Cost-effectiveness of azithromycin for preventing Mycobacterium avium complex infection in HIV-positive patients in the era of highly active antiretroviral therapy

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Abstract: We conducted a cost-effectiveness analysis to determine the clinical and economic consequences of Mycobacterium avium complex (MAC) prophylaxis in HIV-infected patients in the era of highly active antiretroviral therapy (HAART) in a health care system with access unrestricted by financial barriers. The analysis was performed from a health care perspective and compared azithromycin (1200 mg/week) with no prophylaxis over a period of 10 years based on data from the Swiss HIV Cohort Study (SHCS) and randomized controlled trials. The main outcome measures were: expected survival; average health care costs; and cost-effectiveness in 1997 Swiss francs (£1 corresponds to about 2.3 CHF) per life-year saved. In patients with an initial CD4 count <50 cells/mm3 and no AIDS, azithromycin increased expected survival by 4 months. In patients with AIDS, HAART durability had a major impact on expected survival and costs. Incremental survival increased from 2 to 4 months if we assumed a 10 year, instead of a 3 year, HAART effect. The cost-effectiveness of azithromycin relative to no prophylaxis in patients without AIDS was between 47,000 CHF (3-year HAART effect) and 60,000 CHF (10-year HAART effect) per life-year saved. The cost-effectiveness ratio increased to 118,000 CHF per life-year saved in patients with symptomatic AIDS. In conclusion, in the era of HAART, MAC prophylaxis with azithromycin increases expected survival and reduces health care costs substantially. Starting MAC prophylaxis in patients without AIDS is more effective and cost-effective than in patients with AIDS

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Bactericidal effect of antibiotics on *Bartonella* and *Brucella* spp.: clinical implications

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The species *Bartonella* and *Brucella* are phylogenetically closely related bacteria, both of which can produce chronic infections in humans that are difficult to cure with antibiotics. MICs of antibiotics for both species correlate poorly with the *in vivo* efficacy of the antibiotics. In this study we have determined MBCs of several antibiotics for this group of pathogens. Only the aminoglycosides were bactericidal, and this correlates well with the usefulness of these antibiotics for the therapy of human brucellosis and chronic *Bartonella* spp. infections such as endocarditis. Our data indicate that current clinical experience in treating brucellosis may help to define better the optimum antibiotic therapy for *Bartonella*-related diseases.

Introduction

Bartonella and *Brucella* spp. belong to the α2 subgroup of Proteobacteria (Figure 1). The genus *Bartonella* includes 12 validated species, five of which have been associated with human infections: *Bartonella henselae*, *Bartonella quintana*, *Bartonella elizabethae*, *Bartonella clarridgeiae* and *Bartonella bacilliformis*. The spectrum of diseases caused by *Bartonella* spp. includes cat scratch disease, bacillary angiomatosis, peliosis hepatis, endocarditis, trench fever, bacteraemia in homeless people and Carrion's disease which manifests as Oroya fever or verruga peruana.[1] Infections caused by *Brucella* spp. are common zoonoses in many parts of the world and may present with a broad spectrum of clinical manifestations.[2]

These pathogens are Gram-negative bacteria that can be grown *in vitro* in axenic blood-enriched media. MICs have been determined using methods adapted to their fastidious growth and have shown that many antibiotics are bacteriostatic *in vitro* against *Brucella* and *Bartonella* spp.[3,4] However, MICs are poorly correlated with the *in vivo* efficacy of antibiotics in patients suffering from either brucellosis[3] or *Bartonella*-related infections.[4] We hypothesized that bactericidal activity of antibiotics against this group of pathogens may be more critical in predicting their efficacy in humans, especially in chronic or relapsing infections. Thus, we have determined MBCs of several antibiotics for these bacteria and tentatively correlate our results with current clinical experience.

Materials and methods

Bacterial strains are listed in the Table. All bacteria were grown on Columbia agar (bioMérieux, Lyon, France), in a 5% CO_2-enriched atmosphere at 37°C, except for *B. bacilliformis* which was grown at 30°C without CO_2.

Drugs

The antibiotics tested were amoxycillin (Beecham–Sevigne, Paris, France), gentamicin (Dakota Pharm, Creteil, France), streptomycin (Diamant, Puteaux, France), ciprofloxacin (Bayer Pharma, Sebs, France), erythromycin (Abbott, Rungis, France), rifampicin (Cassenne, Puteaux, France) and doxycycline (Pfizer, Neuilly, France).

