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# Predominant Immunoglobulin A Response to Phase II Antigen of *Coxiella burnetii* in Acute Q Fever

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**Diagnosis of acute Q fever is usually confirmed by serology, on the basis of anti-phase II antigen immunoglobulin M (IgM) titers of ≥1:50 and IgG titers of ≥1:200. Phase I antibodies, especially IgG and IgA, are predominant in chronic forms of the disease. However, between January 1982 and June 1998, we observed anti-phase II antigen IgA titers of ≥1:200 as the sole or main antibody response in 10 of 1,034 (0.96%) patients with acute Q fever for whom information was available. In order to determine whether specific epidemiological or clinical factors were associated with these serological profiles, we conducted a retrospective case-control study that included completion of a standardized questionnaire, which was given to 40 matched controls who also suffered from acute Q fever. The mean age of patients with elevated phase II IgA titers was significantly higher than that usually observed for patients with acute Q fever ($P = 0.026$); the patients were also more likely than controls to live in rural areas ($P = 0.026$) and to have increased levels of transaminase in blood ($P = 0.03$). Elevated IgA titers are usually associated with chronic Q fever and are directed mainly at phase I antigens. Although the significance of our findings is unexplained, we herein emphasize the fact that IgA antibodies are not specific for chronic forms of Q fever and that they may occasionally be observed in patients with acute disease. Moreover, as such antibody profiles may not be determined by most laboratories, which test only for total antibody titers to phase I and II antigens, the three isotype-specific Ig titers should be determined as the first step in diagnosing Q fever.**

Q fever is an infectious disease of worldwide significance caused by the obligate intracellular bacterium *Coxiella burnetii*. Clinically, the disease is polymorphic and nonspecific, and patients may present with an acute or chronic form. The most common clinical syndromes of acute Q fever are a self-limited, flu-like syndrome of unknown origin, granulomatous hepatitis, pneumonia, and meningoencephalitis (10), whereas the most common clinical syndromes of chronic Q fever are endocarditis, infection of an aneurysm or vascular graft, chronic hepatitis, or osteoarthritis (1). Therefore, in most instances the diagnosis of Q fever relies on serology.

Although several methods have been described, the most reliable and commonly used is the indirect immunofluorescence assay (IFA) (11). *C. burnetii* demonstrates a particular characteristic: a phase variation, due to a partial loss of lipopolysaccharide, responsible for an antigenic shift. In acute Q fever, antibodies to phase II antigens predominate and their titer is higher than the phase I antibody titer. As with many other infectious diseases, IgM antibodies are usually the first to appear. In the absence of early antibiotic therapy, phase II antigen-specific IgM appears in the circulation between 7 and 15 days after the onset of clinical symptoms and reaches its maximum titer in 4 to 8 weeks. These antibodies remain detectable by IFA for relatively short periods, which vary with the infection and the individual host (3, 5). Titers usually decrease gradually over the 12 months subsequent to infection. Phase II IgG appears somewhat later but can persist for years, even for life. As cutoff values in the IFA, we recommend titers of phase II IgG of ≥1:200 and titers of phase II IgM of ≥1:50 for the diagnosis of acute Q fever (11). However, in chronic forms of the disease, such as endocarditis, elevated levels of phase I antibodies are detected. In such cases, cutoff values of ≥1:800 for phase I IgG are diagnostic of chronic Q fever. The presence of IgA to phase I antigen is strongly correlated with chronic Q fever, especially endocarditis (6, 7, 12), and thus, IgA has long been considered diagnostic of chronic forms of Q fever (6). However, we have recently demonstrated that anti-phase I antigen IgA titers do not contribute to the diagnosis of chronic Q fever (11) but are useful for the follow-up of treated patients (8).

As the French Reference Center for the Diagnosis and Study of Rickettsioses, we receive sera, mainly from France but also from other countries, to be tested for *C. burnetii* infection and collect, when available, clinical and epidemiological data for each case. From January 1982 to June 1998, we collected such information for 1,034 patients presenting with serologically confirmed acute Q fever (unpublished data).

In this report, we describe the 10 patients in this series who had anti-phase II antigen IgA titers either greater than or equal to 1:200 or greater than both anti-phase II antigen IgG and IgM titers in acute-phase sera. In order to determine the factors possibly related to these serological profiles, we compared the epidemiological and clinical features of these 10 patients and those of 40 randomly chosen controls matched for sex, age, time, and geographic origin.

