World Journal of Clinical Infectious Diseases

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5495/wjcid.v5.i3.51

World J Clin Infect Dis 2015 August 25; 5(3): 51-54
ISSN 2220-3176 (online)

EDITORIAL

New tools, new tick-borne diseases?

Aránzazu Portillo, José A Oteo

Aránzazu Portillo, José A Oteo, Infectious Diseases Department, Hospital San Pedro-Center for Biomedical Research from La Rioja (CIBIR), Center of Rickettsioses and Arthropod-Borne Diseases, 26006 Logroño, La Rioja, Spain

Author contributions: Portillo A and Oteo JA contributed to this paper.

Conflict-of-interest statement: Authors declare no conflict of interests.

Correspondence to: José A Oteo, MD, PhD, Head of the Infectious Diseases Department, Hospital San Pedro-Center for Biomedical Research from La Rioja (CIBIR), Center of Rickettsioses and Arthropod-Borne Diseases, C/Piqueras, 98, 26006 Logroño, La Rioja, Spain. jaoteo@riojasalud.es
Telephone: +34-941-278871
Fax: +34-941-298667

Received: February 8, 2015
Peer-review started: February 9, 2015
First decision: March 6, 2015
Revised: March 17, 2015
Accepted: July 29, 2015
Article in press: August 3, 2015
Published online: August 25, 2015

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

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.

Portillo A, Oteo JA. New tools, new tick-borne diseases? *World J Clin Infect Dis* 2015; 5(3): 51-54 Available from: URL: http://www.wjgnet.com/2220-3176/full/v5/i3/51.htm DOI: http://dx.doi.org/10.5495/wjcid.v5.i3.51

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 mongolitimonae* 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* Neoehrlichia 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.

REFERENCES

1 **Oteo JA**, Portillo A. Tick-borne rickettsioses in Europe. *Ticks Tick Borne Dis* 2012; **3**: 271-278 [PMID: 23177355 DOI: 10.1016/j.ttbdis.2012.10.035]

2 **Portillo A**, Santibáñez S, Oteo JA. Lyme disease. *Enferm Infecc Microbiol Clin* 2014; **32** Suppl 1: 37-42 [PMID: 24630582 DOI: 10.1016/S0213-005X(14)70148-X]

3 **García JC**, Núñez MJ, Portillo A, Oteo JA. Human anaplasmosis: two case-reports. *Enferm Infecc Microbiol Clin* 2015; **33**: 68-69 [PMID: 25073813 DOI: 10.1016/j.eimc.2014.05.009]

4 **Paddock CD**, Sumner JW, Comer JA, Zaki SR, Goldsmith CS, Goddard J, McLellan SL, Tamminga CL, Ohl CA. Rickettsia parkeri: a newly recognized cause of spotted fever rickettsiosis in the United States. *Clin Infect Dis* 2004; **38**: 805-811 [PMID: 14999622]

5 **García-García JC**, Portillo A, Núñez MJ, Santibáñez S, Castro B, Oteo JA. A patient from Argentina infected with Rickettsia massiliae. *Am J Trop Med Hyg* 2010; **82**: 691-692 [PMID: 20348520 DOI: 10.4269/ajtmh.2010.09-0662]

6 **Kosoy OI**, Lambert AJ, Hawkinson DJ, Pastula DM, Goldsmith CS, Hunt DC, Staples JE. Novel Thogotovirus species associated with febrile illness and death, United States, 2014. *Emerg Infect Dis* 2015; **21**: 760-764 [DOI: 10.3201/eid2105.150150]

7 **Portillo A**, Santibáñez P, Santibáñez S, Pérez-Martínez L, Oteo JA. Detection of Rickettsia spp. in Haemaphysalis ticks collected in La Rioja, Spain. *Vector Borne Zoonotic Dis* 2008; **8**: 653-658 [PMID: 18454590 DOI: 10.1089/vbz.2007.0272]

8 **Portillo A**, Ibarra V, Santibáñez S, Pérez-Martínez L, Blanco JR, Oteo JA. Genetic characterisation of ompA, ompB and gltA genes from Candidatus Rickettsia rioja. *Clin Microbiol Infect* 2009; **15** Suppl 2: 307-308 [PMID: 19438649 DOI: 10.1111/j.1469-0691.2008.02250.x]

9 **Miranda J**, Portillo A, Oteo JA, Mattar S. Rickettsia sp. strain colombianensi (Rickettsiales: Rickettsiaceae): a new proposed Rickettsia detected in Amblyomma dissimile (Acari: Ixodidae) from iguanas and free-living larvae ticks from vegetation. *J Med Entomol* 2012; **49**: 960-965 [PMID: 22897060]

