Eur. J. Epidemiol. 0392-2990
May 1991, p. 276-281

EUROPEAN JOURNAL OF EPIDEMIOLOGY

Vol. 7, No. 3

ANTIBIOTIC TREATMENT OF RICKETTSIOSIS, RECENT ADVANCES AND CURRENT CONCEPTS[1]

D. RAOULT

Centre National de Référence Unité des Rickettsies C.H.U. La Timone
27 Boulevard Jean Moulin - 13385 MARSEILLE CEDEX 05

Key words: Rickettsiosis - Q fever - Antibiotics - Treatment

The author reviews the recent advances in the treatment of Mediterranean Spotted Fever and Q fever. In mediterranean spotted fever (M.S.F.), in vitro and preliminary in vivo data support the place of quinolones and josamycin in the treatment of M.S.F. In children josamycin could become the first choice drug as well as in pregnant woman. In Q fever chronic disease should be treated using a combination of antibiotic (doxycycline + quinolones) for a minimum of 3 years.

INTRODUCTION

Many changes have occurred in the therapy of rickettsiosis. Two major problems were identified in the treatment of rickettsiosis: the poor prognosis of chronic Q fever and the potential toxicity of cloramphenicol, which was the only compound that could be used when tetracyclines could not be prescribed. In vitro data stimulated by an identification of these questions allowed us to propose a therapeutic alternative. The preliminary human data confirm the reliability of an in vitro model of antibiotic susceptibility evaluation.

Q fever

Q fever is a disease with 2 major clinical forms: acute and chronic (12, 13, 20, 24, 33, 34, 37, 39, 40). In these 2 forms the antibiotic therapy has different goals and different effects. In acute cases the disease is usually self-limiting and not life threatening, in chronic cases the disease is frequently fatal. In fact, the major goal of the antibiotic regimen for acute Q fever is to be bacteriostatic in order to help patient recovery, while in chronic Q fever the goal is to be bacteriocidal in order to cure the patient. As a mater of fact, the treatment duration for acute Q fever is 2 to 3 weeks and for chronic Q fever it is 3 years or more.

The bacteriological data on the antimicrobial susceptibility of *C. burnetii* are controversial and confusing (1, 10, 11, 17, 18, 22, 31, 32, 34, 35, 44, 45). This is due to the kind of model used in antimicrobial testing. Finally we think that 2 models of infection should be used: an acute model and a chronic model. In the first one, the bacteriostatic effect is observed and in the second one the bacteriocidal effect is observed. Among the acute models of infection, animal models, such as guinea pigs, mice, hamsters and rabbits, have been used. Only, guinea pigs were used for antibotic challenges and only streptomycin was tested, and it was not efficient. Embryonated eggs were also used; when inoculated within the yolk sac the eggs died within 5 to 10 days. Antibiotics were added just after inoculation. Using eggs several strains were tested: Nine Mile, Ohio, Cyprus, Scottish, Henzerling, California, Adohr, and Idaho (Table 2). These data showed that *C. burnetii* was resistant to penicillin, aminoglycoside, erythromycin, clindamycin and cephalothin. It was susceptible to rifampin, trimethoprim, doxycycline and tetracycline. Later pefloxacin and ofloxacin were shown to be effective as

[1] Presented at the 4th International Symposium on Rickettsiae and Rickettsial Disease, Pieštany, C.S.F.R., 1-6 October, 1990.

TABLE 1. - Susceptibility of *R. rickettsii* and *R. conorii* to antibiotics.

Drug (reference)	MIC (mcg/ml) for strain with assay type			
	R. rickettsii (Sheila Smith strain)		*R. conorii* (Moroccan strain)	
	Dye uptake	Plaque	Dye uptake	Plaque
Chloramphenicol (29)	0.5	0.5	0.25	0.25
Doxycycline (29)	0.06	0.06	0.12	0.06
Tetracycline (29)	0.25	0.25	0.25	0.25
Erythromycin (27)	8	8	4	4
Spiramycin (27)	32	32	16	16
Josamycin (27)	1	1	1	1
Roxithromycin (5)	1	1	1	1
Pristinamycin (5)	2	2	2	2
P1a (5)	256	256	256	256
P2b (5)	2	2	2	2
Pefloxacin (28)	0.5	1	0.5	0.5
Ciprofloxacin (29)	1	1	0.25	0.25
Ofloxacin (31)	1	1	1	1

a : P1, first compound of pristinamycin.