## MATERIALS AND METHODS

**Study design. (i) Case definition. (a) Serology.** In IFA, patients were considered to have acute Q fever when they had a suggestive clinical background and when their acute-phase anti-phase II antigen IgM titer was ≥1:50 (with or without an IgG titer of ≥1:200) and/or when specific antibody titers in two successive serum samples increased fourfold relative to phase I titers. For each patient, we considered the antibody titers of the acute-phase serum, sampled during the month following the onset of symptoms, and, when available, those of the second serum sample. When convalescence-phase serum was available, both

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acute- and convalescence-phase samples were tested simultaneously to prove seroconversion or increasing titers.

**(b) Clinical symptoms.** Fever of unknown origin was defined as a body temperature greater than or equal to 38°C lasting for more than 2 days in a patient with negative blood cultures. Dyspnea, coughing, expectoration, hemoptysis, or chest pain was defined as a pulmonary symptom. Chest radiographic abnormalities were used to confirm pulmonary involvement. Pneumonia was defined as fever with radiologically confirmed pulmonary signs. The presence of a lumbar puncture for cerebrospinal fluid examination was considered indicative of meningitis or encephalitis. Hepatitis was defined as fever with elevated levels of liver transaminase enzymes 1.5 times above normal levels (levels of aspartate transaminase greater than or equal to 38 IU/liter and levels of alanine transaminase greater than or equal to 44 IU/liter). Cutaneous symptoms were defined as maculopapular or purpuric eruptions. Myocarditis was defined as electrocardiographic abnormalities, and pericarditis was defined as the presence of pericardial fluid on an echocardiogram.

**(ii) Cases.** Between January 1982 and June 1998, among the 92,000 patients tested by our laboratory, we confirmed serologically the diagnosis of acute Q fever for 1,252 patients and collected epidemiological and clinical information for 1,034 of them by means of a standardized questionnaire. Of these, 10 had an acute-phase anti-phase II antigen IgA titer of ≥200, with IgA being the only antibody directed at *C. burnetii*, or an anti-phase II antigen IgA titer higher than those of IgG and IgM in both phases.

For each patient, we selected randomly from our study group four controls suffering from acute Q fever, matched according to age (±5 years), sex, year of diagnosis, and geographic origin. We then compared their epidemiological and clinical features, mean antibody titers, and mean delays between the onset of symptoms and the taking of the first and second serum samples to those of our 10 patients.

The variables which were impossible to compare between patients and controls, such as age and sex ratios, were compared to the variables of the 1,034 patients included in our acute Q fever series.

**(iii) Questionnaire.** A standardized questionnaire was completed for each patient and control. Information obtained included administrative data such as age, sex, zip code, hospital ward, and date of admission; epidemiological data such as profession (farmer, veterinarian, slaughterhouse worker, or other), way of life (rural or urban), risk factors (contact with farm animals [especially newborns] or hides, ingestion of raw milk or farm goat cheese during the month preceding the onset of symptoms, immunodeficiency); clinical data such as the date of onset of symptoms, fever higher than 38.5°C, headache, myalgias, arthralgias, pulmonary signs (dyspnea, coughing, expectoration, hemoptysis, chest pain, auscultation, chest radiographic abnormalities), cutaneous signs (maculopapular or purpuric eruption), neurological signs (lumbar puncture), and cardiac signs (palpitations, electrocardiographic or echocardiographic abnormalities); biological signs (thrombocytopenia, with levels of platelets at less than 150 g/liter; levels of aspartate transaminase greater than or equal to 38 IU/liter; levels of alanine transaminase greater than or equal to 44 IU/liter); the administration of antibiotic therapy; and outcome.

**(iv) Statistical analysis.** Patients were compared with 40 matched controls. Fisher's exact test was used to compare proportions, and Student's *t* test was used to compare means. A difference was considered to be significant when $P$ was $<0.05$. For dichotomous variables, univariate matched odds ratios with 95% confidence intervals were calculated by the Mantel-Haenszel method with Epi Info (2).

