# AN UNUSUAL CASE OF Q FEVER

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**Abstract**

A previously-well, 44-year-old Australian-born male presented to a Melbourne metropolitan hospital with a systemic inflammatory process comprising respiratory and hepatic dysfunction. He was managed initially for presumed acute cholecystitis, with minimal effect. Improvement was seen only after empiric treatment for a zoonotic infection. Diagnosis of acute Q fever was confirmed serologically. This case illustrates a rarely-seen combination of Q fever pneumonia and cholecystitis. A review follows this case report, highlighting the dearth of contemporary literature that categorises the clinical spectrum of disease seen in the Australian population.

**Keywords:** Q fever, *Coxiella burnetii*, pneumonia, acalculous cholecystitis, zoonosis

## Introduction

*Coxiella burnetii* is the causative organism for Q fever, a zoonotic infection present in the majority of populated regions of the world.[1] The reservoir for this organism includes livestock, wildlife, birds, and reptiles. Humans are incidental hosts, acquiring the pathogen primarily through inhalation of infected aerosols from livestock. It is hence unsurprising those at highest risk of contracting Q fever have some form of ongoing exposure to infected livestock or their products.[2] This report details a middle-aged man, with minimal work-related risk factors, who likely acquired Q fever infection from a brief camping trip to rural Victoria.

## Case report

A 44-year-old male first presented to his general practitioner (day 0) with a three-day history of malaise, fevers, rigors, nausea, vomiting, and generalised myalgia. Notably, he was afebrile but had abdominal discomfort. An abdominal ultrasound was performed and was unremarkable. No specific intervention was implemented at that stage. The next day (day 1), he presented to the emergency department. His core temperature measured 37.7 °C, and he had abdominal tenderness on examination. His full blood count (FBC) was normal other than lymphopenia of 0.5 x $10^9$/L (normal range: 1-3 x $10^9$/L). Liver function tests were mildly deranged, with alanine aminotransferase (ALT) of 52 IU/L (normal range: 5-40 IU/L), and gamma-glutamyl transferase (GGT) of 76 IU/L (normal range: 10-71 IU/L). His alkaline phosphatase (ALP) was normal at 81 IU/L (normal range: 30-120 IU/L ). Abdominal X-ray showed non-specific prominent small bowel loops. As his abdominal discomfort was out of proportion to his X-ray findings, a computed tomography (CT) scan of his abdomen was done, which revealed faecal loading but was otherwise normal. He was managed with aperients, anti-emetics, and intravenous fluids. After spending 8 hours in the emergency department, he was discharged with the diagnosis of constipation and an unspecified viral illness.

At home, he continued to deteriorate over the following 72 hours, and was unable to go to work. He re-presented to the emergency department for the second time (day 4), with similar symptoms of fever, uncontrolled rigors, nausea, vomiting, and generalised pain, most prominent in his abdomen. A productive cough had begun to develop. On examination, he appeared clinically unwell, tachycardic, and was febrile (38.3 °C) with generalised abdominal tenderness. His cardiovascular and respiratory examinations were unremarkable. On investigation, liver function tests were more deranged than previously noted. He had a marked elevation of his bilirubin: a conjugated hyperbilirubinaemia, up to 3 times the upper limit of normal at 66 µm/L. GGT was 415 IU/L, ALP was 277 IU/L, and ALT was 188 IU/L. FBC showed a white cell count (WCC) of 4.5 x$10^9$/L, a neutrophil count of 2.9 x$10^9$/L, and a low platelet count of 65 x$10^9$/L. His lymphopenia persisted. C-reactive protein (CRP) was 281 mg/L (Table 1).

