

Acute Q Fever in Israel: Clinical and Laboratory Study of 100 Hospitalized Patients

David Ergas MD¹, Avi Keysari PHD², Victor Edelstein MD¹ and Zev M. Sthoeger MD¹

¹Department of Medicine B, Kaplan Medical Center, Rehovot, Israel

Affiliated to Hadassah-Hebrew University Medical School, Jerusalem, Israel

²Israel National Reference Center for Rickettsioses, Department of Infectious Diseases, Israel Institute for Biological Research, Nes Ziona, Israel

Key words: Q fever, Israel, *Coxiella burnetii*, urinalysis, band forms

Abstract

Background: Q fever is endemic in Israel, yet a large series describing the clinical spectrum of inpatients with acute Q fever in Israel is lacking.

Objectives: To report on the clinical characteristics and outcome of hospitalized patients with acute Q fever in Israel.

Methods: We conducted a retrospective study of 100 patients hospitalized in six medical centers, in whom acute Q fever was diagnosed by the presence of immunoglobulin G and M antibodies to phase II *Coxiella burnetii* antigens.

Results: The mean age of the patients was 42.7 ± 17.3 years with a male to female ratio of 1.6:1. Acute Q fever occurred throughout the year but was more common during the warm season. The most common clinical presentation was acute febrile disease (98%, mean length of fever 15.5 ± 8.6 days), followed by hepatitis (67%) and pneumonia (32%). The prominent laboratory findings included: accelerated erythrocyte sedimentation rate, normal or low white blood count with many band forms, thrombocytopenia, and abnormal urinalysis. Although the diagnosis of acute Q fever was not known during the hospitalization in the majority of patients, about 80% of our patients received appropriate antibiotic therapy and all patients recovered.

Conclusions: Patients with acute Q fever present with a typical clinical picture that enables clinical diagnosis and empiric therapy in most cases. The prognosis of hospitalized patients with acute Q fever is excellent.

IMAJ 2006;8:337-341

Q fever is a worldwide zoonosis caused by *Coxiella burnetii*, a small and highly pleomorphic coccobacillus with a gram-negative cell wall that can survive inside the phagolysosome of the host cells. The most common animal reservoirs are cattle, sheep and goats, as well as ticks, but many other species, including pets, can be infected and serve as reservoirs for Q fever [1]. Infected animals secrete the organism in their urine, feces, milk, and birth products, where it can survive in its spore-like form for several months. Transmission usually occurs by inhalation of infected aerosol particles carried by wind or by direct contact with an animal product [2].

Q fever, the clinical disease caused by *Coxiella burnetii*, is conveniently divided into acute and chronic forms, which are two distinct entities that differ in their clinical course, serologic

markers and therapy [2]. Acute Q fever, the primary infection, is usually a self-limited disease with several clinical presentations. About half the patients are asymptomatic [3], while many others have a non-specific flu-like disease. Only 2% of patients with acute Q fever are hospitalized, usually for prolonged fever, pneumonia or hepatitis. Other, though rare presentations of acute Q fever include neurologic syndromes [4], peri-myocarditis, and acalculous cholecystitis [5]. There are several populations at specific clinical risk for Q fever complications. Pregnant women with acute Q fever are at high risk for abortions, which may be related to the presence of antiphospholipid antibodies and placental thrombosis [6]. Patients with valvular disease or prosthetic grafts are at risk to develop endocarditis and graft infection [7]. Acute Q fever is diagnosed by the presence of immunoglobulin M and G antibodies directed against phase II organisms (organisms that lost certain surface antigens in culture) [1]. Chronic infection, which commonly involves infection of heart valves, vascular aneurysms or prosthesis, is characterized by high titer of IgA and IgG antibodies against phase I organisms (natural organisms found in infected animals and humans) [8].