**Microbiological methods. (i) Antigen preparation.** Phase II Nine Mile strain (ATCC VR 615) was grown in confluent layers of L929 mouse fibroblasts in 150-cm$^2$ culture flasks with minimum essential medium supplemented with 2 mM L-glutamine and 4% fetal bovine serum. Infection was monitored by microscopy of Gimenez dye-stained cells scraped from the bottoms of the flasks (4). When a heavy intracellular infection was observed, the supernatants of 15 flasks were individually pelleted by centrifugation (5,000 × *g*, 15 min) and resuspended in 1 ml of phosphate-buffered saline, pH 7.3 (PBS), with 0.1% formaldehyde. All further steps were conducted under cooling conditions. After being pooled, the remaining cells were broken by sonication. Cellular debris was removed by two successive centrifugations (100 × *g*, 10 min each). The 15-ml suspension was then centrifuged through 20 ml of PBS with 25% sucrose (6,000 × *g*, 30 min, without a break). The resulting pellet was washed three times in PBS (6,000 × *g*, 10 min), resuspended in the smallest possible volume of sterile distilled water, and adjusted to 2 mg/ml by UV spectroscopy. Antigen prepared in this manner was frozen at −20°C for further immunofluorescence tests.

**(ii) Reactivation of phase I antigens.** In order to reactivate phase I antigens, mice were inoculated with phase II *C. burnetii* Nine Mile strain. Ten days after infection, each spleen was removed, ground in 7.5 ml of minimum essential medium, and inoculated into three 75-cm$^2$ culture flasks containing L929 cell monolayers (2.5 ml per flask). The infected cells were then harvested, and the bacteria were purified by the technique described above. All manipulations of live *C. burnetii* were conducted in a biohazard safety laboratory (P3).

**(iii) Microfluorescence.** The two antigens, prepared as described above, were applied with a pen nib at the two poles of each well of 30-well microscope slides (Dynatech Laboratories Ltd., Billingshurst, United Kingdom), air dried, and fixed in acetone for 10 min. Sera were serially diluted (twofold dilutions initially ranging from 1:25 to 1:1,600 and more if needed) in PBS with 3% nonfat powdered milk. The overlaid antigens were incubated in a moist chamber for 30 min at 37°C and then washed three times with PBS for 10 min each time. After air drying, the antibody-antigen complex was overlaid with fluorescein isothiocyanate-conjugated goat anti-human IgG (γ) (Fluoline G; BioMérieux, Marcy l'Etoile, France), anti-human IgM (Fluoline M; BioMérieux), or anti-human IgA (Fluoline A; BioMérieux), diluted 1:300. Incubation, washes, and drying were performed again as described above. The slides were mounted in buffered glycerol (Fluoprep; BioMérieux) and read with a Zeiss fluorescence microscope at a ×400 magnification. In order to remove IgG, rheumatoid factor adsorbant (Boehringer, Mannheim, Germany) was used prior to determination of IgM and IgA titers.

## RESULTS

**Serology.** Two consecutive serum samples were available from 8 of the 10 patients and from 29 of the 40 controls. The remaining 2 patients and 11 controls had only an acute-phase sample tested, which permitted the diagnosis of acute Q fever. Among the patients, a group of two individuals had elevated anti-phase II antigen IgA titers in their first serum sample as the only serological hallmark of acute Q fever. Both of these patients, for both of whom a convalescent-phase sample was available, presented with sera indicating seroconversion in phase II IgG and IgM, confirming the diagnosis. In the second group, comprised of the remaining eight patients, anti-phase II antigen IgM and/or IgG titers were diagnostic of acute Q fever in the first serum sample but the IgA titer was ≥1:200 and greater than that of the other antibody classes. In every case, antibody titers to phase I antigen were lower than those to phase II antigen. Titers of antibodies to phase II *C. burnetii* antigen of both patients and controls are presented in Table 1.

Among the controls, the diagnosis of acute Q fever was confirmed in 37 cases with the first serum sample and in the remaining 3 cases with the convalescent-phase sample. An anti-phase II antigen IgA titer of ≥1:200 was found for 1 control, and titers of <1:200 were found for 12 controls. In all cases, the IgA titer was lower than the phase II IgG titer. Titers of anti-phase I antigen IgA of ≤1:100 were detected in the first serum samples of five controls. For every control patient, antibody titers to phase I antigen were lower than those to phase II antigen.

Mean IgA titers to phase II antigen were significantly higher for patients than for controls in both acute- and convalescence-phase sera ($P < 10^{-6}$ and $P = 0.0002$, respectively) (Table 2). Mean IgG titers to phase II and I antigens were significantly lower for patients than for controls in the acute-phase samples ($P = 0.0001$ and $P = 0.03$, respectively) but not in the convalescence-phase samples ($P = 0.797$ and $P = 0.851$, respectively). Although the mean IgM titer to phase II antigen in the acute-phase sera was not significantly lower for patients than for controls ($P = 0.081$), the mean titer to phase I antigen was ($P = 0.048$). However, no statistical difference was observed for the convalescence-phase samples ($P = 0.590$ and 0.326 for titers to phase II and I antigens, respectively). The mean delay between onset of symptoms and serum testing was significantly shorter for patients than for controls for the first samples ($P = 0.025$), but delays were similar in both groups for the second samples ($P = 0.346$) (Table 2).

