

Antibiotic treatment in pneumonia due to Q fever

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Abstract

Background Whether Q fever responds better to doxycycline or erythromycin is unknown.

Methods The efficacy of doxycycline and erythromycin in the treatment of pneumonia due to Q fever was assessed in a prospective, randomised, double blind study of 82 patients with a diagnosis of pneumonia and features suggestive of Q fever infection; 48 proved to have Q fever. Of the 48, 23 received doxycycline 100 mg twice a day and 25 patients received erythromycin 500 mg six hourly, both for 10 days.

Results Both treatment groups had similar demographic characteristics. Fever showed a more rapid reduction in the doxycycline group (3(1.6) days versus 4.3(2) days). Side effects were observed in two patients receiving doxycycline compared with 11 patients receiving erythromycin ($p < 0.01$). No differences were observed in other clinical or radiological measures. By day 40 the chest radiograph was normal in 47 of 48 patients.

Conclusion The results demonstrate the self limiting and benign nature of most cases of pneumonia due to Q fever. Doxycycline was more effective than erythromycin.

Q fever is a frequent cause of pneumonia in the Basque Country.^{1,2} Diagnosis is usually made retrospectively and treatment is usually with erythromycin to ensure cover also for *Mycoplasma pneumoniae* and *Legionella pneumophila*. Erythromycin has been shown to be ineffective in vitro against Q fever,³ although clinical efficacy in vivo has been suggested.^{4,5} Our retrospective study suggested that doxycycline might be more effective than erythromycin in the reduction of fever in pneumonia due to Q fever.²

This study was undertaken to compare the efficacy of doxycycline and erythromycin in the treatment of Q fever pneumonia.

Methods

The study was carried out from January to June in 1987 and 1988 at the Cruces and Galdacano hospitals. This period was chosen because earlier studies had showed that over 90% of pneumonia due to Q fever in our region occurred in the first six months of the year.²

PATIENTS

We included in the study patients with radiological evidence of consolidation associated with fever ($\geq 37.5^{\circ}\text{C}$) and aged under 40 years, with at least two of the following criteria: (a) absence of cough or productive cough with mucous sputum, (b) absence of pleural pain, (c) myalgia or headache, (d) white blood count $< 12.0 \times 10^9/\text{l}$.

Three samples of blood serum were obtained: at admission, and after three and six weeks. A diagnosis of Q fever was based on a fourfold increase in phase II *Coxiella burnetii* antibody titre assayed by complement fixation at the third or sixth week, or a stable titre $\geq 1/128$.² Complement fixation tests for *M pneumoniae* and *L pneumophila* are also carried out on these samples.

Exclusion criteria were: treatment with doxycycline or erythromycin before admission, absence of pneumonia due to Q fever and loss of the patient to follow up.

TREATMENT

Patients were randomised by means of random table numbers to receive either doxycycline (Vibracina, Pfizer Pharmaceutical, Spain) 100 mg intravenously followed by oral doxycycline 100 mg every 12 hours or erythromycin lactobionate intravenously 500 mg six hourly followed by erythromycin stearate orally (Pantomicina, Abbott Pharmaceutical, Spain) 500 mg every six hours. Intravenous treatment was given until 24 hours after the fever had disappeared and was followed by oral administration until completion of 10 days' treatment. Both drugs were obtained from the Pharmacy Service of Cruces Hospital and were administered in a double blind fashion. Informed consent was obtained from the subjects.

CLINICAL MONITORING AND ASSESSMENT

Liver function tests and full blood cell counts were performed before and after antibiotic treatment. Blood samples were obtained for culture at admission. Chest radiographs were obtained at admission and on days 5, 10, 20 and 40. All patients were monitored daily for adverse drug reactions and a daily record kept of their physical findings and temperature measurement between 7 and 8 am. Cough and production of sputum, collected in a numbered flask, were also recorded.

Three groups were defined by radiographic assessment: group 1—less than 25% reduction of the lung fields; group 2—infection of 25–

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Table 1 Comparison of details of patients at admission with Q fever pneumonia treated with doxycycline or erythromycin

	Doxycycline	Erythromycin
Number	23	25
Mean (SD) age (years)	26.7 (7.2)	25.6 (7.7)
Sex (M:F)	19:4	18:7
Year 1987/1988	7/16	7/18
Previous antibiotic*	8	10
Cough or productive cough	18	22
Expectoration	9	5
Myalgia	19	16
Headache	20	22
Crackles	10	13
Bilateral chest radiograph	6	2
Pleural effusions	1	0
Mean (SD) leucocyte count ($\times 10^9/l$)	8.1 (2.3)	8.2 (1.8)
Altered liver function†	6	8
PaO ₂ < 9.3 kPa	1	1

*16 patients treated with amoxicillin, one with lincomycin, one with tobramycin.

†Increased activity of one or more enzymes.

PaO₂, arterial oxygen tension.

All differences were non-significant.

50% reduction of the lung fields; group 3—more than 75% reduction of the lung fields.