In Israel, Q fever is an endemic disease that was first reported in 1949 [9]. Gross et al. [10] examined 400 pregnant women from southern Israel without a clinical history of Q fever and found that 21.3% of them were seropositive for Q fever. Yarrow and colleagues [11] examined the reported incidence of Q fever in Israel since it was first notifiable in 1951 and concluded that it is both under-diagnosed and under-reported. Between the years 1981 and 1985 the Ministry of Health collected data on seropositive patients from two reference laboratories in Israel. During that time, 687 seropositive patients were identified. In contrast, in the previous years (1963 to 1980) only 62 cases were reported to the Ministry of Health, emphasizing that Q fever is indeed under-reported in Israel [11].

The clinical spectrum of acute Q fever in Israel has not been described in a large series of patients. In the present study, we retrospectively investigated the clinical manifestations and the laboratory abnormalities of 100 unselected patients hospital-

Ig = immunoglobulin

ized in six medical centers with serologic evidence for acute Q fever.

Patients and Methods

The records of the National Reference Center for Rickettsioses (Nes Ziona, Israel) were screened for positive serum samples for acute Q fever. Clinical data, contained in the medical records of such patients, were collected from six medical centers in the country – Soroka (in Beer Sheva), Kaplan (Rehovot), Meir (Kfar Saba), HaEmek (Afula), Poriyah (Tiberias), and Bnei Zion (Haifa) – using a uniform information sheet that included the patient's medical history, physical examination, laboratory findings, clinical course, and response to therapy. Since IgM antibodies may remain for a long time after an acute infection, patients were considered to have acute Q fever only when the serologic data were accompanied by a clinical course that was compatible with acute infection. Patients who had an alternative diagnosis were excluded from the study. The study protocol was approved by our local ethics committee.

Serologic diagnosis

Serum samples were tested for IgG and IgM antibodies to phase I and phase II *Coxiella burnetii* antigens by the indirect immunofluorescence assay as previously described [12]. Patients with high titer ($\geq 1:100$) for both IgG and IgM antibodies to phase II antigens were considered seropositive for acute Q fever [12]. All patients were diagnosed according to one tested serum.

Results

Between the years 1986 and 1996, about 1500 sera samples obtained from 1500 patients were sent annually to the National Reference Center for Rickettsioses (Nes Ziona, Israel) for serologic evaluation of hospitalized patients with suspected diagnosis of acute Q fever. Of those 15,000 sera, about 1% was found to be positive for acute Q fever. We studied the medical records of 100 hospitalized patients with serologic diagnosis of acute Q fever and found that all 100 had acute illness compatible with the diagnosis of acute Q fever. The mean age of these patients – 61 males and 39 females – was 42.7 ± 17.3 years (range 0.8–87). The age distribution of our 100 patients with acute Q fever is demonstrated in Figure 1. As seen in the figure, most patients were of working age, and less than 5% were children (< 15 years old).

Acute Q fever occurred in Israel throughout the year. However, as shown in Figure 2, there is a seasonal distribution with a peak between April and September (64% of patients). During wintertime, November to March, the incidence of acute Q fever was much lower [Figure 2].

The clinical characteristics of our 100 patients with acute Q fever are summarized in Table 1. Most of the patients had no underlying disease, and only 24% of them suffered from any chronic disorder (e.g., heart or lung disease). More males than females were hospitalized for acute Q fever (1.6:1 ratio), and this male preponderance was observed in all age groups. In almost all our patients (98%) fever was the presenting symptom. Muscle

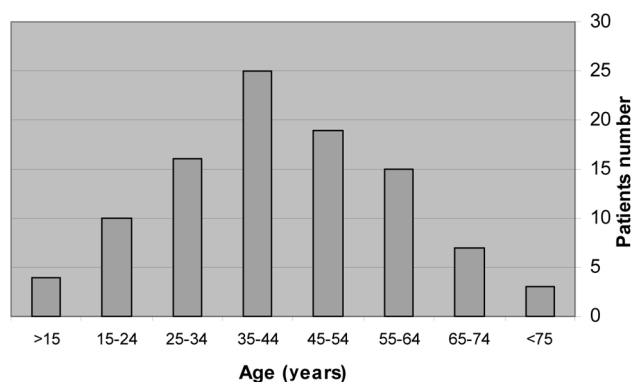


Figure 1. Age distribution of 100 unselected hospitalized patients with acute Q fever in Israel