10 **Palomar AM**, Portillo A, Santibáñez P, Santibáñez S, García-Álvarez L, Oteo JA. Genetic characterization of Candidatus Rickettsia vini, a new rickettsia amplified in ticks from La Rioja, Spain. *Ticks Tick Borne Dis* 2012; **3**: 319-321 [PMID: 23140892 DOI: 10.1016/j.ttbdis.2012.10.025]

11 **Lopez-Velez R**, Palomar AM, Oteo JA, Norman FF, Pérez-Molina JA, Portillo A. Novel Candidatus rickettsia species detected in nostril tick from human, Gabon, 2014. *Emerg Infect Dis* 2015; **21**: 325-327 [PMID: 25625886 DOI: 10.3201/eid2102.141048]

12 **Palomar AM**, Portillo A, Crespo A, Santibáñez S, Mazuelas D, Oteo JA. Prevalence of 'Candidatus Rickettsia vini' in Ixodes arboricola ticks in the North of Spain, 2011-2013. *Parasit Vectors* 2015; **8**: 110 [PMID: 25889739 DOI: 10.1186/s13071-015-0724-6]

13 **Pesquera C**, Portillo A, Palomar AM, Oteo JA. Investigation of tick-borne bacteria (Rickettsia spp., Anaplasma spp., Ehrlichia spp. and Borrelia spp.) in ticks collected from Andean tapirs, cattle and vegetation from a protected area in Ecuador. *Parasit Vectors* 2015; **8**: 46 [PMID: 25616567 DOI: 10.1186/s13071-015-0662-3]

14 **Palomar AM**, García-Álvarez L, Santibáñez S, Portillo A, Oteo JA. Detection of tick-borne 'Candidatus Neoehrlichia mikurensis' and Anaplasma phagocytophilum in Spain in 2013. *Parasit Vectors* 2014; **7**: 57 [PMID: 24484637 DOI: 10.1186/1756-3305-7-57]

15 **Estrada-Peña A**, Palomar AM, Santibáñez P, Sánchez N, Habela MA, Portillo A, Romero L, Oteo JA. Crimean-Congo hemorrhagic fever virus in ticks, Southwestern Europe, 2010. *Emerg Infect Dis* 2012; **18**: 179-180 [PMID: 22261502 DOI: 10.3201/eid1801.111040]

16 **Grankvist A**, Andersson PO, Mattsson M, Sender M, Vaht K, Höper L, Sakiniene E, Trysberg E, Stenson M, Fehr J, Pekova S, Bogdan C, Bloemberg G, Wennerås C. Infections with the tick-borne bacterium "Candidatus Neoehrlichia mikurensis" mimic noninfectious conditions in patients with B cell malignancies or autoimmune diseases. *Clin Infect Dis* 2014; **58**: 1716-1722 [PMID: 24647019 DOI: 10.1093/cid/ciu189]

17 **Brouqui P**, Bacellar F, Baranton G, Birtles RJ, Bjoërsdorff A, Blanco JR, Caruso G, Cinco M, Fournier PE, Francavilla E, Jensenius M, Kazar J, Laferl H, Lakos A, Lotric Furlan S, Maurin M, Oteo JA, Parola P, Perez-Eid C, Peter O, Postic D, Raoult D, Tellez A, Tselentis Y, Wilske B. Guidelines for the diagnosis of tick-borne bacterial diseases in Europe. *Clin Microbiol Infect* 2004; **10**: 1108-1132 [PMID: 15606643]

18 **Commins SP**, James HR, Kelly LA, Pochan SL, Workman LJ, Perzanowski MS, Kocan KM, Fahy JV, Nganga LW, Ronmark E, Cooper PJ, Platts-Mills TA. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-α-1,3-galactose. *J Allergy Clin Immunol* 2011; **127**: 1286-93.e6 [PMID: 21453959 DOI: 10.1016/j.jaci.2011.02.019]

19 **Venturini M**, Lobera T, Portillo A, Oteo JA, Blasco A, González I. Sensibilización a alfa-gal en pacientes con múltiples picaduras por garrapata en La Rioja. *J Investig Allergol Clin Immunol* 2013; **23** Suppl 2: 170

20 **Melničáková J**, Derdáková M, Barák I. A system to simultaneously detect tick-borne pathogens based on the variability of the 16S ribosomal genes. *Parasit Vectors* 2013; **6**: 269 [PMID: 24330462 DOI: 10.1186/1756-3305-6-269]

21 **Jääskeläinen AJ**, Viitala SM, Kurkela S, Hepojoki S, Sillanpää H, Kallio-Kokko H, Bergström T, Suni J, Närvänen A, Vapalahti O, Vaheri A. Performance of a multiplexed serological microarray for the detection of antibodies against central nervous system pathogens. *J Microbiol Methods* 2014; **100**: 27-31 [PMID: 24594410 DOI: 10.1016/j.mimet.2014.02.011]

