cell tissue culture, lab techniques, *etc.* Various other related fields like medical microbiology, pharmacology of herbs, bioinformatics, *etc.* will be included.

We encourage authors to submit their manuscripts to *WJCID*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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New tools, new tick-borne diseases?

Aránzazu Portillo, José A Oteo

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Abstract

Tick-borne diseases (TBDs) are a major public health concern that has increased in the past three decades. Nevertheless, emerging or reemerging TBDs may be still misdiagnosed. Molecular biology techniques for the screening of ticks, use of "Omics" approaches and

the incorporation of analytical methods such as mass spectrometry or nuclear magnetic resonance, to the study of ticks and their associated pathogens or potential pathogens are promising tools for a more accurate differential diagnosis of TBDs. However, this huge amount of data needs to be carefully interpreted before being incorporated to the routine of clinical practice. In the meantime, a clinical approach and high level of suspicion keep being essential for the diagnosis and proper handling of TBDs.

Key words: Ticks; Tick-borne diseases; Tick-borne pathogens; Molecular biology tools; DNA-arrays; "Omics" approaches; Analytical tools; Mass spectrometry; Nuclear magnetic resonance

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Core tip: Tick-borne diseases (TBDs) are a major public health concern that has increased in the past three decades. Molecular biology techniques for the screening of ticks, use of "Omics" approaches and the incorporation of analytical methods to the study of ticks and their associated microorganisms are promising tools for a more accurate differential diagnosis of TBDs. Nevertheless, a clinical approach and high level of suspicion remain essential for the diagnosis and proper handling of TBDs before the incorporation of these innovative technologies to the routine in clinical practice.

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TEXT

Tick-borne diseases (TBDs) are a major public health concern that has increased in the past three decades.

Thus, for instance, in 1988 only Mediterranean spotted fever caused by *Rickettsia conorii*, and babesiosis caused by *Babesia* spp., were recognized as TBDs in Spain (southern Europe). Nowadays the list of known TBDs has grown thanks to clinical observation together with the use and development of new microbiological techniques. To date, patients diagnosed of Lyme borreliosis, Spotted Fever due to *Rickettsia* spp. (*R. conorii*, *Rickettsia monacensis*, *Rickettsia sibirica mongolimitimoniae* and *Rickettsia massiliae*), *Dermacentor*-borne necrosis, erythema and lymphadenopathy/Tick-borne lymphadenopathy (DEBONEL/TIBOLA) caused by *Rickettsia slovaca*, *Rickettsia rioja* and *Rickettsia raoultii*, besides human anaplasmosis, human babesiosis and tick paralysis have been reported in our country^[1-3]. The discovery of new TBDs and the identification of TBDs in new geographical regions have also occurred in other parts of the world. Rickettsioses caused by *Rickettsia parkeri* or by *R. massiliae* or the Bourbon virus disease caused by Bourbon virus, a new virus thought to be transmitted by ticks, serve as examples^[4-6]. Not only we have involved microorganisms in different syndromes and diseases but also, using new techniques, we have discovered "new microorganisms" that are good candidates to be considered pathogens for humans and animals^[7-13]. Nevertheless, we assume that other TBDs in our environment may have been misdiagnosed due to the lack of clinical suspicion or diagnostic tools, or because to date they have been absent.

In the last years, the identification of tick-associated pathogens has been frequently based on polymerase chain reaction screening, sequencing and subsequent nucleotide sequence analyses. Supported on the aphorism "If you do not look for it, you do not find it", our team has been able to detect tick-borne bacteria and viruses, such as *Candidatus* Neohrlichia mikurensis and Crimean-Congo hemorrhagic fever virus, for the first time in ticks from Spain^[14,15]. As it has occurred with other human pathogens previously described in arthropods worldwide, these evidences of the presence of microorganisms are useful tools to be aware of the risk of exposure to certain infections in an area. Clinicians must include unexpected TBDs in the differential diagnosis of patients with epidemiological background and unspecific clinical manifestations, especially if they are elderly people with underlying diseases. In these cases, failure of diagnosis may lead to a fatal outcome^[16].

Microbial culture is the gold-standard diagnostic method in microbiology. However, bacteria transmitted by ticks are fastidious and difficult to grow in axenic media, and many of them are obligate intracellular bacteria. Cell-culture procedures are time-consuming and isolation of microorganisms is not always successful^[17].

Serologic methods, especially immunofluorescence assays, support the diagnosis of TBDs but sera samples of patients in acute and convalescent phases of the disease are needed and cross-reactions are a common problem. Hence and up to date, serologic assays are

accepted as valid to confirm a rickettsial syndrome but not an infection caused by a certain *Rickettsia* spp.^[17].

More recent, and still non-commercial for diagnosis, are sandwich immunoassays for the quantification of IgE specific antibodies that have enabled to associate tick bites and food allergy. Patients frequently bitten by ticks have shown an increased level of IgE antibodies to the oligosaccharide galactose- α -1,3-galactose (alpha-gal) that seems related to delayed red meat anaphylaxis^[18]. In our area (northern Spain), where ticks are endemic, a study performed with risk population by our group revealed nearly 30% sensitization to alpha-gal^[19].

In the post-genomic era, DNA microarrays-based technologies have enabled simultaneous identification of several tick-borne pathogens in ticks^[20]. Nevertheless, the application of DNA arrays to the diagnoses of TBDs using human samples is still in progress^[21]. Based on complete genome sequences, these methods have been also used for the global analysis of gene expression patterns (transcriptome) in *R. conorii*^[22,23] and *Borrelia burgdorferi*^[24]. DNA microarrays can be useful for the identification of markers to provide a guide on the etiology and virulence or to monitor the course or treatment of a TBD.

Recently, the analysis of the tick microbiome (bacterial communities associated with ticks) is possible using next generation sequencing (NGS) methods based on 16S rRNA sequencing^[25,26]. It has been evidenced that interactions among microbes within the tick vector can at least modulate pathogen transmission, vector competence and tick reproductive fitness^[27-30]. Also in this context, the study of relationships between tick-transmitted pathogens and their environment (a term coined as pathobiome) is increasing the knowledge on TBDs from a new multidisciplinary point of view.

Other novel "Omics" technologies such as proteomics, metabolomics, immunomics, and vaccinomics provide a huge amount of data with relative low cost and effort^[31,32]. These innovative approaches will contribute to predict emerging TBDs in a near future that has already started.

Moreover, in the last few years matrix-assisted laser desorption/ionization time-of-flight mass spectrometry has become a powerful tool for the rapid one-shot identification of ticks and cultured tick-borne bacteria such as *Borrelia* spp. and *Rickettsia* spp.^[33-35].

Other techniques, such as nuclear magnetic resonance spectroscopic methods applied to the study of the metabolism of tick-borne bacteria such as *Rickettsia* species also provide a challenging approach in this research field^[36].

Despite the development of molecular and analytical tools, there are still patients bitten by ticks with unspecific clinical manifestations of unknown etiology. Nowadays, NGS methods combined with bioinformatics are providing an inventory of predicted and/or unexpected pathogenic bacteria harbored by ticks. These findings will enable to include novel potential pathogens, in addition to known species, in the differential diagnosis of TBDs. At the same

time that these tools are incorporated into the routine, a clinical approach and high level of suspicion remain necessary for diagnosis and proper handling of TBDs.

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