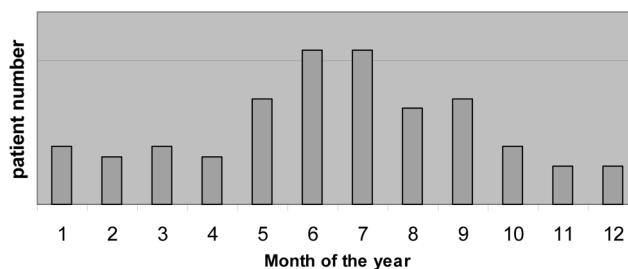


Figure 2. Seasonal distribution of acute Q fever in 100 unselected hospitalized patients in Israel.

Table 1. Demographic and clinical features of 100 unselected hospitalized patients with acute Q fever

Demographic features	
Mean age (\pm SD) (yrs)	42.7 \pm 17.3
Male/Female	1.6:1
Mean duration of symptoms before admission (days)	9.7 \pm 8.0 (range 2–20)
Total days of fever (\pm SD)	15.5 \pm 8.6
Clinical features	
Fever ($> 38.0^{\circ}\text{C}$)	98%
Myalgia	39%
Headache	37%
Cough	35%
Chills	34%
Nausea, vomiting	33%
Prostration	27%
Night sweats	15%
Arthralgia	7%
Dyspnea	6%
Diarrhea	5%

pain, headache, shivering and cough were observed in 39%, 37% and 35% of the patients respectively [Table 1]. The mean length of symptoms before admission was 9.7 ± 6.0 days and total days of fever averaged 15.5 ± 8.6 days (range 3–41 days). The results of the physical examination at admission are summarized in Table 2. As shown in the table, physical examination was completely normal in about one-quarter of the patients. Abnormal

Table 2. Clinical and laboratory findings at admission in 100 unselected hospitalized patients with acute Q fever

Clinical findings	
Normal physical examination	24%
Abnormal lung auscultation	26%
Splenomegaly	23%
Hepatomegaly	16%
Heart murmur	15%
Rash or purpura	9%
Lymphadenopathy	5%
Neurologic findings	2%
Jaundice	3%
Laboratory findings	
Accelerated ESR (> 20 mm/hr)	94% (63/68)
Leukopenia (< 4500/ μ l)	33% (33/100)
Leukocytosis (> 11,000/ μ l)	7% (7/100)
Shift to the left (> 6% band forms)	89% (48/54)
Average band forms	15% \pm 12
Thrombocytopenia (< 150,000/ μ l)	45% (45/99)
Elevated AST (> 35 U/ml)	63% (60/96)
Elevated ALT (> 35 U/ml)	67% (64/96)
Abnormal urinalysis	64% (51/80)

AST = aspartate aminotransferase, ALT = alanine aminotransferase

lung auscultation findings, splenomegaly and hepatomegaly were detected in 26%, 23% and 16% of the patients, respectively. Most patients demonstrated a high sedimentation rate (in 70% of the patients at admission ESR was higher than 60 mm/hour), 33% of the patients had leukopenia (< 4,500/ μ l) and 45% had thrombocytopenia (< 150,000/ μ l). Almost all patients had a prominent shift to the left (89% of manual counts). Elevated liver enzymes were present in 67% of patients. Abnormal urinalysis was present in more than half the patients (64%), and included microscopic hematuria (50%), leukocyturia (38%), proteinuria (17%), and casts (7%). Rheumatoid factor was present in 7/16 tested patients (43%). In 10 patients, serum protein immunoelectrophoresis was performed which, interestingly, detected one or more monoclonal peak proteins in 5 of them (50%) (IgG kappa in 3, IgM kappa in 2).

Chest X-ray results were available in 73 of our patients. In 27 of them (36.9%) some abnormalities were noted, which were evenly distributed between right and left lungs. Pneumonia when present was usually unilateral (22/27, 81%), and was more common in the lower lobes of the lungs (19/27, 70%). Only three of the patients with infiltrate had pleural effusion (12%).