22 **La MV**, François P, Rovery C, Robineau S, Barbry P, Schrenzel J, Raoult D, Renesto P. Development of a method for recovering rickettsial RNA from infected cells to analyze gene expression profiling of obligate intracellular bacteria. *J Microbiol Methods* 2007; **71**: 292-297 [PMID: 17964675]

23 **Renesto P**, Rovery C, Schrenzel J, Leroy Q, Huyghe A, Li W, Lepidi H, François P, Raoult D. Rickettsia conorii transcriptional response within inoculation eschar. *PLoS One* 2008; **3**: e3681 [PMID: 18997861 DOI: 10.1371/journal.pone.0003681]

24 **Ellis TC**, Jain S, Linowski AK, Rike K, Bestor A, Rosa PA, Halpern M, Kurhanewicz S, Jewett MW. In vivo expression technology identifies a novel virulence factor critical for Borrelia burgdorferi persistence in mice. *PLoS Pathog* 2013; **9**: e1003567 [PMID: 24009501 DOI: 10.1371/journal.ppat.1003567]

25 **Carpi G**, Cagnacci F, Wittekindt NE, Zhao F, Qi J, Tomsho LP, Drautz DI, Rizzoli A, Schuster SC. Metagenomic profile of the bacterial communities associated with Ixodes ricinus ticks. *PLoS One* 2011; **6**: e25604 [PMID: 22022422 DOI: 10.1371/journal.pone.0025604]

26 **Vayssier-Taussat M**, Moutailler S, Michelet L, Devillers E, Bonnet S, Cheval J, Hébert C, Eloit M. Next generation sequencing uncovers unexpected bacterial pathogens in ticks in western Europe. *PLoS One* 2013; **8**: e81439 [PMID: 24312301 DOI: 10.1371/journal.pone.0081439]

27 **Macaluso KR**, Sonenshine DE, Ceraul SM, Azad AF. Rickettsial infection in Dermacentor variabilis (Acari: Ixodidae) inhibits transovarial transmission of a second Rickettsia. *J Med Entomol* 2002; **39**: 809-813 [PMID: 12495176]

28 **Burgdorfer W**, Brinton LP, Hughes LE. Isolation and characterization of symbiotes from the Rocky Mountain wood tick, Dermacentor andersoni. *J Invertebr Pathol* 1973; **22**: 424-434 [PMID: 4202564]

29 **Clay K**, Klyachko O, Grindle N, Civitello D, Oleske D, Fuqua C. Microbial communities and interactions in the lone star tick, Amblyomma americanum. *Mol Ecol* 2008; **17**: 4371-4381 [PMID: 19378409]

30 **Zhong J**, Jasinskas A, Barbour AG. Antibiotic treatment of the tick vector Amblyomma americanum reduced reproductive fitness.

PLoS One 2007; **2**: e405 [PMID: 17476327]

31 **Marcelino I**, de Almeida AM, Ventosa M, Pruneau L, Meyer DF, Martinez D, Lefrançois T, Vachiéry N, Coelho AV. Tick-borne diseases in cattle: applications of proteomics to develop new generation vaccines. *J Proteomics* 2012; **75**: 4232-4250 [PMID: 22480908 DOI: 10.1016/j.jprot.2012.03.026]

32 **de la Fuente J**, Merino O. Vaccinomics, the new road to tick vaccines. *Vaccine* 2013; **31**: 5923-5929 [PMID: 24396872]

33 **Yssouf A**, Flaudrops C, Drali R, Kernif T, Socolovschi C, Berenger JM, Raoult D, Parola P. Matrix-assisted laser desorption ionization-time of flight mass spectrometry for rapid identification of tick vectors. *J Clin Microbiol* 2013; **51**: 522-528 [PMID: 23224087 DOI: 10.1128/JCM.02665-12]

34 **Calderaro A**, Gorrini C, Piccolo G, Montecchini S, Buttrini M, Rossi S, Piergianni M, Arcangeletti MC, De Conto F, Chezzi C, Medici MC. Identification of Borrelia species after creation of an in-house MALDI-TOF MS database. *PLoS One* 2014; **9**: e88895 [PMID: 24533160 DOI: 10.1371/journal.pone.0088895]

35 **Yssouf A**, Almeras L, Terras J, Socolovschi C, Raoult D, Parola P. Detection of Rickettsia spp in ticks by MALDI-TOF MS. *PLoS Negl Trop Dis* 2015; **9**: e0003473 [PMID: 25659152 DOI: 10.1371/journal.pntd.0003473]

36 **García-Álvarez L**, Busto JH, Peregrina JM, Fernández Recio MA, Avenoza A, Oteo JA. Nuclear magnetic resonance applied to antimicrobial drug susceptibility. *Future Microbiol* 2013; **8**: 537-547 [PMID: 23534364 DOI: 10.2217/fmb.13.8]

P- Reviewer: Bonilauri P, Garcia-Elorriaga G, Moschovi M
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com