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ANTIBIOTIC SUSCEPTIBILITY OF RICKETTSIA  
AND TREATMENT OF RICKETTSIOSES<sup>1</sup>

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The author describes the in vitro data for antibiotic susceptibility of *Rickettsia* and *Coxiella burnetii*. Tetracyclines are still the first antibiotic choice in spotted fevers, typhus and Q fever. In spotted fever a shortened treatment is suggested and the place of macrolide antibiotics, such as Josamycin, in treating children may be evaluated. In Q fever, according to the new biological data, an association of tetracyclines and Rifampin or Quinolones is suggested.

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Rickettsioses are distributed worldwide and can be divided into three groups of diseases:

1 - *The eruptive rickettsioses* are transmitted by arthropods and three groups of diseases are observed. (i) The typhus group, including epidemic typhus caused by *R. prowazeki*, which is transmitted by the body louse or flying squirrel ectoparasite in the USA (11), and murine typhus caused by *R. typhi* which is transmitted by the rat flea. (ii) The spotted fever group, which includes tick bite fevers, such as Rocky Mountain spotted fever (due to *R. rickettsii*), Mediterranean spotted fever (due to *R. conorii*) and other spotted fevers reported from Africa (*R. conorii*), Israel, USSR and China (*R. siberica*), Thailand and Pakistan (*R. conorii*), Japan (*Rickettsia japonica*) and Australia (*R. australis*). The rickettsial pox, transmitted by murine ectoparasites and caused by *R. akari*, is included in this group. (iii) The scrub typhus due to *R. tsutsugamushi*.

2 - *Q fever* is a zoonosis caused by *Coxiella burnetii*. It is generally transmitted by aerosol or close contacts with infected animals. Clinically this bacteria is able to determine two major forms of the disease: an acute form and a chronic form.

The latter form currently requires treatment for years (16).

3 - *Human ehrlichiosis* has been known in Japan for years. The vector is unknown and it is caused by *E. sennetsu*. More recently a human disease related to an *Ehrlichia* has been described. It is serologically related to *E. canis* (9).

*Rickettsia as organisms*

*Rickettsia* spp. are strict intra-cellular bacteria (with the exception of *Rochalimea*). After phagocytosis the intra-cellular parasites have 3 possibilities to resist the bactericidal effects of phagolysosomal fusion. The bacteria of the genus *Rickettsia* escape very quickly from the phagosome before lysosome fusion, the bacteria of the genus *Ehrlichia* (as well as *Chlamydia*) inhibit this fusion and the bacteria of the genus *Coxiella* survive in the phagolysosome and seem to be able to have a biochemical activity only at this acid pH (6). These facts are important to consider due to the fact that antibiotics, to be effective, have to be concentrated into the cells and at the site of multiplication of the bacteria. In fact some antibiotics can be concentrated in the phagolysosome, such as weak bases (macrolides

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antibiotics) or into the cytosol (4). In this site an important point to mention is that the low pH of the phagolysosome (pH 5) may inhibit the function of antibiotics such as macrolides (4).

#### Spotted fever rickettsiosis

In vitro susceptibility testing has been evaluated using *R. conorii* Moroccan strain and *R. rickettsii* Sheila Smith. These bacteria were tested using embryonated eggs (7, 24), then cell cultures. Some antibiotics, such as beta lactams, aminoglycosides, sulfamides, and trimethoprim, are ineffective.

Tetracycline and doxycycline are highly effective as well as chloramphenicol and Rifampin (see Table 1) (20). Recently three quinolone antibiotics (Ciprofloxacin, Ofloxacin and Pefloxacin) have been shown to be effective with MICs of 1 mcg/ml or less (17, 23). As for macrolide antibiotics, the susceptibilities of the compounds vary. Erythromycin has an MIC between 3 and 8 mcg/ml and should be considered as ineffective. Spiramycin has an MIC of 32 mcg/ml, Josamycin (17) and Roxithromycin (5) have MICs of 1 mcg/ml and pristinamycin has an MIC of 2 mcg/ml (14).

As for patient treatment the tetracyclines, especially doxycycline, are recommended. Short-term treatment prescribed for a single day using this latter compound has been shown to be effective (2). When tetracyclines could not be used, as in children, chloramphenicol is the classic alternative treatment (21). Ciprofloxacin has been demonstrated to be

TABLE 1. - *R. conorii* (Moroccan strain) and *R. rickettsii* susceptibility to antibiotics in cell cultures (MIC in mcg/ml).