**Table 1.** Selected laboratory results

| Investigation* (normal range) | 29/1/2014 (day 0) | 1/2/2014 (day 4) | 3/2/2014 (day 6) | 5/2/2014 (day 8) | 7/2/2014 (day 10) |
|---|---|---|---|---|---|
| WCC (4-10) x$10^9$/L | 5.4 | 4.5 | 5.6 | 10.5 | 13.5 |
| Neutrophils (2-7) x$10^9$/L | 4.7 | 2.9 | 4.4 | 5.8 | 8.9 |
| Lymphocytes (1-3) x$10^9$/L | 0.5 | 0.5 | 0.6 | 4.0 | 3.8 |
| CRP (<5) mg/L | - | 281 | 289 | 191 | 84 |
| Platelets (150-410) x$10^9$/L | 155 | 65 | 51 | 51 | 86 |
| Bilirubin (<22) µm/L | 7 | 66 | 96 | 197 | 337 |
| ALT (5-40) IU/L | 52 | 188 | 203 | 157 | 155 |
| GGT (10-71) IU/L | 76 | 415 | 388 | 438 | 773 |
| ALP (30-120) IU/L | 81 | 277 | 258 | 305 | 547 |

*WCC: white cell count, CRP: C-reactive protein, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase, ALP: alkaline phosphatase

A chest X-ray was normal. A liver ultrasound elicited tenderness in the right upper quadrant on ultrasound device probing, and showed a thickened gallbladder wall of 6 mm (normal ≤4 mm), but no choledolithiasis. The common bile duct was not dilated. The working diagnosis at that time was that of acalculous cholecystitis. Intravenous (IV) ampicillin, ceftriaxone, and metronidazole were commenced and a laparoscopic cholecystectomy was performed the following day (day 5), due to concerns of an evolving necrotising cholecystitis. The surgically-removed gallbladder appeared oedematous with grossly normal surrounding hepatic architecture. An intraoperative cholangiogram did not reveal a biliary tree filling defect. Gallbladder histopathology subsequently reported changes of chronic cholecystitis.

Further history revealed that fourteen days prior to onset of clinical symptoms, the patient took a brief three-day camping trip with his family to Woodside Beach, a coastal town in the Gippsland region of rural southeastern Victoria, Australia. He denied any water activities. The rest of his family remained well during and after his illness. The patient was an industrial air-conditioner technician by profession, working at numerous sites around metropolitan Melbourne. This included a research facility known to house livestock, including sheep. His last exposure there was 10 days prior to first onset of clinical symptoms (day -13). His work there involved, as usual, entrance into the air ventilation systems. His past medical history was unremarkable. He drank minimal alcohol and occasionally smoked marijuana. He lived with his family, comprising his spouse and two young children aged 5 and 7, in a standard housing property. He did not own pets, and aside from his recent travel to rural Victoria, reported no other travel.

Despite removal of his gallbladder (day 5), the patient deteriorated clinically and biochemically. Over the next four days, he became progressively more dyspnoeic and hypoxic with type 1 respiratory failure, necessitating supplemental high-flow oxygen to maintain adequate oxygenation. On chest X-ray imaging, airspaces initially clear on re-presentation (day 4) now showed progression with multilobular consolidation, in particular over the lower lung zones bilaterally (Fig. 1).

