Chronic Q fever endocarditis

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SUMMARY Eight patients with chronic Q fever endocarditis were treated with tetracycline for up to 40 months. In addition, five of these patients received co-trimoxazole. Six patients had prosthetic valves. Two patients who had Q fever endocarditis on their native valves required valve replacement because of haemodynamic difficulties: in only one did the Q fever endocarditis contribute to the haemodynamic difficulty. One patient died.

It is suggested that medical treatment is continued until clinically and haematologically there is no evidence of endocarditis and the Q fever phase 1 antibody titre is less than 200. No recurrence of Q fever endocarditis has been detected in three of our patients who have now stopped treatment.

Q fever was first recognised as a clinical entity by Derrick¹ as a result of an outbreak of febrile disease among abattoir workers in Brisbane, Australia. It was shown by Burnet and Freeman² to be due to a rickettsia-like organism now classified as *Coxiella burnetii*.

Clinically acute Q fever may present as an atypical pneumonia or as a febrile illness which lasts two to three weeks. However, Q fever also exists in a chronic form, and endocarditis is a feature of the chronic disease.

This report describes the management of chronic Q fever endocarditis in eight patients. Six of the patients had prosthetic valves.

Patients and methods

From 1975 to 1979 we treated eight patients with chronic Q fever endocarditis from different areas

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of Northern Ireland. There were five men and three women, aged between 24 and 67 years (Table 1). Their occupations were farmer, farmer's wife, farm-feed salesman, housewife, labourer, two factory workers, and a civil servant. All the patients were either in contact with cattle or sheep or had drunk unpasteurised milk.

All patients had rheumatic valve disease. Six of the eight patients had previous heart surgery, where the valves had been replaced by prosthetic valves (Table 1). All valves removed at the time of operation were studied microscopically and showed no evidence of microbial infection.

Sera from the patients were tested against Q fever phase 1 and phase 2, psittacosis-lymphogranuloma venereum, and yolk sac antigens using the complement fixation technique as described by Bradstreet and Taylor³ and the microtitre system. All antibody titres were expressed as reciprocals of

Table 1 Clinical data

Case no.	1	2	3	4	5	6	7	8
Sex	M	F	M	M	F	M	M	F
Age (y)	33	40	67	37	34	52	24	57
Estimated duration of illness before diagnosis (wk)	4	12	4	6	6	12	4	12
Original valve lesion	M	M/A	M	A	M	A	M/A	M/A
Prosthetic valve/valves before Q fever	-	S-E	S-E	S-E	S-E	-	D-V	S-E
Pyrexia	+	+	+	+	+	+	+	+
Hepatomegaly	+	+	+	+	+	+	+	+
Splenomegaly	+	+	+	+	+	+	+	+
Haematuria	+	+	+	+	+	+	+	+
Purpuric rash	-	+	+	-	-	-	-	-
Finger clubbing	-	+	-	+	+	-	-	-

M, mitral valve; A, aortic valve; S-E, Starr-Edwards valve; D-V, De Vega annuloplasty; C-E, Carpentier-Edwards valve.

Table 2 Haematological data

Case no.	1	2	3	4	5	6	7	8
Hb (g)	9.5	12.0	7.8	8.7	13.3	14.0	14.5	10.3
ESR	42	72	60	150	61	14	5	125
Platelets	—	28 000	22 000	62 000	200 000	125 000	180 000	260 000
Gamma globulin	18.0	22.0	28.0	36.0	28.0	24.0	—	30.0
IgG	16.5	35.0	22.0	> 30	18.5	24.0	—	29.0
IgA	—	—	4.50	—	—	7.0	—	4.50
IgM	3.5	2.4	1.8	> 3	3.0	1.55	—	> 3.5

Normal ranges: Platelets 150 to 450 000/ μ l; gamma globulin 7 to 15 g/l; IgG 5 to 16 g/l; IgA 1.25 to 4.25 g/l; IgM 0.47 to 1.7 g/l.

dilutions. Antigens and antisera were kindly supplied by the Standards Laboratory for Serological Reagents, Central Public Health Laboratory, London.