Antibiotics	Reference	<i>R. conorii</i>	<i>R. rickettsii</i>
Tetracycline	20	0,25	0,25
Doxycycline	20	0,12	0,12
Chloramphenicol	20	0,25	0,5
Rifampin	20	0,25	0,5
Erythromycin	10	4	8
Spiramycin	10	16	32
Josamycin	10	1	1
Roxythromycin	5	1	1
Pristynamycin	14	2	2
Ciprofloxacin	17	0,25	0,25
Pefloxacin	19	1	1
Ofloxacin	23	1	1

effective in treating adults with Mediterranean spotted fever (16) as have ofloxacin (3) and pefloxacin (3). As for macrolide antibiotics, erythromycin has been shown to be less effective than tetracycline in children (11). Josamycin is currently being evaluated against doxycycline and appears to be effective (Bella, personal communication). If this is confirmed josamycin should become the treatment of choice for pregnant women and children due to its lack of toxicity.

There is no published data as for Rifampin.

TABLE 2. - (MIC in mcg/ml) Susceptibility of typhus group Rickettsia and *R. tsutsugamushi* to antibiotics in cell cultures.

Reference	<i>R. prowazeki</i> (27)	<i>R. typhi</i> (1)	<i>R. tsutsugamushi</i> (12)
Tetracycline	/	0.1	0.15
Doxycycline	0.1	/	/
Rifampin	0.008	/	0.3
Chloramphenicol	1	/	1.25 - 2.5
Erythromycin	0.06	1	2.5 - 10

#### Typhus group rickettsioses

The susceptibility of the bacteria has been evaluated in embryonated egg and in cell cultures and some authors are using body lice to evaluate antibiotic susceptibility (1, 7, 8). The reference strains are *R. typhi* (Wilmington), *R. prowazekii* (Breinl and Madrid E). Aminoglycosides and sulfamides are ineffective. Penicillin is effective at high concentrations and determines the formation of spheroplasts(26). As for tetracycline and doxycycline, they are highly effective as is chloramphenicol (27). Erythromycin is effective in vitro, but some strains, such as Madrid E, are resistant and *R. prowazekii* becomes resistant very easily in culture. The treatment of the typhus group of rickettsioses is based on tetracyclines. A shortened treatment has been proposed, but relapses may follow a single day schedule (13).

#### Scrub typhus

*R. tsutsugamushi* has been tested in Vero cells. Five strains were used (12). It is susceptible to tetracycline, Rifamycin and chloramphenicol. Erythromycin has an MIC between 2.5 and 10 mcg/ml. Ciprofloxacin has been shown to be effective in a mouse challenge (9). Tetracycline and chloramphenicol are both effective in treating scrub typhus. Relapse may occur, and a two-week schedule is recommended.

TABLE 3. - Antibiotic susceptibility of *Coxiella burnetii* in eggs and in persistently infected L cells.

Method	Eggs (per egg)	Persistently infected cells (mcg/ml)
Reference	22,24	22,28
Tetracycline	50	>10
Doxycycline	50	>10
Rifampim	50	1
Ciprofloxacin	50	1.8
Ofloxacin	50	0.3
Pefloxacin	50	1.4
Trimethoprim	50	>10

*Q fever*

*Coxiella burnetii* was first tested in embryonated eggs. Three strains were used: Nine Mile, BB Ohio and CB Cyprus (24). In this work *C. burnetii* was resistant to beta lactam and macrolide antibiotics. It was susceptible to rifampin, trimethoprim, tetracycline and doxycycline. However one of the tested strains (Cyprus) was less susceptible to tetracycline and doxycycline. This fact indicates that some strains are naturally resistant to tetracyclines. Using the model of chronic infection, M. Yeaman et. al. (28) carried out a new test on persistently infected L 929 cells. In this technique 90% infected cells are grown with different antibiotic concentrations and stained every day for 10 days. Surprisingly tetracycline and trimethoprim were ineffective. Only Rifampim and quinolones (Ciprofloxacin, Difloxacin and Oxolinic acid) were able to diminish the percentage of infected cells. Since this work Ofloxacin and Pefloxacin have been shown to be effective in both this model and embryonated eggs (22). Using the Priscilla strain, which is the reference strain for chronic infection, M. Yeaman was able to demonstrate a decreased susceptibility (submitted for publication).

In patients the clinical efficacy of antibiotics is difficult to evaluate. No randomized trial have been carried out mainly because the diagnosis of acute forms is confirmed serologically later in the course of the disease. In chronic forms the lethality is still very high (15). In some cases *C. burnetii* was isolated after several years of tetracycline treatment (25). However tetracycline treatment allows the apparent cure of the patient, but relapses may occur. Currently the recommended schedule is a three-year treatment including tetracycline. We suggest adding rifampin or one of the effective quinolones. The major problem in evaluating this treatment is that the serological examination remains highly positive for years.

There is also no parameter that can confirm that the patient is cured and may not relapse.

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