b : P2, second compound of pristinamycin.

c : PW, present work.

well as ciprofloxacin using the Nine Mile strain. We recently tested a new model of acute infection using cell culture (unpublished data). In this model we used monolayers of cells which do not grow because of either contact inhibition or metabolic inhibition using cycloheximide. This method allows one to test many more strains and to confirm the heterogeneity of susceptibility of different isolates as previously reported (37). As for chronic infection only cell models are currently described. Two kinds of cell cultures are used. The first described used persistently infected L929 cells (46, 47) growing with *C. burnetii*. In this case antibiotics are added to growing cells and the percentage of infection is determined using Gimenez staining. In this model 3 strains have been tested: Nine Mile, Priscilla and "S" (46, 47) (Table 3). The general conclusion of this data is that trimethoprim and doxycycline are ineffective (except in recently infected cells) and only rifampin and quinolones are effective (ciprofloxacin, ofloxacin, pefloxacin). The authors also showed an heterogeneity of susceptibility. I recently described a model of cell culture where infected cells are cycloheximide blocked, in which no single antibiotic compound was bacteriocidal. Only a combination of chloroquine or amantadine to doxycycline made it possible to kill intracellular *C. burnetii* (22). We think that the high acidity of the phagolysosome where *C. burnetii* lives (9) explains the lack of bacteriocidal effect of antibiotics. Clinical data from the literature are controversial as well. As for acute Q fever, most infections resolve without antibiotic therapy and controlled studies have been carried out only with tetracyclines which reduced the duration of fever (19). Doxycycline is superior to tetracycline which is superior to placebo. Treatment has been prescribed using ofloxacin (4), pefloxacin (4), chloramphenicol (30), erythromycin (16, 25) and cotrimoxazole (6). In some cases a third generation cephalosporin, ceftriaxone, was successfully prescribed (J.C. Auvergnat, personnal communication). On the other hand failures have been reported even with tetracyclines. Some of these failures may be related to immune disorders (15). In fact, the first choice drug remains doxycycline, when it can not be used rifampin or a quinolone should be used. The optimal treatment duration is unknown; 3 weeks are currently prescribed.

As for chronic Q fever, antibiotic treatment remains a real problem. The mortality of Q fever

TABLE 2. - Effect of antibiotics on the suppression of embryo mortality during *Coxiella burnetii* infection: concentrations required to obtain a difference in the mean survival time between infected eggs and controls 2.4 days.

Drug (mg/egg) (reference)	MIC50 (mcg/ml) and MIC90 for *Coxiella burnetii* in persistently infected L 929 cells					
	Nine Mile	Cyprus	Scottish	Ohio	Dyer	Henzerling
Streptomycin (10)	NRa	NR	NR	NR	500	500
Chloromycetin (35)	NR	NR	NR	NR	NR	500
Terramycin (18)	150	NR	NR	NR	NR	NR
Aureomycin (18)	125	NR	NR	NR	NR	NR
Chloramphenicol (18)	500	NR	NR	NR	NR	NR
Erythromycin (18)	700	NR	NR	NR	NR	NR
Erythromycin (18)	250	NR	NR	NR	NR	NR
Cephalotin (37)	250	250	250	250	NR	NR
Clindamycin (37)	250	250	250	250	NR	NR
Trimethoprim (37)	50	50	250	50	NR	NR
Rifampin (37)	50	50	50	50	NR	NR
Doxycycline (37)	50	250	50	50	NR	NR
Tetracycline (37)	50	250	50	50	NR	NR
Pefloxacin (31)	50	NR	NR	NR	NR	NR
Ofloxacin (31)	50	NR	NR	NR	NR	NR

a: Not reported.

TABLE 3. - Susceptibility of *Coxiella burnetii* to antibiotics in persistently infected cell model.