**Patients.** Forty controls with acute Q fever were selected from our study to match our 10 patients by age, sex, year of diagnosis, and geographic origin. Thus, their mean age and sex ratios were similar, with the mean age of the 10 patients being 59.1 ± 13.4 years (range, 40 to 80 years) and with six (60%) of them being male and with the mean age of the controls being 58.4 ± 11.8 years (range, 38 to 80 years) ($P = 0.87$) and with 24 (60%) of them being male. Compared epidemiological and clinical features of patients and controls are presented in Table

TABLE 1. Acute- and convalescence-phase titers of antibodies to phase I and II *C. burnetii* antigens

| Patient | Titer in acute-phase serum of indicated antibody to: | | | | | | Titer in convalescence-phase serum of indicated antibody to: | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Phase II antigen | | | Phase I antigen | | | Phase II antigen | | | Phase I antigen | | |
| | IgG | IgM | IgA | IgG | IgM | IgA | IgG | IgM | IgA | IgG | IgM | IgA |
| 1 | 1:50 | 1:25 | 1:200 | 0 | 0 | 0 | 1:200 | 1:50 | 1:200 | 0 | 0 | 0 |
| 2 | 1:100 | 1:200 | 1:3,200 | 0 | 1:25 | 0 | 1:800 | 1:200 | 1:200 | 1:200 | 1:50 | 0 |
| 3 | 0 | 1:50 | 1:800 | 0 | 0 | 1:50 | NA | NA | NA | NA | NA | NA |
| 4 | 0 | 1:100 | 1:200 | 0 | 0 | 0 | 1:3,200 | 1:800 | 1:100 | 0 | 1:800 | 0 |
| 5 | 0 | 0 | 1:800 | 0 | 0 | 1:50 | 1:800 | 1:200 | 1:800 | 1:200 | 1:50 | 1:50 |
| 6 | 0 | 1:200 | 1:800 | 0 | 1:25 | 1:50 | 1:400 | 1:400 | 1:400 | 0 | 1:25 | 0 |
| 7 | 0 | 1:50 | 1:400 | 0 | 0 | 1:100 | 1:1,600 | 1:200 | 1:200 | 1:200 | 1:100 | 1:50 |
| 8 | 0 | 0 | 1:400 | 0 | 0 | 1:100 | 1:800 | 1:800 | 1:50 | 1:400 | 1:800 | 0 |
| 9 | 1:50 | 1:200 | 1:1,600 | 0 | 0 | 1:800 | NA | NA | NA | NA | NA | NA |
| 10 | 0 | 1:25 | 1:200 | 0 | 0 | 1:25 | 1:400 | 1:25 | 1:200 | 1:200 | 0 | 1:25 |

[a] Data are for 10 patients and 40 controls with acute Q fever and elevated IgA titers. Acute-phase serum samples were obtained between 5 and 15 days following the onset of symptoms, whereas convalescence-phase serum samples were obtained between the 18 and 91 days following the onset of symptoms. NA, not available.

2. Eight (80%) patients lived in rural areas; five of them were farmers and had had some contact with newborn mammals and/or hides during the month preceding the onset of symptoms, and four of them had eaten cheese made from raw milk during the same period. Although the remaining two patients lived in urban areas, one worked as a veterinarian and had had some contact with newborn farm mammals. None of the patients was immunocompromised. Regarding clinical presenta-

TABLE 2. Epidemiological and clinical features of 10 patients with acute Q fever and predominant IgA titers and of 40 controls with acute Q fever and usual serological antibody profiles