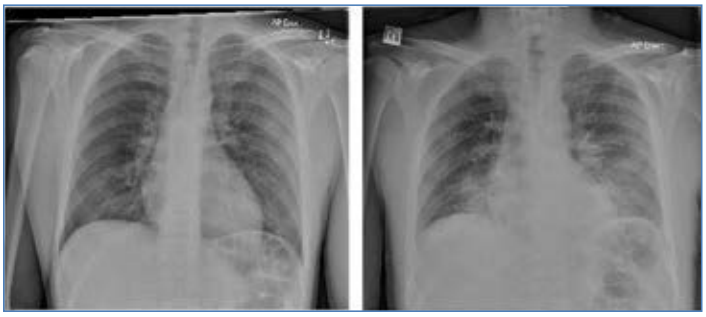

**Figure 1.** Interval chest X-ray change from day 4 (L) to day 8 (R)

Daily spiking fevers above 38.5 °C were noted. In all, his fevers persisted for almost two weeks (days 0 to 12). Liver function tests continued to worsen, with a predominantly cholestatic picture. A more than four-fold rise in his ALT and ALP, and a ten-fold rise in his GGT were observed (Table 1). Ongoing sepsis, atypical pneumonia, ascending cholangitis, pulmonary emboli, and antibiotic-related acute hepatitis were all considered. IV piperacillin/tazobactam was commenced to replace ceftriaxone, ampicillin, and metronidazole. CT pulmonary angiogram did not reveal pulmonary emboli and magnetic resonance cholangiopancreatography (MRCP) showed no biliary tree abnormalities to account for a diagnosis of ascending cholangitis. Four sets of blood cultures were taken; all had no growth after 5 days of incubation. Hepatitis A, B, and C, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) serologies were all negative. His CRP level improved following his cholecystectomy but in all other ways, he appeared to be worsening.

On day 10, the Infectious Diseases Unit was first consulted. Azithromycin was commenced for possible atypical pneumonia, in particular to cover for *Legionella pneumophila*. Because of concerns of a drug reaction, antibiotics were changed from piperacillin/tazobactam to meropenem. The history of recent rural and occupational exposure led to concerns of a systemic zoonotic infective process, including Q fever, rickettsial disease, and leptospirosis, hence doxycycline was added. Serological tests for rickettsial subspecies, *Coxiella burnetii*, leptospirosis, and atypical pneumonia agents were ordered.

The patient defervesced 48 hours (on day 12) after commencement of doxycycline and azithromycin and showed parallel improvement clinically and biochemically. His myalgias, rigors, and cough abated. Bilirubin and liver enzymes improved. On day 16, he had a bilirubin level of 72 µm/L, ALT of 106 IU/L, GGT of 429 IU/L, and ALP of 468 IU/L. Urinary *Legionella* serogroup 1 antigen, urinary *Streptococcus pneumoniae* antigen, sputum *Legionella* spp. and *Chlamydia pneumoniae* PCR were all negative. Transthoracic echocardiogram (TTE) was not consistent with infective endocarditis.

Initial serological testing by enzyme-linked immunosorbent assay (ELISA), taken at day 10 of hospital presentation showed positive Q fever phase 2 IgM and IgG. The following day, meropenem and azithromycin were ceased. Doxycyline 100 mg BD was continued on discharge. He completed a total of 14 days of doxycycline. A rise in phase 2 IgM titre was demonstrated on convalescence 14 days (day 24) after the initial assay, confirming the diagnosis of acute Q fever. On retrospective analysis, the immunofluorescence (IF) assay method during his acute illness revealed negative *Coxiella burnetii* phase 2 IgM and IgG results (day 10), with titres <25. On convalescent serology performed two weeks later (day 24), there was IFA seroconversion of both his phase 2 IgG, phase 2 IgM (titres >3 200), and phase 1 IgM (Fig. 2). Again, this was consistent with acute Q fever infection. Follow-up IFA at his 6-month outpatient clinic visit revealed a persistent rise in phase 1 IgG and IgA, titres 12 800 and 6 400 respectively. Despite normalisation of his LFTs and FBC, he reported ongoing lethargy. Three-monthly Q fever serology testing continued.

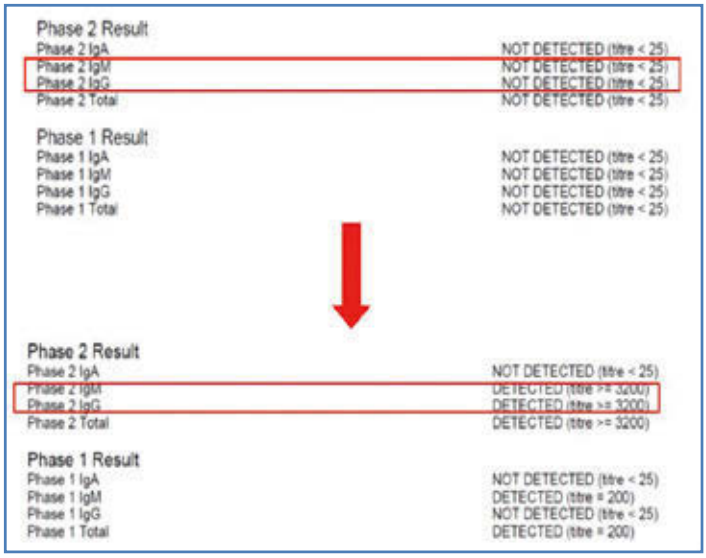


**Figure 2.** Q fever initial (top) and convalescent serology indicating seroconversion, by IFA test (with permission of Australian Rickettsial Reference Laboratory)