Drug (reference)	Nine Mile strain		Priscilla strain	
	50%	90%	50%	90%
Chloramphenicol (46)	10	NAa	NRb	NR
Trimethoprim (46)	10	NA	NR	NR
Doxycycline (46)	9.5	NA	NA	NA
Rifampin (46)	0.08	0.3	NA	NA
Oxolinic acid (46)	3.2	4.5	NR	NR
Ciprofloxacin (46, 48)	0.5	1.7	2.5	NA
Norfloxacin (46, 48)	1.1	4.6	2.4	NA
Pefloxacin (46, 48)	0.6	1.4	2.2	NA
Ofloxacin (46, 48)	0.3	0.7	0.5	NA

a : NA, not achieved.

b : NR, not reported.

endocarditis is still high and could exceed 65% (25, 38, 40). The major questions for chronic Q fever therapy are:

- what are the most efficient antibiotics?
- how long should treatment be prescribed?
- what role does valve replacement play in the therapy?
- what are the criteria for cure?

As we have seen, "in vivo" efficacy of antibiotic compounds is still controversial. Two kinds of regimen can be chosen-a combination of antibiotics using doxycycline + rifampin or quinolones or a combination of doxycline + a lysosomotropic alkalinizant agent such as chloroquine. Until now only antibiotic combinations have been reported. The combination of quinolones to doxycycline seems to correlate with better outcome. In a series of 25 patients with Q fever endocarditis (14), 6 out of 9 treated with doxycycline alone died as compared to 0/16 treated with doxycycline + quinolone. This does not allow a shorter treatment. Patients with doxycycline + quinolones can relapse when the treatment is stopped after one year and it has been possible to isolate *C. burnetii* from valves removed after 4 months and 1 year of therapy. Our conclusions are that a minimum duration of treatment of 3 years with combined therapy is necessary.

As for valve replacement, it is not clear that it helps to cure. In fact, the pathological examination of the heart shows that several valves are frequently involved, and organ biopsies (liver, bone marrow) generally show the presence of *C. burnetii.* We consider valve replacement for cases of hemodynamic failure. As for criteria for cure, we did not have a clear antibody response. We decided to treat patients as long as they had IgA anti-phase I superior to a titer of 25 and IgG anti-phase I superior to a titer of 200. Only 10% of patients had titers at such levels after 3 years of therapy.

Spotted fever

Spotted fever treatment has also changed in these last years. Until recently only tetracyclines and chloramphenicol were used. They were demontrated to be effective in vitro (1, 29, 30). Recently, many works have demonstrated that some quinolones, such as ofloxacin (31), pefloxacin (28), ciprofloxacin (26, 29) and sparfloxacin (unpublished data), were effective. Among macrolide antibiotics a wide heterogeneity of susceptibility is noticed. In cell cultures spiramycin is not effective (MIC 16 mcg/ml) nor is erythromycin (MIC 4 to 8 mcg/ml). Josamycin (21, 27), roxythromycin (5) and pristinamycine (5) are effective with MIC of 1-2 mcg/ml (Table 1). As a result of these data, several investigators have treated patients with such compounds. Erythromycin has been used in a randomized trial by Munoz et al. (16). Their data confirm that erythromycin is not as efficient as tetracycline in Mediterranean Spotted Fever (MSF). As for chloramphenicol, despite the fact that it has been recommended for years, failures and relapses have been noted following its use. In Israel, an 80 year old man suffering from Mediterranean Spotted Fever was treated with chloramphenicol, relapsed and died (35), and in the U.S.A., Fishbein (6) reported that the outocome of patients suffering from Rocky Mountain Spotted fever and treated with chloramphenicol was poorer that the outcome of those treated with tetracyclines. Given these data and the fact that chloramphenicol can be responsible for aplastic anemia, chloramphenicol should not be recommended. The drug of choice in the treatment of Spotted Fever group rickettsiosis remains doxycycline (30). The treatment duration is controversial. Bella-Cueto et al. (3), in Spain, compared 2 doses of doxycycline over a 12 hour period in 37 patients with MSF to a 10-day course of tetracycline hydrochloride in 33 patients with MSF and did not find any significant differences. Yagupsky and Gross (45), in Israel, reported a case of relapse following a treatment of 5 doses of doxycline. In fact, the only real limitation of a prolonged therapy is the risk of tooth coloring in children. For this purpose Bella et al. (2) compared in a randomized trial josamycin to doxycycline. When using josamycin, high doses (100 mg/kg/day in children and 3 g/day in adults) gave clinical results comparable to those of doxycycline. The main difference is that josamycine has to be prescribed for 5 days and doxycycline is a single day. I personally treated and cured 2 pregnant women with 10 days of josamycin at 3 g/day. Following the demonstration of the efficiency of quinolones in vitro, several trials were carried out in MSF. Open studies were made using ciprofloxacin (23), pefloxacin (4) and ofloxacin (4). A randomized double-blind study compared ciprofloxacin (1 g/day for 1 day) to doxycycline (200 mg/day for days) in 43 patients (8). All patients were cured but doxycycline produced a more rapid defervescence. These data showed that eventually quinolones could be used in MSF. Finally, we recommend doxycycline as the first drug of choice for adults at 200 mg/day for 2 to 5 days, including the 24 hours after defervescence. For children, in whom the disease in often milder, a single day of doxycycline (2 doses) or 5 days of josamycin (100 mg/kg/day) seems to be the best choice.