| Variable | Value for patients | Value for controls | *P* value |
|---|---|---|---|
| No. of cases | 10 | 40 | |
| Incidence of: | | | |
| Subjects living in rural housing (%) | 80.0 | 40.0 | 0.026 |
| Subjects living in urban housing (%) | 20.0 | 60.0 | 0.026 |
| Contact with farm newborn mammals and/or hides during the month preceding the onset of symptoms (%)[a] | 60.0 | 45.0 | 0.30 |
| Consumption of raw cheese during the month preceding the onset of symptoms (%) | 40.0 | 17.5 | 0.15 |
| Immunodeficiency (%) | 0 | 2.5 | 0.40 |
| Fever (%) | 100 | 97.5 | 0.79 |
| Headache (%) | 50.0 | 37.5 | 0.34 |
| Myalgias and/or arthralgias (%) | 50.0 | 35.0 | 0.50 |
| Clinical signs of pneumonia (%) | 40.0 | 37.5 | 0.57 |
| Chest radiographic abnormalities evocative of interstitial pneumonia (%) | 30.0 | 45.0 | 0.32 |
| Maculopapular eruption (%) | 10.0 | 5.0 | 0.51 |
| Purpuric eruption (%) | 10.0 | 0 | 0.21 |
| Neurological symptoms (%) | 10.0 | 0 | 0.21 |
| Cardiac symptoms (%) | 0 | 5.0[b] | 0.62 |
| Thrombocytopenia (<150,000 platelets/mm$^3$) (%) | 60.0 | 37.5 | 0.17 |
| Aspartate transaminase level ≥38 IU/liter, alanine transaminase level 44 IU/liter (%) | 100 | 65.0 | 0.03 |
| Mean delay between onset of symptoms and first serum sample (days) ± SD | 11.1 ± 4.8 | 15.5 ± 5.5 | 0.025 |
| Mean acute-phase IgG titer to phase II antigen | 1:21 | 1:128 | 0.0001 |
| Mean acute-phase IgM titer to phase II antigen | 1:46 | 1:103 | 0.081 |
| Mean acute-phase IgA titer to phase II antigen | 1:565 | 1:20 | $<10^{-6}$ |
| Mean acute-phase IgG titer to phase I antigen | 0 | 1:658 | 0.03 |
| Mean acute-phase IgM titer to phase I antigen | 1:14 | 1:149 | 0.048 |
| Mean acute-phase IgA titer to phase I antigen | 1:46 | 1:24 | 0.126 |
| Mean delay between onset of symptoms and second serum sample (days) ± SD | 34.6 ± 10.7 | 41.2 ± 18.6 | 0.34 |
| Mean convalescence-phase IgG titer to phase II antigen | 1:731 | 1:28 | 0.79 |
| Mean convalescence-phase IgM titer to phase II antigen | 1:200 | 1:35 | 0.59 |
| Mean convalescence-phase IgA titer to phase II antigen | 1:200 | 1:14 | 0.0002 |
| Mean convalescence-phase IgG titer to phase I antigen | 1:77 | 1:86 | 0.85 |
| Mean convalescence-phase IgM titer to phase I antigen | 1:70 | 1:42 | 0.32 |
| Mean convalescence-phase IgA titer to phase I antigen | 1:19 | 1:39 | 0.45 |
| Outcome (%) | | | |
| Recovery | 100 | 97.5 | 0.29 |
| Chronic Q fever | 0 | 0 | NA[c] |
| Death | 0 | 2.5 | 0.79 |
| Sequellae | 0 | 0 | NA |

[a] Five patients were farmers, and one was a veterinarian who worked frequently with farm mammals such as cattle, sheep, and goats.
[b] One control suffered from acute pericarditis, and one suffered from myocarditis.
[c] NA, not available.

tion, pulmonary symptoms of four patients (40%) were evocative of interstitial pneumonia and one (10%) underwent a lumbar puncture because of obnubilation.

Blood results revealed that all patients had elevated levels of liver enzymes and that six (60%) had thrombocytopenia.

When compared to the patients in our study of 1,034 cases of acute Q fever, our 10 patients were significantly older (59.1 ± 13.4 years for the patients in this study versus 46.5 ± 17.7 years for the patients in the acute Q fever study [$P = 0.026$]).

## DISCUSSION

Diagnosis of Q fever usually relies on serology by the IFA reference technique (11). Since 1982, our laboratory has been involved in the diagnosis of rickettsioses and Q fever. During this time, we have confirmed serologically the diagnoses of acute Q fever for 1,252 patients and collected epidemiological and clinical data for 1,034 of them. Among these, we have observed unusually elevated anti-phase II antigen IgA titers in 10 patients, representing 0.96% of the patients in our study. IgA has long been considered to be specific for chronic Q fever. Peacock et al. (6) have not found diagnostic titers of IgA in sera from patients with acute Q fever. However, in a previous work, we observed that IgA to phase II antigen was detectable between weeks 2 and 3 after the onset of acute Q fever but that its titers remained below 50 and lower than titers to other anti-*C. burnetii* antibodies (11). In the same study, we demonstrated that the determination of IgA titers to phase I antigens did not contribute to the diagnosis of chronic Q fever (11) but was useful for the follow-up of patients who had been treated for chronic Q fever (8). To our knowledge, patients with acute Q fever and their predominant titers of IgA to phase II antigen have never been reported in the literature.

