Newer Macrolides as Empiric Treatment for Acute Q Fever Infection

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The effectiveness of newer macrolides in acute Q fever for 113 patients was recorded. The mean times to defervescence were 2.9 days for doxycycline and 3.3, 3.9, and 6.4 days for clarithromycin, roxithromycin, erythromycin, and β-lactams, respectively (P < 0.01 for macrolides versus β-lactams). We conclude that macrolides may be an adequate empirical antibiotic therapy for acute Q fever.

Acute Q fever disease is a zoonosis with a worldwide distribution and is caused by Coxiella burnetii, an obligate intracellular parasite. It is characterized by a wide variety of clinical manifestations, such as prolonged fever, pneumonia, granulomatous hepatitis, and meningocerebral disease. It is characterized by a wide variety of clinical manifestations, such as prolonged fever, pneumonia, granulomatous hepatitis, and meningocerebral disease. Furthermore, information about the course of untreated infection, or infection treated with ineffective antibiotics, is also lacking.

In order to assess the clinical responsiveness of C. burnetii to the new macrolides, we reviewed the clinical features, antibiotic treatments, and outcomes of 113 patients hospitalized between 1989 and 1996 with acute Q fever infection. To our knowledge, this is the largest study assessing the efficacy of clarithromycin in acute Q fever in most published studies (3, 10, 14, 16).

Our knowledge about various features of acute and chronic disease, such as who will develop chronic disease, remains incomplete. Furthermore, information about the course of untreated infection, or infection treated with ineffective antibiotics, is also lacking.

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The role of macrolides in the treatment of Q fever is not clear. In a previous work, the MIC of clarithromycin for C. burnetii was found to range from 2 to 4 μg/mL (3, 8, 16). There are also few reports of erythromycin inactivity in vitro against C. burnetii (9). A limited number of publications about its clinical response, especially in severe cases, have come up with contradictory results (8). Since atypical pneumonia is the most frequent clinical presentation of Q fever in areas of endemicity (3, 8, 16), C. burnetii infection is empirically treated with erythromycin and other new macrolides.

Our data suggest that erythromycin and other new macrolides could be considered a reasonable treatment for acute C. burnetii infection. Pharmacokinetic factors may account for this clinical efficacy of macrolides. Factors related to liposolubility and high intracellular concentrations might influence the potential of this class of drugs to treat intracellular microorganisms. Data on erythromycin have been presented in other published reports but are lacking for the newer macrolides (1, 2, 4, 6, 13). It is well known that the newer macrolides, such as clarithromycin and roxithromycin, in terms of days to apyrexia, differed significantly from doxycycline (P < 0.001). Clarithromycin also differed significantly from doxycycline (P < 0.05), but macrolides did not differ from each other. β-Lactams differed significantly from both doxycycline and macrolides (P < 0.001).

All patients within the doxycycline group became afebrile on day 4, while patients in the macrolide group became afebrile on day 9. Fever subsided in all patients treated with β-lactams on day 16 of treatment (Fig. 1). There were no relapses or complications registered independently of the antibiotic administration or deaths related to infection, although one patient died from an unrelated tumor and another with a serious underlying disease.

This study provides evidence that although tetracycline is the treatment of choice in acute Q fever infection, macrolides (mainly the newer ones) could be a valuable alternative. β-Lactams seem to have no role in the treatment of C. burnetii, as previously described (11, 17). Coxiella multiplies in the phagolysosomes of infected cells at a pH lower than 5, making previous descriptions (11, 17) unlikely for the antibiotic to be active (13). The in vitro activities of various antibiotics against C. burnetii were well studied by Yeaman et al. (17, 18) and others (5, 6, 9). However, data about the clinical activity of drugs with high intracellular concentrations, such as quinolones and macrolides, are lacking.

The treatment of choice for C. burnetii is doxycycline, which does not have a bactericidal effect against the microorganism (8, 15). The treatment must be initiated within the first 3 days of illness in order to be effective. Its use is limited because of the late diagnosis, depending mainly on serology, and the atypical presentation of the acute illness. Other antibiotics, such as chloramphenicol, co-trimoxazole, quinolones, and rifampin, are effective in vitro against C. burnetii and have been used, but few clinical data are available (17, 18).

Fever subsided after a mean of 2.39 (1.88 to 2.89) days after administration of doxycycline. Mean times to defervescence were 3.33 (2.63 to 4.04) days with clarithromycin, 3.89 (3.32 to 4.47) days with roxithromycin, and 3.93 (3.32 to 4.53) days with erythromycin. In patients receiving β-lactams, fever subsided after a mean of 6.42 (4.66 to 8.18) days (Table 2).

TABLE 1. Clinical and demographic data of 113 cases of acute Q fever

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>84 (74.3)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (25.7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>107 (94.7)</td>
</tr>
<tr>
<td>Febrile illness</td>
<td>6 (5.3)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>6 (5.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (4.4)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>7 (6.2)</td>
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</tbody>
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* The mean age for all patients was 37.6 (15 to 91) years.

TABLE 2. Antibiotics used in 113 patients with acute Q fever

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>No. (%) of patients</th>
<th>Mean days to defervescence</th>
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<tbody>
<tr>
<td>Doxycycline</td>
<td>18 (15.9)</td>
<td>2.39 (1.88–2.89)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>42 (37.2)</td>
<td>3.93 (3.32–4.53)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>15 (13.3)</td>
<td>3.33 (2.63–4.04)</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>19 (16.8)</td>
<td>3.89 (3.32–4.47)</td>
</tr>
<tr>
<td>β-Lactams</td>
<td>19 (16.8)</td>
<td>6.42 (4.66–8.18)</td>
</tr>
</tbody>
</table>
clarithromycin (MIC, 1.0 to 4.0 mg/liter), attain higher intracellular concentrations than erythromycin and could potentially be more effective against C. burnetii infection (5, 6, 9).

To our knowledge the use of clarithromycin in acute Q fever has been described once for only four patients (7), and there are no clinical data in the international literature about the clinical activity of roxithromycin against C. burnetii.

In this study, clinical improvement, apyrexia, and shortening of acute disease were achieved in 3.33 and 3.89 days, respectively, when clarithromycin and roxithromycin were used. We believe that the 1-day delay to apyrexia with clarithromycin compared to doxycycline is a clinically meaningful end point. On the other hand, all newer macrolides were more efficacious than β-lactams in terms of fever duration (P < 0.001).

In summary, in acute Q fever infection, a relatively frequent cause of community-acquired pneumonia in areas of endemicity, macrolides—especially the newer ones, such as clarithromycin and roxithromycin, which have the advantages of fewer side effects and higher intracellular concentrations—seem to be adequate alternative treatments.

Further prospective studies are needed to better evaluate the efficacy and safety of the macrolides in the treatment of acute Q fever infection.

REFERENCES