Other Rickettsioses

In other Rickettsioses, such as typhus or scrub typhus, there have been few changes in therapy in the last years (35, 43, 44). Doxycycline is still the reference therapy in these diseases. Relapses may occur, therefore a 2-week schedule is recommended. Chloramphenicol has been used but can result in failures or relapses.

REFERENCES

1. *Barker C.F.* (1986): Determination of antibiotic susceptibility of Rickettsiae and Chlamydiae in BS-

C-1 cell cultures. - Antimicrob. Agents Chemother. *1969: 1968:* 425-428.

2. *Bella F., Font B., Uriz S., Munoz Espin T., Espejo Arenas E., Traveria J., Serrano J.A.* and *Segura F.* (1990): Randomized trial of Doxycycline versus Josamycin for Mediterranean Spotted Fever. - Antimicrob. Agents Chemother. *34:* 937-938.
3. *Bella Cueto F., Font Creus B., Segura Porta F., Espejo Arenas E., Lopez Pares P.* and *Munoz Espin T.* (1987): Comparative, randomized trial of one day Doxycycline versus 10/day Tetracycline therapy for Mediterranean Spotted Fever. - J. Infect. Dis. *155:* 1056-1058.
4. *Bertrand A., Jambon F., Jonquet O.* and *Reynes J.* (1988): Infections par les rickettsiales et fluoroquinolones. - Path. Biol. *36:* 493-495.
5. *Drancourt M.* and *Raoult D.* (1989): In vitro susceptibilities of *Rickettsia rickettsii* and *Rickettsia conorii* to Roxithromycin and Pristinamycin.. - Antimicrob. Agents Chemother. *33:* 2146-2148.
6. *Fishbein D.B., Frontini M.G., Giles R.* and *Vernon L.L.* (1990): Fatal cases of Rocky Mountain Spotted Fever in the United States, 1981-1988. - Ann. N.Y. Acad. Sc. *590:* 246-247.
7. *Freeman R.* and *Hodson M.* (1972): Q fever endocarditis treated with Trimethoprim-sulfamethoxazole. - Br. Med. J. *1:* 419.
8. *Guchiol F., Pallares R., Carratala J., Bolao F., Ariza J., Rufi G.* and *Viladrich P.F.* (1989): Randomized Double-blind evaluation of Ciprofloxacin and Doxycycline for Mediterranean Spotted Fever. - Antimicrob. Agents Chemother. *33:* 987-988.
9. *Hackstadt T.* and *Williams J.C.* (1981): Biochemical stratagem for obligate parasitism of eukaryotic cells by *Coxiella burnetii.* - Proc. Natl. Acad. Sci. USA *78:* 3240-3244.
10. *Huebner R.J., Hottle G.A.* and *Robinson E.B.* (1948): Action of Streptomycin in experimental infection with Q fever. - Publ. Health Rept. *63:* 357.
11. *Jackson E.B.* (1951): Comparative efficacy of several antibiotics on experimental Rickettsial infections in embryonated eggs. - Antibiotics and Chemotherapy. *1:* 231-241.
12. *Kimbrough R.C. III, Ormsbee A., Peacock N., Rogers W.R., Bennetts R.W., Raaf J., Krause A.* and *Gardner C.* (1979): Q fever in the United States. - Ann. Inter. Med. *91:* 400-402.
13. *Langley J.M., Marrie T.J., Covert A., Waag D.M.* and *Williams J.C.* (1988): Poker players' pneumonia. An urban outbreak of Q fever following exposure to a parturient cat. - N. Engl. J. Med. *319:* 354-357.