In the present study, we observed that the 10 patients presented with a mean titer of IgA to phase II antigen significantly higher than that of controls (Table 2). We also observed that the mean titers of IgG to phase II and I antigens in acute-phase sera of patients were significantly lower than for controls. Although IgM titers in the phase I sera of patients and controls were only significantly different, IgM titers in their phase II sera were lower for patients. We demonstrated previously that phase II IgM usually reaches the diagnostic level (titer = 50) between weeks 2 and 3 and that IgG titers are over 200 after 4 weeks (11). In order to determine whether the delay between the onset of symptoms and the collection of serum samples plays a role in serological profiles, we compared the mean delays between the onset of symptoms and the collection of the first samples for patients and controls. We believe that the shorter delay between the onset of symptoms and the first serum sample for patients (Table 2) may explain the difference in IgG and IgM titers between patients and controls. Indeed, the IgG and IgM titers determined for the convalescence-phase sera, sampled after similar delays for patients and controls, were comparable in both groups (Table 2). However, this difference in the delay of sampling cannot be responsible for the observed difference in IgA titers since a statistically supported difference in IgA titers between patients and controls was observed with both acute- and convalescence-phase samples. Therefore, we are confident that the observed difference in IgA titers was not due to a sampling bias. We also tried to identify other biases which might have been responsible for the observed serological results. Among the several factors which can give an inaccurate determination of antibody titers, two are of particular concern with *C. burnetii*, a deficiency in the purification of antigens used for IFA and the presence of a rheumatoid factor (6, 9). Indeed, both factors may be responsible for discrepancies such as false-positive anti-*C. burnetii* antibody titers. In our laboratory, in order to avoid these false-positive results, we use highly purified antigens and a rheumatoid factor adsorbant before determining IgM and IgA titers. Moreover, the same technique was used to determine levels of antibodies in all serum samples. We are therefore confident that the IgA titers obtained in these cases were not false-positive results and that the reliability of IFA for the diagnosis of acute Q fever is very high.

Among the environmental exposure factors usually associated with acute Q fever, the only one specifically associated with our 10 patients was a rural way of life. Moreover, no specific clinical feature was observed in our patients, except the older mean age of patients in this study compared to that of the patients in our acute Q fever study and hepatic involvement. Since the distribution of clinical syndromes exhibited by the controls was similar to that of our series of 1,034 patients with acute Q fever, we are confident that the observed difference was not due to a recruitment bias. We observed previously that hepatic involvement is the major clinical feature of acute Q fever in France and that it occurs more frequently in sheep- and goat-breeding areas and in persons eating farm-made cheese, with the incidence of liver dysfunction usually being minimal (10). This was also the case in the present study, with 100% of patients and 65% of controls presenting with liver involvement and with a rural lifestyle being statistically more frequent among the patients. All 10 patients and 36 controls received antibiotics. All patients and 39 controls recovered without any sequellae. One control developed acute respiratory distress and died despite the fact that appropriate therapy was given.

It is of importance that 2 of the 10 patients had elevated anti-phase II antigen IgA titers as the only serological hallmark of acute Q fever in their acute-phase serum samples. Both would probably have remained undiagnosed without our systematic testing for IgG, IgM, and IgA as the first step in diagnosing acute Q fever. Therefore, we believe that IgA testing should be included in the serological screening of patients with Q fever.

Although it has often been reported, Q fever remains a disease of which new aspects need to be described. Indeed, many chronic cases, such as endocarditis or infections of aneurysms or vascular grafts, remain undiagnosed, sometimes for years, and manifestations of acute Q fever are so polymorphic that its prevalence is probably underestimated. We therefore believe that although acute Q fever is usually diagnosed on the basis of the presence of IgM and/or IgG to phase II *C. burnetii* antigens and that IgA is occasionally (approximately 1% of cases) considered specific for chronic forms of the disease, acute Q fever may also be diagnosed on the basis of unusual antibody profiles characterized by elevated IgA titers and low IgG and IgM titers, particularly among older patients living in rural areas and presenting with hepatitis.

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