CLINICAL FEATURES OF PRESENTING ILLNESS

The estimated duration of the illness before diagnosis was from four to 12 weeks (Table 1). Six patients had prosthetic valves and, of the two patients without prosthetic valves, one (case 1) had severe mitral stenosis and the other (case 6) had aortic stenosis with regurgitation. On admission, all patients had pyrexia associated with night sweats. Seven patients had hepatomegaly, and seven patients had splenomegaly. The hepatic enlargement was from one to five finger breadths and the splenic enlargement was from one to eight finger breadths. All the patients had haematuria on ward testing. Two patients had purpura either at the time of admission or during the course of the illness.

HAEMATOLOGICAL FEATURES

Four patients presented with anaemia (Table 2). Six out of eight patients had a raised ESR (maximum 150 mm in the hour). Three patients had thrombocytopenia. The lowest platelet count recorded was 22 000/ μ l. Serum immunoglobulin studies were performed on seven of the eight patients. In all seven, gamma globulin and IgG were raised and in all but one of them IgM was also raised. All patients had more than three routine blood cultures which were negative.

DIAGNOSIS AND TREATMENT

The diagnosis was established by raised complement fixing antibody titres to phase 1 and phase 2 Q fever antigens (Table 3) along with clinical signs of endocarditis. No antibody was detected to psittacosis-lymphogranuloma venereum or yolk sac antigens. Seven of the eight patients had significantly raised phase 1 titres indicative of chronic infection. Though one of the patients (case 7) had a phase 1 antibody titre of 160 and a phase 2

antibody titre of 640 he had the clinical manifestations of endocarditis.

Six patients were treated medically and two had a combination of medical and surgical treatment (Table 3). All were started on tetracycline 2 g/day. Five patients were also given co-trimoxazole (trimethoprim 320 mg and sulphamethoxazole 1600 mg/day). During treatment the Q fever phase 1 and phase 2 antibody titres were monitored. Case 1 stopped co-trimoxazole after two-and-a-half months. Case 2 had co-trimoxazole for one week and then developed a rash which necessitated the drug's withdrawal. In one patient (case 5) tetracycline was discontinued after six months since no significant reduction in phase 1 and phase 2 antibody titres

Table 3 Q fever phase 1 and phase 2 antibody titres

Case no.	Serum	Q fever antibody		Months between first and last serum	Treatment period
		Phase 1	Phase 2		
1*	First	1280	5120	31	T — 11 mth
	Last	40	160		Co — 2.5 mth
2	First	1280	10 240	41	T — 20 mth
	Last	20	80		Co — 1 wk
3†	First	< 10	< 10	6	T — 23 d
	Last	5120	10 240		
4	First	10 240	10 240	17	T } 24 mth
	Last	1280	5120		Co }
5	First	10 240	10 240	14	T — 6 mth
	Last	1280	1280		Co — 14 mth
6*	First	2560	2560	31	T — 21 mth
	Last	40	160		
7	First	160	640	6	T } 7 mth
	Last	80	640		Co }
8	First	2560	20 480	39	T — 13 mth
	Last	< 10	40		

* Required surgery. † Died.
T, tetracycline (2 g/day); Co, Co-trimoxazole (320 mg trimethoprim, 1600 mg sulphamethoxazole).

had occurred. Co-trimoxazole was then started and after two months of treatment a significant reduction in phase 1 antibody titre occurred. The remaining two patients (cases 4 and 7) have received tetracycline and co-trimoxazole for 24 and seven months, respectively, and continue with the treatment without side effects.

With the exception of case 3 who died after 23 days and case 7 who has been on treatment for seven months, the other six patients have shown a significant reduction in Q fever phase 1 and phase 2 antibody titres.