14. *Levy P.J., Drancourt M., Etienne J., Auvergnat J.C., Beytout J., Sainty J.M., Goldstein F.* and *Raoult D.* (1991): Antibiotic therapy of 32 cases of Q fever endocarditis: comparison of different regimens. - Antimicrob. Agents Chemother. *35:* 88-91.
15. *Levy P.Y., Raoult D.* and *Razongles J.J.* (1989): Q fever and autoimmunity. - Eur. J. Epidemiol. *5:* 447-452.
16. *Munoz Espin T., Lopez-Pares P., Espejo Arenas E., Font Creus B., Martinez Vila I., Traveria-Casanova J., Segura-Porta F.* and *Bella-Cueto F.* (1986): Erythromycin versus Tetracycline for treatment of Mediterranean Spotted Fever. - Arch. Dis. Child. *61:* 1027-1029.
17. *Ormsbee R.A.* and *Pickens E.G.* (1951): A comparative by means of the complement-fixation test of the relative potencies of chloramphenicol, aureomycin, and terramycin in esperimental Q fever infections in embryonated eggs. - J. Immunol. *67:* 437-447.
18. *Ormsbee R.A., Parker H.* and *Pickens E.G.* (1955): The comparative effectiveness of aureomycin, terramycin, chloramphenicol, erythromycin and thiomycetin in suppressing experimental rickettsial infections in chick embryos. - J. Infect. Dis. *96:* 162-169.
19. *Powell O.W., Kennedy K.P., McIver M.* and *Silverstone H.* (1962): Tetracycline in the treatment of "Q" fever. Australian Annals of Medecine. *11:* 184.
20. *Raoult D.* (1990): Host factors in the severity of Q fever. - Ann. N.Y. Acad. Sci. *590:* 33-38.
21. *Raoult D.* and *Drancourt M.* (1988): Macrolides et rickettsioses dans Macrolides et Synergistine. Pocidalo J.J., Vachon J., Coulaud J.P., Vilde J.L. Librairie Arnette-Paris. - 183-186.
22. *Raoult D., Drancourt M.* and *Vestris G.* (1990): Bactericidal effect of Doxycycline combined with lysosomotropic agents against *Coxiella burnetii.* - Antimicrob. Agents Chemother. *34:* 1512-1514.
23. *Raoult D., Gallais H., De Micco Ph.* and *Casanova P.* (1986): Ciprofloxacin therapy in Mediterranean Spotted Fever. - Antimicrob. Agents Chemother. *30:* 606-607.
24. *Raoult D., Piquet Ph., Gallais H., De Micco Ph., Drancourt M.* and *Casanova P.* (1986): *Coxiella burnetii* infection of a vascular prosthesis. - N. Engl. J. Med. *315:* 1358.
25. *Raoult D., Raza A.* and *Marrie T.* (1990): Q fever endocarditis and other forms of Chronic Q fever in T.J. Marrie. Q fever. The disease. - Volume I. - CRC Book (Boca Raton, FLA. - USA) p. 179-200.
26. *Raoult D., Roussellier P., Galicher V., Perez R.* and *Tamalet J.* (1986): In vitro susceptibility of *Rickettsia conorii* to Ciprofloxacin as determined by suppressing lethality in chicken embryos and by plaque assay. - Antimicrob. Agents Chemother. *29:* 424-425.
27. *Raoult D., Roussellier P.* and *Tamalet J.* (1988): In vitro evaluation of Josamycin, Erythromycin and

Spiramycin against *Rickettsia rickettsii* and *Rickettsia conorii*. - Antimicrob. Agents Chemother. *32:* 255-256.