Seventy-one of our patients received at least one antibiotic with activity against *Coxiella burnetii*. Fifty of those patients were treated with tetracycline preparations (mostly doxycycline). Fourteen patients received macrolides and 7 received quinolones. Eight patients received antibiotics without activity against *Coxiella burnetii* (cephalosporin in 4, penicillin in 3, chloramphenicol in 1),

and 21 patients recovered without any antibiotic therapy. Despite a protracted course in several cases, all patients with acute Q fever eventually recovered completely.

Discussion

We describe the clinical and laboratory characteristics of 100 unselected hospitalized patients with acute Q fever, diagnosed by the presence in one sample of high titer for both IgM and IgG antibodies against *Coxiella burnetii* phase II antigens [12] as well as symptoms of acute disease without any other alternative diagnosis. Almost all patients had fever (98%), about two-thirds had elevated liver enzymes without jaundice, and a third of the patients presented with pneumonia. Characteristic laboratory findings included accelerated ESR, normal or low white blood count with many band forms, thrombocytopenia, and abnormal urinalysis.

The serologic diagnosis of acute Q fever in our study was based on the detection by indirect immunofluorescence of high titers (> 1:100) for both IgM and IgG antibodies directed against phase II antigens [1,15] in one serum sample (see Patients and Methods). Since the sera were obtained from hospitalized patients with symptoms of acute illness that presented about 10 days prior to their admission, we believe that our serologic results defined true illness of acute Q fever. Nevertheless, due to the absence of repeated sera testing we cannot completely rule out the possibility of false positive results (because of cross-reactivity or remote infection).

The mean age of our patients (42.7 ± 17.3 years) is similar to other series from France and Israel [8,13] but is slightly higher than reported from Spain [14]. As observed in other series, children are rarely affected [15] and there is a male preponderance among hospitalized patients with acute Q fever [8,14]. In contrast to a previous report from Israel [11], we found a seasonal distribution with a peak in the warm season [Figure 2], similar to reports from France and Spain showing that Q fever is more common during spring and early summer [2,14]. This peak may be due to the fact that during the warm season more infected aerosols are generated.

The clinical presentation, physical findings and laboratory abnormalities observed in our patients [Tables 1 and 2] are generally comparable to those described in previous series [1,2, 8,14]. Prolonged febrile illness is the most common presentation [15,16]. The relatively low proportion (37%) of patients with documented headache in our retrospective study may be due to lack of documentation of this symptom in the medical files. Similar to previous series, about two-thirds of our patients also had elevated liver enzymes without jaundice. Cholestatic hepatitis with significant elevation of serum conjugated bilirubin is uncommon in patients with acute Q fever, although it has been observed in a few patients [8,16]. In all five patients who underwent liver biopsy in our study, granulomatous hepatitis was present.

Community-acquired pneumonia is another major presentation of acute Q fever, though only 6% of patients with community-acquired pneumonia have Q fever [13]. As in other reports, it

ESR = erythrocyte sedimentation rate

comprised about one-third of clinical presentations [2]. When Q fever presents as community-acquired pneumonia, it is probably impossible to differentiate it clinically from "atypical pneumonia" caused by other organisms. As demonstrated in previous publications [13], Q fever pneumonia is usually unilateral. In contrast to the recent series reported by Gikas et al. [17], who found predominant upper lobe involvement [17], the pneumonia in our patients was more common in the lower lobes. Moreover, multiple round opacities, which were reported to be characteristic of acute Q fever pneumonia [18], were not present in any of our patients. Pneumonia was usually mild and dyspnea was noted in only 6% of our hospitalized patients.

Mild and transient leukopenia and thrombocytopenia, reminiscent of viral disease, were more common in our patients than in previous reports [1,2]. Normal or low white blood counts with excess of band forms (> 6%) on peripheral blood film, which is only rarely mentioned in the literature [14,19], were present in 89% of our patients and may serve as a clue for the diagnosis.