In light of his substantial abdominal discomfort, deranged liver enzymes, and abnormal abdominal ultrasound, Q fever acalculous cholecystitis was considered. Three paraffin block shavings of the gallbladder were were positive for *Coxiella burnetii* by polymerase chain reaction (PCR), which involved amplification of two separate coding regions of the *C. burnetii* genome (*com 1* and *htpAB* genes). We believe our case to be the second reported in the literature of positive *C. burnetii* PCR from the gallbladder.

## Discussion

Q fever remains a largely unrecognised disease unless the treating clinician has a high index of suspicion. This is in part due to the myriad number of clinical manifestations that can arise. Q fever was first described by Edward Derrick, an Australian pathologist, in 1937.[3] This followed a two-year period in which he investigated nine Queensland men with unspecified febrile illnesses, drawn together by the fact that they all worked in abattoirs. MacFarlane Burnet and Herald Cox independently isolated the causative organism, resulting in the name given to this pathogen – *Coxiella burnetii. C. burnetii* is a pleomorphic, obligate intracellular, small Gram-negative organism. Similar to other Gram-negative pathogens, it possesses an outer lipopolysaccharide cell membrane.[1] In its natural state it exists in two forms - large and small cell variants. The small cell variant, though having minimal metabolic activity, possesses a spore-like structure which resists desiccation, heat, acid and ultraviolet rays, enabling it to survive freely in the environment for weeks.[4] Humans are incidental hosts, with fauna being environmental reservoirs. These are not limited to livestock, arthropods, birds, and reptiles. Livestock remain the largest source of human infection. The majority of human infection are believed to arise from inhalation of the aerosolised infected bodily fluids of livestock.[1] Other means of transmission are less common, but still well recognised, such as via ingestion of unpasteurised milk, blood transfusion, sexual transmission, and vertical transplacental transmission.[5, 6] The survivability of this organism in the natural environment and the ease at which it can infiltrate its large potential reservoir has led to spread to all regions of the world, with the exception of New Zealand and French Polynesia. The reported incubation period of Q fever varies from 12 to 37 days. A shorter incubation period is postulated to arise from higher inoculation doses.[7]

It is suspected that there may be regional differences in the clinical manifestation of acute Q fever, yet the reason for this variation remains elusive. Theories include regional clinician reporting bias, and sub-strain variation in virulence, host factors, and route of inoculation.[1, 2] There is a dearth of recent data about the clinical manifestations of this disease in Australia. Table 2 summarises the clinical spectrum of disease within Australia, and globally.[2, 8-14]

**Table 2.** Clinical spectrum of acute Q fever illness

| Condition | World rates ( %) | Australian rates (%) |
|---|---|---|
| Asymptomatic | 50-60% | 50-60% |
| Febrile illness | 85-100% | 82% |
| Pneumonia | 10-35% | 7-20% |
| Hepatitis (abnormal LFTs) | 25-80% | 5-85% |
| Hepatomegaly | 10-25% | 20- 50% |
| Splenomegaly | 5-17% | 15-30% |
| Acalculous cholecystitis | <20 cases reported worldwide | 1 reported case |
| Neurological manifestations | 0.2-1.3% | - |
| Cardiac (pericarditis/ myocarditis) | 0.5-1% | 1% |
| GI - diarrhoea | 5-20% | 7% |
| Arthralgia | 10-60% | 20% |
| Rash | 5-20% | 7% |

The last substantial Q fever case series in Australia was published in 1982.[11] Pneumonia, as defined by chest X-ray changes, was seen in 5% (6 of 111 patients). Despite derangement of liver enzymes being remarkably common in that case series (85%), marked hyperbilirubinaemia was exceedingly rare (only one patient had a serum bilirubin >60 µmol/L). This is consistent with the reported clinical manifestations of Q fever in contemporaneous Australian papers. Two distinct large case reports showed that 4 of 72 (5%) and 10 of 273 (4%) had manifestations of this disease on chest X-ray.[12, 13] Clinical jaundice was only seen in 3 of 72 (4%) and 3 of 273 (1%) respectively.