Chest radiographs were read independently by two physicians. Discrepant results were reviewed jointly until agreement was reached.

STATISTICAL ANALYSIS

On the basis of our retrospective study,^{2,6} we calculated that 47 patients were needed to obtain a power of 90% at the level of $p = 0.05$, provided that the mean (SD) difference in the number of days with fever between the two antibiotic treatments was 1.2 (1.4) days.

Statistical analysis was performed by the χ^2 test for discrete variables and the Mann-Whitney U test for continuous variables, $p < 0.05$ being considered significant.

Table 2 Clinical response in patients with Q fever pneumonia treated with doxycycline or erythromycin (mean (SD) values)

	Doxycycline (n = 23)	Erythromycin (n = 25)	p
Fever (°C)			
Before treatment	38.7 (0.67)	39.0 (0.82)	NS
Days after start of treatment			
1	38.1 (0.91)	38.6 (0.86)	NS
2	37.4 (0.82)	38.0 (0.86)	0.05
3	36.9 (0.66)	37.5 (0.93)	0.05
4	36.5 (0.45)	37.0 (0.83)	0.05
5	36.4 (0.45)	36.7 (0.52)	NS
Duration of symptoms before and after start of treatment (days)			
Fever			
Before	4.3 (1.9)	4.0 (1.6)	NS
After	3.0 (1.6)	4.3 (2.0)	0.05
Cough			
Before	2.5 (1.9)	2.6 (2.1)	NS
After	4.2 (1.2)	4.0 (1.9)	NS
Expectoration			
Before	2.4 (1.7)	4.2 (1.9)	NS
After	2.5 (1.0)	2.6 (2.3)	NS
Myalgia			
Before	4.8 (1.6)	4.0 (1.8)	NS
After	3.2 (2.0)	3.4 (1.6)	NS
Headache			
Before	4.0 (1.7)	3.4 (1.9)	NS
After	3.2 (1.5)	3.5 (1.8)	NS
Crackles			
After	4.0 (2.0)	4.1 (1.9)	NS

Results

A total of 82 patients initially entered the study: 27 in 1987 and 55 in 1988. A definite diagnosis of pneumonia due to Q fever was made in 48 patients, and the results of this group are reported. In 46 cases the diagnosis was based on a fourfold increase in phase II *C burnetti* antibody titre and in two cases on the presence of steady titres ($\geq 1/256$). Thirty patients were excluded because their pneumonia was not caused by Q fever, and four patients (two in the doxycycline group and two in the erythromycin group) were lost to follow up.

Of the 48 patients with Q fever pneumonia, 23 received doxycycline and 25 erythromycin (table 1). There were no significant differences between the groups with regard to age, sex, previous antibiotic therapy and clinical, radiological, and laboratory findings. Blood cultures were negative in all cases.

CLINICAL RESPONSE

Symptoms before treatment were similar in the two groups (table 2). After the start of treatment, fever reduced more rapidly in the group receiving doxycycline, with significant differences appearing on the second day of treatment. The mean (SD) differences in the reduction in fever were present in the patients without expectoration (doxycycline 2.9 (1.3) days after start of fever versus erythromycin 4.4 (2.3) days; $p < 0.05$).

RADIOLOGICAL RESPONSE

The radiological outcome did not differ between the treatment groups. After 10 days of treatment three quarters of the patients had substantial clearing of the chest radiograph (groups 2 and 3). After 40 days only one patient still showed consolidation.

ADVERSE EFFECTS

Eleven patients treated with erythromycin complained of gastrointestinal discomfort, epigastric pain, or nausea and vomiting compared with only two patients receiving doxycycline ($p < 0.01$). In nine of the 11 patients receiving erythromycin the gastrointestinal adverse effects occurred while on intravenous treatment. In no case was treatment discontinued.

PNEUMONIA NOT DUE TO Q FEVER

Of the 29 patients without Q fever who completed treatment, two had pneumonia due to *M pneumoniae*; no diagnosis was reached in the other patients. Of these, 16 received doxycycline and 11 erythromycin. No differences in clinical outcome or radiological course were seen between the two groups.

Discussion

Assessment of the effectiveness of antibiotic treatment in pneumonia is difficult, especially in self limited forms such as Q fever, since they frequently resolve without treatment and diagnosis is usually made late.^{2,7,8} Thus patients for such studies have to be selected by clinical and epidemiological criteria. These criteria are

nevertheless adequate as 58.5% of the patients included in our protocol had a definite diagnosis of Q fever. Our study showed that doxycycline reduced the period of fever faster than erythromycin, though it did not affect the overall resolution time. This confirms the findings of our earlier retrospective study.² Powell *et al*,⁹ in a prospective and randomised study, compared tetracycline with placebo in the treatment of Q fever and found a faster decline of fever with tetracycline (1.7 versus 4.1 days) with a similar febrile period before treatment (4.7 versus 4.2 days). The results with placebo are similar to our results with erythromycin, whereas the decline of fever in patients treated with tetracycline is faster than in our patients treated with doxycycline. This difference may be due to the different selection of patients as Powell *et al* included patients with acute Q fever in whom the incidence of lung infection was unknown. Other retrospective studies comparing tetracyclines and penicillin or in which no antibiotic treatment was used¹⁰⁻¹² have shown similar results, though in all these studies the acute Q fever infection finally resolves, thus confirming the self limiting nature of this condition.