Abnormal urinalysis, but with preserved renal function, was very common among our hospitalized patients with acute Q fever. Acute glomerulonephritis, although rare, is a well-known presentation of Q fever [20]. The high prevalence of abnormalities in urine analysis has not been previously reported and together with other clinical characteristics may help in clinical diagnosis. Due to the low number of patients who were tested for the presence of rheumatoid factor and monoclonal gammopathy, the significance of those abnormalities cannot be evaluated. Moreover, we cannot rule out that these abnormalities reflect cross-reactivity due to hypergammaglobulinemia.

Most hospitalized patients with acute Q fever, without pneumonia, present with a characteristic clinical picture that includes an acute febrile disease with few physical findings, normal or "viral" blood count with many band forms, accelerated ESR, and mild elevation of liver enzymes. It is interesting to note that despite such a non-specific clinical picture, appropriate empiric antimicrobial therapy was given to most patients (79%) before a definitive laboratory diagnosis was available. Patients with pneumonia routinely receive macrolides or doxycycline for their pneumonia, but many other patients also receive empiric therapy for "suspected rickettsial disease." It seems that many hospital physicians in Israel tend to treat such hospitalized patients with empiric tetracycline, macrolides or quinolones. The fact that only 1% of all suspected sera was found to be positive for acute Q fever also supports the high suspicion rate of Israeli physicians for the latter diagnosis. Eleven of our patients (11%) recovered without any treatment and another 10 patients recovered despite receiving antibiotics that are considered ineffective against *Coxiella burnetii* (e.g., beta-lactams) [21,22], suggesting that acute Q fever is a self-limited disease even among hospitalized patients.

Twelve patients with acute Q fever also demonstrated low titer of antibodies directed against phase I antigens in their sera. None of them developed chronic Q fever and all of them recovered uneventfully. Such a serologic response was previously reported by Worswick and Marmion [23]. Antibodies against phase I antigens during acute Q fever are targeted against a different

repertoire of antigens compared to the antibodies in patients with chronic Q fever and they slowly disappear with therapy [24]. Fifteen percent of our patients had a heart murmur. It is advised to search for a valve disorder in such patients, since the risk to develop Q fever endocarditis is high in this subgroup of patients with acute Q fever. A recent report emphasized the risk of developing chronic Q fever in patients with valvular heart disease and recommends that those patients be treated with a combination therapy of doxycycline 200 mg/day with hydroxychloroquine 600 mg/day for 1 year [25].

Conclusion

Acute Q fever among Israeli hospitalized patients has a characteristic clinical picture that includes an acute febrile disease with few physical findings, normal or "viral" blood count with many band forms, accelerated ESR, mild elevation of liver enzymes, and abnormal urinalysis without impaired renal function. The prognosis of acute Q fever in our hospitalized patients was excellent. Despite a protracted course in a small number of patients, all recovered with or without antibiotic treatment.