Of those that contract acute Q fever, only 60% are symptomatic. Globally, there are variable rates of Q fever pneumonia, but it still more common elsewhere than in Australia (5% of cases). As more contemporary data from Australia is elucidated, this difference might indeed be negligible. Q fever pneumonia is the predominant clinical presentation in Nova Scotia in Canada, Switzerland, and in the Basque region of Spain.[2] The other major clinical presentation is acute hepatitis, seen more commonly in California (USA), Ontario (Canada), and Andalusia (Spain). Q fever hepatic changes on biopsy typically show multiple granulomas with the characteristic central 'doughnut hole' and a surrounding fibrin ring.[15] Though not established, variation within a country's regional areas point towards differences in infection route (inhalation from work practices, in comparison to ingestion of contaminated food products, such as unpasteurised milk). A large retrospective analysis of almost 1 400 patients with acute Q fever looked at host factors and their association with clinical manifestations.[2] Patients with hepatitis had a tendency to be younger, with more systemic symptoms such as headaches and myalgias, and be less immunocompromised. Those with pulmonary involvement were older and had concomitant medical reasons for immunosuppression. A non-specific rash is uncommon, observed in less than 20%, and can help in differentiation of this condition from vector-borne rickettsial disease. Acute cardiac issues manifest in the form of myocarditis and pericarditis, which are seen rarely (<1%). The spectrum of neurological involvement varies considerably, from a non-specific headache to seizures and encephalitis. It is well established that adult males have a greater propensity to manifest symptomatic disease.[1]

Q fever acalculous cholecystitis is an underappreciated entity that was first recognised and reported in the literature in 2003.[16] This seminal case series looked at seven patients with serologically-proven acute Q fever. All seven had deranged liver function tests, ultrasonographic evidence of a dilated gallbladder wall, and absence of gallstones. Five of these seven patients had a cholecystectomy during the acute illness setting. It is notable that none had histological changes consistent with acute cholecystitis. A subsequent case report from Australia described Q fever cholecystitis.[14] Not only was there histopathological evidence of acute cholecystitis, but specific PCR testing (*com1* and *htpAB* genes) of these inflamed specimens was positive for *C. burnetii*. This is believed to be the first and only report thus far in the literature that has correlated acute changes of cholecystitis with PCR-confirmed *C. burnetii* sequences. Reported cases of Q fever-associated acalculous cholecystitis are likely a gross underestimation of cases seen, as clinicians may alternatively attribute the presence of acalculous cholecystitis to an acute systemic inflammatory process.

By conservative estimate, up to 5% of acute Q fever, despite treatment, progresses to a chronic state. Endocarditis forms the majority of chronic Q fever, accounting for two-thirds of all cases.[1] Pre-existing cardiac valve disease is a major risk factor in the development of Q fever endocarditis. One large study cited 88% of those with proven endocarditis had pre-existing valvular abnormalities.[2] Vegetations are usually small or absent, so diagnosis is often delayed.[17] Vascular infections are less common than chronic Q fever endocarditis, which in itself is a rare entity. When present, Q fever-associated vascular infections can be catastrophic. As with endocarditis, there are often predisposing factors, such as a known large vessel aneurysm, or a previous vascular graft. A recent study proposes the utility of fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT as a means to pinpoint infected vasculature.[18] Q fever chronic osteomyelitis and pulmonary fibrosis are rarely observed. Hepatitis in isolation, without concomitant endocarditis, is also an uncommon feature of chronic disease. Q fever chronic fatigue syndrome is well recognised, the pathophysiology less well so. Immune dysregulation has been put forward as a possible explanation for this condition.[19, 20] One should always remain vigilant in the exclusion of other chronic complications of Q fever, which may present in a protean manner with non-specific symptoms akin to that of Q fever chronic fatigue syndrome.