28. *Raoult D., Roussellier P., Vestris G., Galicher V., Perez R.* and *Tamalet J.* (1987): In vitro and in ovo susceptibility of *Rickettsia conorii* and *Rickettsia rickettsii* to pefloxacin. - J. Antimicrob. Chemother. *19:* 303-305.
29. *Raoult D., Roussellier P., Vestris G.* and *Tamalet J.* (1987): In vitro susceptibility of *Rickettsia rickettsii* and *Rickettsia conorii* as determined by plaque assay and by microplaque colorimetric assay. - J. Infect. Dis. *155:* 1059-1062.
30. *Raoult D.* and *Walker D.H.* (1990): *Rickettsia rickettsii* (Rocky Mountain Spotted Fever and other Spotted Fevers). *In:* Mandell, Douglas, Bennett. Principles and Practice of Infections disease. - Churchill Livingstone (New York) p. 1465-1470.
31. *Raoult D., Yeaman M.R.* and *Baca O.* (1989): Susceptibility of *Coxiella burnetii* to Pefloxacin and Ofloxacin in ovo and in persistently infected L929 cells. - Antimicrob. Agent Chemother. *33:* 621-623.
32. *Raoult D., Yeaman M.R.* and *Baca O.* (1989): Susceptibility of *Rickettsia* and *Coxiella burnetii* to quinolones in vitro. - Rev. Infect. Dis. Vol. 11 Supplements 1989. p. S986.
33. *Sawyer L.A., Fishbein D.A.* and *McDade J.E.* (1987): Q fever: current concepts. - Rev. Infect. Dis. *9:* 935-940.
34. *Shaked Y., Samra M., Maeir K.* and *Rubinstein E.* (1988): Murine typhus and Spotted Fever in Israel in the eighties: retrospective analysis. - Infection. vol. 16, *5:* 283-287.
35. *Smadel J.E., Jackson E.B.* and *Cruise A.B.* (1949): Chloromycetin in experimental rickettsial infections. - J. Immunol. *62:* 49-57.
36. *Spelman D.W.* (1982): Q fever. A study of 111 consecutive cases. - Med. J. Aust. *1:* 547-557.
37. *Spicer A.J., Peacock M.G.* and *Williams J.C.* (1981): Effectiveness of several antibiotics in suppressing chick embryo lethality during experimental infections by *Coxiella burnetii, Rickettsia typhi* and *R. rickettsii. In:* W. Burgdorfer and R.L. Anaker. Rickettsiae and Rickettsial Diseases. - Academic Press, edit. New York. p. 375.
38. *Subramanya N.I., Wright J.S.* and *Khan M.A.R.* (1982): Failure of rifampin and cotrimoxazole in Q fever endocarditis. - Br. Med. J. *283:* 343.
39. *Tobin M.J., Cahill N., Gearty G., Maurer B., Blake S., Daly K.* and *Hone R.* (1982): Q fever endocarditis. - Am. J. Med. *72:* 396.
40. *Tunstall P.* (1970): Apparent recurrence of Q fever endocarditis following homograft replacement of aortic valve. - Br. Heart J. *32:* 568.
41. *Turck W.P.G., Howitt G., Turnberg L.A., Fox H., Longson M., Mattews M.B.* and *Das Mgupta R.* (1976): Chronic Q fever. Q. J. Med. *45:* 193-197.
42. *Varma M.P.S., Adgey A.A.J.* and *Connolly J.H.* (1980): Chronic Q fever endocarditis. - Br. Heart J. *43:* 695.
43. *Wisseman C.L. Jr., Silverman D.J., Waddell A.* and *Brown D.T.* (1982): Penicillin-induced unstable intracellular formation of sheroplasts by Rickettsiae. - J. Infect. Dis. *146:* 147-158.
44. *Wisseman C.L. Jr., Waddell A.D.* and *Walsh W.T.* (1974): *In:* vitro studies of the action of antibiotics on *Rickettsia prowazekii* by two basic methods of cell culture. - J. Infect. Dis. *130:* 564-574.
45. *Yagupsky P.* and *Gross E.M.* (1984): Relapse of Israeli spotted feve treated with doxycycline. - Trop. Med. Hyg. : 139-140.
46. *Yeaman M.R., Mitsher L.A.* and *Baca O.* (1987): In vitro susceptibility of *Coxiella burnetii* to antibiotics, including several Quinolones. - Antimicrob. Agents Chemother *31:* 1079-1084.
47. *Yeaman M.R.* and *Baca O.* (1990): Unexpected antibiotic susceptibility of a chronic isolate of *Coxiella burnetii*. - Ann. N.Y. Acad. Sci. : 297-305.
48. *Yeaman M.R., Roman M.J.* and *Baca O.G.* (1989): Antibiotic susceptibility of two *Coxiella burnetii* isolates implicated in distinct clinical syndromes. - Antimicrob. Agent Chemother. *33:* 1052-1057.