Of the surgically treated patients, case 1 had chronic Q fever endocarditis in association with severe mitral stenosis. After diagnosis he discharged himself from hospital. Two-and-a-half months later he stopped co-trimoxazole. He stopped tetracycline after 11 months. He was readmitted to hospital 15 months after the initial admission in distinct congestive heart failure. Despite bed rest, digoxin and diuretic treatment, and the restarting of tetracycline and co-trimoxazole, right ventricular failure persisted. At operation the severely stenosed and heavily calcified mitral valve was replaced by a Carpentier-Edwards valve. No vegetations were noted on the valve. His postoperative course was complicated by a left-sided hemiplegia which was not thought to be associated with Q fever endocarditis. Tetracycline and co-trimoxazole were stopped after continuing treatment for 29 months. During the period of treatment no prosthetic valve regurgitation was detected. Case 6, who was known to have mixed aortic valve disease, developed severe aortic regurgitation probably caused by Q fever endocarditis. Despite bed rest and treatment with tetracycline, digoxin, and diuretics, gross aortic regurgitation persisted. At operation the aortic valve was found to be thickened with retraction of all three cusps, calcified, and detached from one-third of the circumference of the aortic wall. No vegetations were noted. The aortic valve was replaced by a Hancock valve. The postoperative course was uneventful. He continued on tetracycline therapy for a total of 21 months. During the treatment and follow-up periods the Hancock valve has remained competent. The valves excised from these two patients were stained using Giemsa and Macchiavello stains. Both valves showed organisms consistent with *Coxiella burnetii*. Brown's modification of Gram stain, and PAS stain of both valves showed no bacteria or fungi.

The patient (case 3) who died was the oldest. He had a Starr-Edwards valve inserted in the mitral area for mitral regurgitation four years before the diagnosis of Q fever endocarditis. At the time of surgery he was noted to have poor left ventricular

function. Postoperatively he continued in congestive heart failure. Seven months before death he was readmitted for further treatment of chronic heart failure. Q fever phase 1 and phase 2 antibody titres at that time were less than 10. However, three months before death he was again readmitted because of gross congestive heart failure. One month before death the Q fever phase 1 antibody titre was 5120 and the phase 2 antibody titre, 10 240. Treatment with tetracycline was begun. No surgery was contemplated in view of the poor left ventricular function. He died 23 days after starting treatment with tetracycline. No necropsy was carried out because of the danger to mortuary staff and pathologists.

Three patients (cases 2, 6, and 8) have now stopped treatment 20, 21, and 13 months, respectively, from starting it and have been followed-up from 18 to 41 months. At the time of stopping treatment all clinical signs of Q fever endocarditis had resolved. Haemoglobin and ESR were normal and phase 1 Q fever antibody titres were less than 200. One patient (case 8) who was treated with tetracycline alone, stopped treatment at 13 months. She had increased skin pigmentation which was proven on biopsy. However, clinically, haematologically, and serologically there was no evidence of Q fever endocarditis (phase 1 antibody titre < 10). Subsequently the increased skin pigmentation resolved. During the period of follow-up there has been no evidence of recurrence of Q fever endocarditis. The longest period of survival since diagnosis has been four years.

Discussion

Although Q fever has a worldwide distribution, the first known case in Ireland was that of a Co. Down farmer with pneumonia in February 1962.⁴ Before this, serological surveys carried out in the Republic of Ireland,⁵ and in Northern Ireland⁶ showed no evidence of Q fever infection. Subsequent studies⁷⁻⁹ have confirmed that Q fever is now endemic in Ireland. In Northern Ireland from February 1962 until April 1979 138 cases of Q fever have been diagnosed. Also in Northern Ireland the first case of Q fever endocarditis was diagnosed in 1974 and 12 cases have now occurred. Three of these patients have died. Eight of these 12 patients came under our care.

The aortic and mitral valves are predominantly involved in Q fever endocarditis.¹⁰ It has been suggested that thrombocytopenia is more common in Q fever endocarditis than in bacterial endocarditis. Turck *et al.*¹⁰ found thrombocytopenia in 12 out of their 16 patients. Nevertheless, in our patients

thrombocytopenia was found in only three patients. Gamma globulin fraction was raised in seven out of the eight patients and, as was noted by Turck *et al.*,¹⁰ we found raised IgM and IgG fractions. The average duration of illness before diagnosis in our patients was much shorter than that recorded by other workers.¹⁰ Only one of our patients developed an arterial embolus. None of our patients developed venous thrombosis, nor did they manifest significant hepatocellular damage during the course of their illness.

