International Journal of Infectious Diseases xxx (2013) xxx.e1–xxx.9

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Treatment outcomes of human bartonellosis: a systematic review and meta-analysis

Gabriela Prutsky [a,b,*], Juan Pablo Domecq [a,b], Laura Mori [b,c], Serge Bebko [b], Melissa Matzumura [b,d], Amar Sabouni [a], Anas Shahrour [a], Patricia J. Erwin [e], Thomas G. Boyce [f], Victor M. Montori [a,b,g], German Malaga [b], M. Hassan Murad [a,h]

[a] *Knowledge and Evaluation Research Unit (KER), Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA*
[b] *Unidad de Conocimiento y Evidencia (CONEVID), Universidad Peruana Cayetano Heredia, Lima, Peru*
[c] *Departamento de Farmacología, Facultad de Ciencias y Filosofía "Alberto Cazorla Talleri", Universidad Peruana Cayetano Heredia, Lima, Peru*
[d] *Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA*
[e] *Mayo Clinic Libraries, Mayo Clinic, Rochester, Minnesota, USA*
[f] *Division of Pediatric Infectious Diseases, Mayo Clinic, Minnesota, USA*
[g] *Division of Endocrinology, Diabetes, Metabolism, Nutrition, Mayo Clinic, Minnesota, USA*
[h] *Division of Preventive, Occupational and Aerospace Medicine, Mayo Clinic, Minnesota, USA*

ARTICLE INFO

Article history:
Received 25 September 2012
Received in revised form 12 February 2013
Accepted 15 February 2013

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Bartonellosis
Bartonella henselae
Bartonella quintana
Bartonella bacilliformis
Cat scratch disease
Bacillary angiomatosis
Antibiotic treatment

SUMMARY

Background: *Bartonella henselae*, *Bartonella quintana*, and *Bartonella bacilliformis* are responsible for the majority of cases of bartonellosis in humans. These species have various unique epidemiologic characteristics, clinical manifestations, and treatment approaches. The objective of this study was to summarize the evidence on the treatment for the three most common species of Bartonella in humans.
Methods: We searched electronic databases through August 2011 for randomized controlled trials and observational studies designed to evaluate the efficacy and safety of the regimens used to treat diseases produced by *B. henselae*, *B. quintana*, and *B. bacilliformis*. Study selection and appraisal were done in duplicate.
Results: We found two randomized and seven non-randomized studies at high risk of bias. For cat scratch disease, antibiotics did not significantly affect the cure rate or time to achieve cure. In chronic bacteremia, gentamicin and doxycycline significantly increased the resolution rate. The recommended treatment was not better than other regimens for infectious endocarditis and bacillary angiomatosis.
Conclusions: Current clinical practice for the treatment of bartonellosis relies mostly on expert opinion and antimicrobial susceptibility data. Randomized controlled trials are needed in the field to compare different treatment options.

1. Introduction

Three species of Bartonella are responsible for the vast majority of infections in humans: *B. henselae*, *B. quintana*, and *B. bacilliformis*. Each one of these species leads to different clinical manifestations and requires different treatment approaches.[1,2] While the infection caused by *B. henselae* has a worldwide distribution,[3] with an incidence of 3.7 per 100 000 (according to a study from the USA),[4] *B. quintana* and *B. bacilliformis* cases are geographically and demographically limited. *B. quintana* has predominantly involved homeless persons with head or body lice exposure in Europe and the USA.[5] Its incidence is unclear, as only a small portion of the infected population will develop overt clinical disease.[5,6] On the other hand, *B. bacilliformis* is restricted to certain mountain regions of Peru, Ecuador, and Colombia, known as the 'verruge zone',[7] having an incidence in the general population of 2.7 cases of bartonellosis (either Oroya fever, verruga peruana, or asymptomatic infection) per 100 person-years.[8]

In immunocompetent patients, *B. henselae* can cause an acute infection called cat scratch disease (CSD), which usually manifests as subacute, regional lymphadenopathy. Likewise, infection caused by *B. bacilliformis* can manifest as an acute phase called Oroya fever or as a chronic phase in Oroya fever survivors called verruga peruana. The acute and chronic states of *B. quintana* infection are trench fever and chronic bacteremia, respectively.[9,10]

When the affected patients are immunocompromised subjects, mainly but not limited to HIV patients, Bartonella species can produce a broad array of manifestations, including bacillary

* Corresponding author. Tel.: +1 507 266 1846.
E-mail address: prutskylopez.gabriela@mayo.edu (G. Prutsky).