MIC determination

A modified version of the antibiotic agar dilution method of the National Committee for Clinical Laboratory Standards (NCCLS) was used for determination of MICs, as described previously.[4,5] The optimum time for visualization of bacterial growth was 3 days for *Brucella* spp., 5 days for *B. quintana* and *B. henselae*, and 6 days for *B. bacilliformis*. The MIC was defined as the lowest concentration of the antibiotic tested giving complete inhibition of bacterial growth as compared with a drug-free control.

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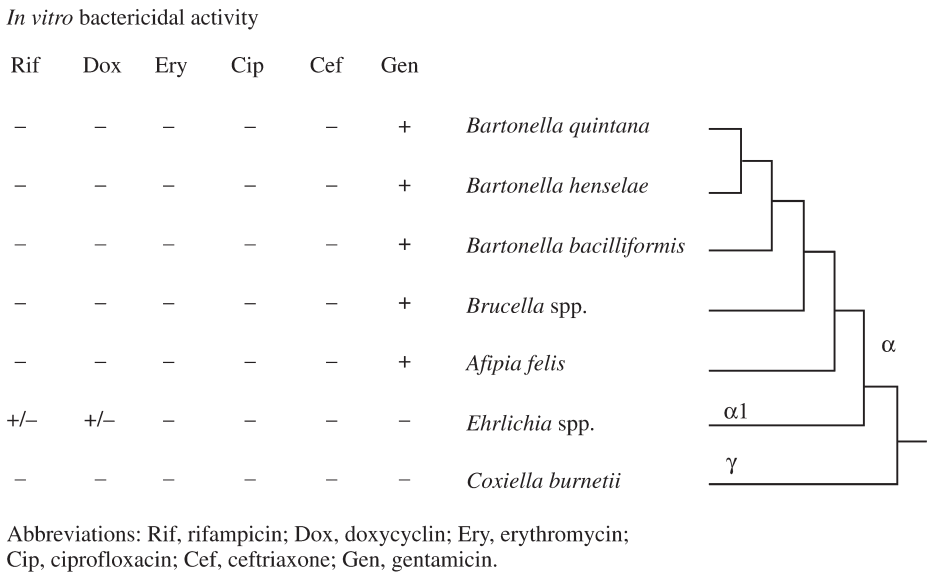

Abbreviations: Rif, rifampicin; Dox, doxycyclin; Ery, erythromycin; Cip, ciprofloxacin; Cef, ceftriaxone; Gen, gentamicin.

Figure. Phylogenetic relationships in the α2 subgroup of *Proteobacteria* and bactericidal activity of antibiotics.

MBC determination

The bactericidal activity of antibiotics was determined in a broth assay with Schaedler medium (bioMérieux) supplemented with either 5% or 10% sheep blood, respectively, for *Brucella* and *Bartonella* spp. A series of glass tubes were filled with 0.9 mL of a bacterial inoculum of 10^6 cfu/mL and 0.1 mL of two-fold serial dilutions of each antibiotic tested. One tube receiving 0.1 mL of saline served as a growth control. Tubes were incubated for 24 h, according to NCCLS guidelines, at 30°C for *B. bacilliformis* or 37°C for other species. After incubation for 24 h, 10-fold serial dilutions of the different bacterial suspensions were then plated on to blood agar (bioMérieux) and reincubated for 3–6 days before enumeration of colonies. The MBC was defined as the lowest concentration of the antibiotic inducing a 99.9% decrease in bacterial inocula following the 24 h incubation period, as compared with the primary inoculum dose.

Controls

Escherichia coli C.I.P. 53126 and *Staphylococcus aureus* C.I.P. 103811 (Institut Pasteur, Marnes-la-Coquette, France) were used as controls. The medium used was either Mueller–Hinton or Columbia agar (bioMérieux) enriched with 10% horse blood. MICs were evaluated after 1, 3, 5 and 6 days of incubation. For determination of MBCs, bacterial suspensions (10^6 cfu/mL) were incubated for 24 h in liquid Schaedler medium at 37°C, with or without horse blood, and in the presence or absence of CO_2. After 1 day of exposure to antibiotics, 10-fold serial dilutions of each bacterial suspension were plated on to agar (Mueller–Hinton or Columbia) and colonies were counted after various incubation times.

Results

MICs and MBCs for the *E. coli* and *S. aureus* control strains, as determined in Mueller–Hinton agar, were similar to those determined by the Pasteur Institute and conditions of culture did not influence the MIC and MBC results more or less than one dilution. *Brucella* and *Bartonella* spp. strains showed similar antibiotic susceptibilities (Table). All strains were highly susceptible to the β-lactams amoxycillin and ceftriaxone, aminoglycosides, doxycycline, rifampicin, erythromycin and ciprofloxacin (Table). In contrast, in our experimental conditions, only the aminoglycosides, and to a lesser extent doxycycline were bactericidal (Table).