The diagnosis of chronic Q fever endocarditis is confirmed when antibody titres to both phase 1 and phase 2 antigens are raised. A phase 1 complement fixing antibody titre of greater than 200 is usually regarded as good evidence of chronic Q fever infection.¹¹ All our patients with the possible exception of case 7 had phase 1 antibody titres in excess of this. Antibody to phase 1 antigen does not normally develop during acute Q fever infection.

The management of chronic Q fever endocarditis is still controversial. In 1965, Ormsbee¹² stated that "Q fever endocarditis has been, so far as is known, uniformly fatal". Darrell¹³ maintained that the antibiotics of choice, tetracycline and chloramphenicol on their own, never achieved a cure since they are rickettsiostatic rather than rickettsiocidal. Oakley¹⁴ advocated valve replacement under antibiotic cover to eradicate infection. However, Wilson *et al.*¹⁵ studied 16 patients with Q fever endocarditis and suggested that the infection can be controlled by prolonged tetracycline therapy. During treatment they showed a fall in phase 1 antibody titre. Turck *et al.*¹⁰ using tetracycline and lincomycin in 14 patients with chronic Q fever endocarditis, also showed a reduction in phase 1 antibody titres. Freeman and Hodson¹⁶ reported a fall in the phase 1 titres in a patient with Q fever endocarditis treated with tetracycline and co-trimoxazole for a period of slightly over four months. Operation was performed in the patients of Wilson *et al.*,¹⁵ and Turck *et al.*¹⁰ only for symptomatic and haemodynamic indications. We were able to treat five out of our six patients who developed Q fever endocarditis on prosthetic valves with either tetracycline or co-trimoxazole or a combination of these drugs for a prolonged period. No side effects were noted in patients on prolonged oral tetracycline treatment other than increased skin pigmentation in one patient. None of the patients has required an operation as their haemodynamic condition has remained satisfactory throughout the period of treatment and follow-up. Two patients whose native valves were damaged by rheumatic valvular disease required operation. However, in only one patient did the Q fever endocarditis

contribute to the haemodynamic difficulty.

The response to treatment using tetracycline, either on its own or in combination with cotrimoxazole, was considered successful in six patients when improvement was noted clinically, haematologically, and by a fall in phase 1 and phase 2 antibody titres. One patient (case 7) has now been on treatment for seven months and has not shown a significant reduction in his Q fever phase 1 or phase 2 antibody titres, though clinically there has been no deterioration in his overall condition. Another patient with a prosthetic valve died from gross congestive heart failure caused by poor left ventricular function diagnosed before Q fever infection.

It has been suggested that after stopping treatment careful follow-up is mandatory to ensure that there is no recurrence of Q fever endocarditis.¹⁰ Three patients have discontinued treatment after an average course of 18 months and have been followed up for on average 22 months. At the time of stopping treatment phase 1 and phase 2 antibody titres were less than 200. During the period of follow-up of the three patients there was no recurrence of Q fever endocarditis as judged clinically, haematologically, and serologically.

For the successful treatment of Q fever endocarditis tetracycline 2 g/day alone or in combination with co-trimoxazole (320 mg trimethoprim and sulphamethoxazole 1600 mg) per day should be given for a prolonged period. Co-trimoxazole therapy alone might be appropriate treatment but this is unproven. Surgery is indicated when significant haemodynamic difficulties occur but is rarely necessary to eradicate infection. *Coxiella burnetii* is very resistant to chemical and physical agents and the organism can remain viable for long periods in the environment.¹⁷ Attempts to isolate *Coxiella burnetii* in the laboratory are hazardous to staff¹⁸ and if an infected patient dies, pathologists and mortuary staff are at risk.¹⁹ *Coxiella burnetii* has been isolated from the blood of a patient with chronic Q fever endocarditis during life and the vegetations from the aortic valve removed at necropsy showed high infectivity when inoculated intraperitoneally into guinea-pigs.²⁰ Presumably there is also a risk to operating theatre staff during open heart surgery, when infected valves are removed. Ideally, surgery should be carried out after a period of treatment with tetracycline and co-trimoxazole. This study indicates that if medical treatment is continued until all clinical signs of endocarditis have resolved, and haemoglobin and erythrocyte sedimentation rate have returned to normal, and Q fever phase 1 antibody titres are less than 200, then Q fever endocarditis does not recur.

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