Our results suggest that no change in the therapeutical approach to community acquired pneumonia is needed. The most common organisms causing this type of pneumonia are *Streptococcus pneumoniae*, *M pneumoniae* and *L pneumophila*, while *C burnetti* accounts for less than 4% of all diagnosed cases.^{13,14} Erythromycin has extensive coverage for the common pathogens and should continue to be the antibiotic of first choice,¹⁵ though Q fever infection may cause delayed complications, especially endocarditis, that are associated with appreciable mortality.⁸ There is no evidence that treating the acute stage may prevent the development of a chronic stage, but it seems reasonable to treat acute infection with effective antibiotics such as doxycycline, even in cases where the diagnosis has been delayed.

We believe that in areas with a high prevalence of Q fever pneumonia,¹⁶ when strict epidemiological and clinical criteria are applied, doxycycline can be used as the first choice antibiotic. In our study in this selected group of patients the results in cases of

pneumonia not due to *C burnetti* were similar to those obtained with erythromycin. An additional advantage of doxycycline is the lower frequency of side effects, although the possibility of a lower incidence of gastrointestinal discomfort might have occurred if erythromycin ethylsuccinate had been given orally.¹⁷

- 1 Ansolá P, Sobradillo V, Baranda F, Gaztelurrutia L, Llorente JL, Antoñana JM. Neumonias adquiridas en la comunidad de Vizcaya. *Arch Bronconeumol* 1990;26:103-7.
- 2 Sobradillo V, Ansolá P, Baranda F, Corral C. Q fever pneumonia: a review of 164 community-acquired cases in the Basque Country. *Eur Respir J* 1989;2:263-6.
- 3 Spicer AJ, Peacock MG, Williams JC. Effectiveness of several antibiotics in suppressing chick embryo lethality during experimental infections by *Coxiella burnetti*, *Rickettsia typhi* and *R. rickettsii*. In: Dorfer W, Anacker RL, eds. *Rickettsiae and rickettsial disease*. New York: Burg Press, 1981:375-83.
- 4 Ellis ME, Dungar EM. In vivo response of acute Q fever to erythromycin. *Thorax* 1982;37:867-8.
- 5 D'Angelo LF. Q fever treated with erythromycin. *BMJ* 1979;iii:305-6.
- 6 Carne X, Moreno V, Porta Serra M, Velilla E. El calculo de pacientes necesarios en la planificación de un estudio clinico. *Med Clin (Barc)* 1989;92:72-7.
- 7 Chow JW, Yu V. Antibiotic studies in pneumonia. Pitfalls in interpretation and suggested solutions. *Chest* 1989;96:453-6.
- 8 Sawyer LA, Fishbein D, McDade JE. Q fever: current concepts. *Rev Infect Dis* 1987;9:935-46.
- 9 Powell OW, Kennedy KP, McIver M, Silverstone H. Tetracycline in the treatment of Q fever. *Australas Ann Med* 1962;11:184-8.
- 10 Clark WH, Lennette EH, Meiklejohn G. Q fever in California. III. Aureomycin in the therapy of Q fever. *Arch Intern Med* 1951;87:204-17.
- 11 Spelman DW. Q fever: a study of 111 consecutive cases. *Med J Aust* 1982;i:547-53.
- 12 Lennette EH, Meiklejohn G, Thelen HM. Treatment of Q fever in man with aureomycin. *Ann N Y Acad Sci* 1948;51:331-8.
- 13 British Thoracic Society Research Committee. Community-acquired pneumonia in adults in British hospitals in 1982-1983: a BTS/PHLS survey of aetiology, mortality, prognostic features and outcome. *Q J Med* 1987;239:195-200.
- 14 Bernstsson E, Blomberg J, Lagergard T, Trollfors B. Etiology of community-acquired pneumonia in patients requiring hospitalization. *Eur J Clin Microbiol* 1985;4:268-72.
- 15 Pennington JE. Community-acquired pneumonia and acute bronchitis. In: Pennington JE, ed. *Respiratory infections. Diagnosis and management*. New York: Raven Press, 1989:159-70.
- 16 Marrie Th, Haldane E, Faulkner RS, Carol RT, Grant B, Cook F. The importance of *Coxiella burnetti* as a cause of pneumonia in Nova Scotia. *Can J Public Health* 1985;76:233-6.
- 17 Macklin J, Barden R, Coles S. Comparison of two oral forms of erythromycin in the treatment of acute respiratory tract infections. A multicentre general practice study. *J Int Med Res* 1989;17:287-94.