References

1. Maurin M, Raoult D. Q fever. *Clin Microbiol Rev* 1999;12:518-53.
2. Raoult D, Tissot-Dupont H, Foucault C, et al. Q fever 1985-1998. Clinical and epidemiologic features of 1,383 infections. *Medicine* 2000;79:109-23.
3. Luoto L, Casey ML, Pickens EG. Q fever studies in Montana. Detection of asymptomatic infection among residents of infected dairy premises. *Am J Epidemiol* 1965;681:356-69.
4. Bernit E, Pouget J, Janbon F, et al. Neurological involvement in acute Q fever: a report of 29 cases and review of the literature. *Arch Intern Med* 2002;162:693-700.
5. Rolain JM, Lepidi H, Harle JR, et al. Acute acalculous cholecystitis associated with Q fever: report of seven cases and review of the literature. *Eur J Clin Microbiol Infect Dis* 2003;22:222-7.
6. Raoult D, Fenollar F, Stein A. Q fever during pregnancy: diagnosis, treatment, and follow-up. *Arch Intern Med* 2002;162:701-4.
7. Fenollar F, Fournier PE, Carrieri MP, Habib G, Messana T, Raoult D. Risks factors and prevention of Q fever endocarditis. *Clin Infect Dis* 2001;33:312-16.
8. Tissot-Dupont H, Raoult D, Brouqui P, et al. Epidemiologic features and clinical presentation of acute Q fever in hospitalized patients: 323 French cases. *Am J Med* 1992;93:427-34.
9. Klopstock A, Klopstock E, Rosencranz G. The first diagnosed outbreak of Q fever in Israel. *Harefuah* 1949;6:89 (Hebrew).
10. Gross EM, Goldwasser RA, Bearman JE, et al. Rickettsial antibody prevalence in southern Israel: antibodies to *Coxiella burnetii*, *Rickettsia typhi* and Spotted Fever group; Rickettsiae among urban and rural-dwelling Bedouin women. *Am J Trop Med Hyg* 1983;32:1387.
11. Yarrow A, Slater PE, Costin C. Q fever in Israel. *Public Health Rev* 1990/91;18:129-37.
12. Siegman-Igra Y, Kaufman O, Keysary A, Rzotkiewicz S, Shalit I. Q fever endocarditis in Israel and a worldwide review. *Scand J Infect Dis* 1997;29:41-9.
13. Lieberman D, Lieberman D, Boldur I, et al. Q-fever pneumonia in the Negev region of Israel: a review of 20 patients hospitalized over a period of one year. *J Infect* 1995;30:135-40.
14. Domingo P, Munoz C, Franquet T, Gurgui M, Sancho F, Vazquez G. Acute Q fever in adult patients: report on 63 sporadic cases in an urban area. *Clin Infect Dis* 1999;29:874-9.

15. Maltezou HC, Raoult D. Q fever in children. *Lancet Infect Dis* 2002;2:686–91.
16. Alarcon A, Villanueva JL, Viciano P, et al. Q fever: epidemiology, clinical features and prognosis. A study from 1983 to 1999 in the South of Spain. *J Infect* 2003;47:110–16.
17. Gikas A, Kofteridis D, Bouros D, Voloudaki A, Tselentis Y, Tsaparas N. Q fever pneumonia: appearance on chest radiographs. *Radiology* 1999;210:339–43.
18. Caron F, Meurice JC, Ingrand P, et al. Acute Q fever pneumonia: a review of 80 hospitalized patients. *Chest* 1998;114:808–13.
19. Ruiz-Contreras J, Gonzalez Montero R, Ramos Amador JT, Giancaspro Corradi E, Scarpellini Vera A. Q fever in children. *Am J Dis Child* 1993;147:300–2.
20. Korman TM, Spelman DW, Perry GJ, Dowling JP. Acute glomerulonephritis associated with acute Q fever: case report and review of the renal complications of *Coxiella burnetii* infection. *Clin Infect Dis* 1998;26:359–64.
21. Gikas A, Kofteridis DP, Manios A, Padiaditis J, Tselentis Y. Newer macrolides as empiric treatment for acute Q fever infection. *Antimicrob Agents Chemother* 2001;45:3644–6.
22. Sobradillo V, Zalacain R, Capelastegui A, Uresandi F, Corral J. Antibiotic treatment in pneumonia due to Q fever. *Thorax* 1992;47:276–8.
23. Worswick D, Marmion BP. Antibody responses in acute and chronic Q fever and in subjects vaccinated against Q fever. *J Med Microbiol* 1985;19:281–96.
24. Blondeau JM, Williams JC, Marrie TJ. The immune response to phase I and phase II *Coxiella burnetii* antigens as measured by western immunoblotting. *Ann N Y Acad Sci* 1990;590:187–202.
25. From the Centers for Disease Control and Prevention. Q fever – California, Georgia, Pennsylvania, and Tennessee, 2000–2001. *JAMA* 2002;288:2398–400.

Correspondence: Dr. Z.M Stoeher, Dept. of Medicine B, Kaplan Medical Center, P.O. Box 1, Rehovot 76100, Israel.

Phone: (972-8) 944-1357

Fax: (972-8) 944-1826

email: stoeher@012.net.il; zev_s@clalit.org.il