Discussion

We found in this study that both the *Brucella* and *Bartonella* spp. were highly susceptible to most antibiotics tested, which is consistent with previous reports.[3,4,6] However, MICs do not correlate well with clinical experience.[1,3] Failures of monotherapy using a β-lactam, a macrolide, a tetracycline, rifampicin or a fluoroquinolone for either disease have been reported.[1,3,4] Relapses are also frequent following withdrawal of treatment. Such discrepancies between *in vitro* and clinical data may be explained by the lack of bactericidal activity of most antibiotics against these pathogens. In our study only aminoglycosides displayed a bactericidal activity against both *Brucella* and *Bartonella* spp. strains tested at concentrations achievable in human serum. MBC results for *B. henselae* were consistent with a previous report from our team.[7] Rubinstein *et al.*[6] also reported that only streptomycin exhibited a bactericidal activity against *Brucella* spp. within the first 24 h of antibiotic exposure, whereas a bactericidal activity was shown with minocycline, rifampicin and ciprofloxacin after 48 h of antibiotic

Table. MICs and MBCs (mg/L) for *Brucella*, *Bartonella henselae*, *Bartonella quintana* and *Bartonella bacilliformis*

		Brucella ($n = 2$)[a]	*B. henselae* ($n = 2$)[a]	*B. quintana* ($n = 2$)[a]	*B. bacilliformis* ($n = 2$)[a]
Doxycycline	MIC	0.06–0.25	0.12	0.12	0.03
	MBC	16–32	16–32	16–32	16
Rifampicin	MIC	0.5–1	0.03	0.12–0.25	0.003
	MBC	>32	>32	>32	>325
Gentamicin	MIC	0.25–0.5	0.12–0.25	1	1
	MBC	2–4	2	2–4	2
Streptomycin	MIC	1–2	0.5–1	2	2–4
	MBC	4	4–16	16	4
Ciprofloxacin	MIC	0.5–1	0.25–0.5	0.5–1	0.25
	MBC	>16	>16	>16	>16
Amoxycillin	MIC	0.12–0.25	0.06	0.06	0.03
	MBC	>64	>64	>64	>64
Ceftriaxone	MIC	0.25–0.5	0.12–0.25	0.25	0.003
	MBC	>64	>64	>64	>64
Erythromycin	MIC	0.12–0.25	0.06–0.12	0.06–0.12	0.06
	MBC	>32	>32	>32	>32

[a]Bacterial strains: *Brucella abortus* S19 strain (ATCC S19), *B. bacilliformis* KC583 (ATCC 35685) and KC584 (ATCC 35686), *B. henselae* Houston-1 strain (ATCC 49882), *B. quintana* Oklahoma strain (ATCC 49793). Three strains were isolated in our laboratory: *B. henselae* UR.L.IE.9, *B. quintana* UR.P.IE.H2 and a *Bartonella melitensis* strain.

exposure. Fluoroquinolones have been shown to be bactericidal against *Brucella* spp. *in vitro*,[6] but these results are controversial.[8] *Bartonella* and *Brucella* spp. share a common ability to multiply within eukaryotic cells, which allows them to be protected against antibiotics. The *in vitro* activity of aminoglycosides against intracellular *Brucella* sp. has been demonstrated previously.[3] Moreover, we have shown that only aminoglycosides were bactericidal against *B. henselae* within a cell system.[7]

Current knowledge indicates that brucellosis and *Bartonella*-related infections share comparable microbiological, pathophysiological and clinical findings. Brucellosis and *Bartonella* spp. infections are characterized mainly by two clinical forms: an acute and a chronic stage. There is a broad spectrum of chronic infections due to *Bartonella* or *Brucella* spp.: endocarditis, cutaneous tumour (verruga peruana due to *B. bacilliformis* and bacillary angiomatosis due to *B. henselae* and *B. quintana*) and osteoarticular damage. Combinations of doxycycline plus streptomycin or rifampicin are recommended for human brucellosis,[3] and only streptomycin is considered consistently effective for the treatment of verruga peruana.[9] Aminoglycosides, especially gentamicin, are also used to treat patients with *Bartonella*-related endocarditis. In our experience (unpublished results) as well as in that reported in the literature,[1] all patients treated with a combination of tetracycline for 6 weeks and aminoglycoside for 2 weeks recovered fully without any relapse, although valve replacement was required for most of the patients, because of extensive valvular damage.[10]

In conclusion, because human infections with *Brucella* and *Bartonella* spp. share many similarities discussed previously, we propose that our current knowledge in treating human brucellosis may help to define the optimum treatment for infections due to *Bartonella* spp. In particular, the use of an aminoglycoside seems critical in patients with endocarditis.

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