1201-9712/$36.00 – see front matter © 2013 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijid.2013.02.016

angiomatosis, peliosis hepatis, splenitis, osteomyelitis, and bacteremia.[11,12]

Bartonella infections present a unique challenge for several reasons, including the high mortality of infected humans who do not receive treatment in the case of *B. bacilliformis* acute infection,[13,14] and the persistence and frequent relapses due to the existence of an intraerythrocytic phase that may provide a protective niche for the bacteria.[15]

Current recommendations for the choice, route, and extent of an antimicrobial treatment for infections caused by *Bartonella spp* are made depending on the infective species, the clinical course, and the immunological state of the patient. They are mainly based on nonsystematic clinical observations and expert panel consensus statements.[16–18] Unfortunately these approaches are limited by deficiencies in the human process of making inferences.[19]

No systematic reviews have been done to summarize and appraise the evidence informing the treatment decisions for infections caused by *Bartonella spp*. We believe that by gathering and analyzing the current evidence concerning the therapeutics of Bartonella infections, we may be able to draw evidence-based conclusions or, in the lack of it, incite future development of evidence-based knowledge concerning this important infection. Therefore, we conducted this systematic review to inform current treatment decisions and future research activities.

2. Methods

Search and analysis methods, eligibility criteria, and the outcomes of interest were specified in advance in a protocol developed by the study investigators.

2.1. Eligibility criteria

We included randomized controlled trials (RCTs) and observational studies that enrolled patients of any age and gender, designed to evaluate the efficacy and safety of the different regimens used to treat diseases produced by the three most common species of human Bartonella (Table 1).

2.2. Search methods

An expert reference librarian (PJE) designed and conducted an electronic search strategy following the protocol (Table 2). We searched electronic databases to identify relevant studies (Ovid Medline, Ovid EMBASE, Ovid Cochrane Library, Web of Science, Scopus, PsycInfo, and CINAHL) from their inception through August 2011. To identify additional candidate studies, we reviewed the reference lists of the eligible primary studies, narrative reviews, and systematic reviews. We also contacted experts on the topic for this purpose and performed a manual search for unpublished studies or studies published in non-indexed journals (1. The Brazilian Journal of Infectious Diseases, 2. Revista Medica Herediana, 3. Diagnóstico, 4. Folia Dermatológica Peruana, 5. Revista del Instituto de Medicina Tropical de Sao Paulo, 6. Acta Medica Peruana, 7. Revista Peruana de Enfermedades Infecciosas y Tropicales, 8. CID (Clinical Infectious Diseases), 9. Revista de Gastroenterología del Perú, 10. Revista de Neuro-Psiquiatría).

Table 1
Diseases produced by the most common species of human Bartonella.

Bartonella henselae:
Cat scratch disease (CSD)
Bacillary angiomatosis
Peliosis hepatis
Infectious endocarditis
Chronic bacteremia
Bartonella quintana:
Bacillary angiomatosis
Trench fever
Infectious endocarditis
Chronic bacteremia
Bartonella bacilliformis:
Carrion disease
Acute phase
Chronic phase

2.3. Selection of studies

Two reviewers working independently considered the potential eligibility of each of the abstracts and titles that resulted from executing the search strategy. Eligible studies were reviewed in full text versions (all available versions of each study). There were no disagreements between the reviewers in the full text screening.

2.4. Data extraction and management

Using a standardized, piloted, and web-based data extraction form and working in duplicate, we abstracted the following descriptive data from each study: full description of participants enrolled (age, diagnosis criteria, severity), interventions they received (type, frequency, and route), control interventions, monitoring methods for efficacy of the follow-up and adherence to the treatment, measures of outcome (specifically defined as event or measure and time frame for the ascertainment of this outcome), and source of funding. We extracted the outcomes of interest at the longest point of complete follow-up.

2.5. Outcomes of interest

After the screening process, we extracted the following outcomes from the included studies: clinical cure or response to therapy, death rate, superimposed infectious disease, time to achieve clinical cure, severe adverse effects (defined as any drug effect that was strong enough to force the patient to stop the treatment, grade 2–4[20]), and relapse rates.

2.6. Author contact

When data were not available from the published papers, repeated efforts were made to contact the authors. We decided a priori to e-mail the authors twice, 2 weeks apart, and to use mail when an e-mail address was not available.

2.7. Assessment of the risk of bias in included studies

To assess the methodological quality of the included RCTs we used the Cochrane risk of bias assessment tool to evaluate: randomization performance and methods, allocation concealment, baseline imbalances, extent of blinding (patients, caregivers, data collectors, outcome assessors, and data analysts), rate of loss to follow-up, and whether adherence was monitored. For observational studies we used the Newcastle–Ottawa quality assessment tool to evaluate how the groups were selected, the comparability between them, whether there was adequate follow-up, and how the outcomes and exposure were ascertained.

2.8. Meta-analysis

For dichotomous outcomes we estimated the odds ratio (OR) and for continuous outcomes we estimated the weighted mean difference (WMD). The I^2 statistic was used to measure inconsistency in results across studies not attributable to chance.[21] To pool data across studies, we tested a random effects model and a fixed

Please cite this article in press as: Prutsky G, et al. Treatment outcomes of human bartonellosis: a systematic review and meta-analysis. Int J Infect Dis (2013), http://dx.doi.org/10.1016/j.ijid.2013.02.016