High risk occupational groups include those with animal exposure such as abattoir workers, farmhands, veterinarians, and certain medical laboratory personnel.[2] Plumbers and similar tradesmen are at unspecified risk. A large case study identified transmission via an infected air-conditioning ventilation system.[21] In summary, a single boarding school in Israel was shown to have an acute Q fever outbreak, in which 108 of 164 cases were confirmed serologically as acute Q fever. Several swabs on filters and inlets of the air-conditioning units were positive on PCR testing for *C. burnetii*, highly suggestive of it as a mode for facilitation and transmission of disease. The Israeli outbreak provides a different perspective to the traditional, better-known means of disease acquisition.

Various serological tests are available to the clinician for acute Q fever testing. Commonly utilised are the immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), and the complement fixation (CF) assay.[8] Immunofluorescence assay is still regarded as the standard reference method for serological diagnosis and follow up, reflected in algorithms for serological follow-up in chronic Q fever.[9,22] Serological diagnosis rather than culture isolation of this organism is sought given its extreme infectivity, confining culture methods to biosafety level 3 laboratories and above. *Coxiella burnetii* exists in two antigenic phases.[23] In its natural state, *C. burnetii* is considered virulent, in the phase 1 state. The avirulent phase 2 variant is derived from passages of *C. burnetii* culture in egg yolk sacs through several generations.[8] On immunofluorescence assay, IgM phase 2 antibodies appear first, 10-17 days after the onset of acute illness.[24] This is followed by IgG antibodies to phase 2. Persistent phase 1 antibodies, with a compatible clinical picture, can be a useful measure of Q fever chronicity. IgG phase 1 antibodies can take up to 6-8 weeks before there is a noticeable increase in titre.[23] Both phase 1 and 2 antibodies can persist, with half-time decay rates measured by years rather than months.[25] PCR testing for Q fever utilises a combination of 2 separate coding regions of the *C. burnetii* genome. The *com1* gene is a 27-kDa outer membrane protein that is related to pathogenesis and protective immunity.[26] The *htpAB* gene is flanked by a repetitive DNA element IS*1111a*, which functions as a transposase.[27] Studies show that on serum, a PCR-positive result for *C. burnetii* drops drastically after the second week of the illness, in conjunction with the rise in phase 2 antibodies.[28]

The recommended antimicrobial agent for treatment of acute Q fever is doxycycline, at a dose of 100 mg twice daily for 14 days.[17] Resistance to doxycycline has not been documented.[29] Macrolides show promise as an

alternative treatment choice in those intolerant of the tetracyclines.[30] In pregnant women, treatment is warranted to reduce foetal complications. As doxycycline and macrolides are undesirable during pregnancy, high-dose cotrimoxazole is a viable option, although often not curative. Definitive treatment is undertaken in the postpartum period.[31] There is a school of thought which emphasises treatment only if symptomatic.[32] Others however, advocate treatment acutely irrespective of symptoms, with the overarching concern of progression to chronic disease, a difficult to treat condition at best.[17, 22] Endocarditis, being the most common manifestation of chronic Q fever, necessitates both surgical and medical considerations. Surgical management, in conjunction with medical therapy, has a role in those with substantial valvular damage or heart failure.[22] Suggested duration of drug treatment varies, from lifelong treatment to a minimum of 18 months of dual antimicrobial agents - doxycycline and hydroxychloroquine.[33] Chloroquine facilitates the bactericidal activity of doxycycline. Despite guidelines assessing fall in phase 1 antibody titres to aid in the decision-making process in chronic Q fever endocarditis therapy, there is no single test that can definitively prove complete cure.[32]

There is no consensus on serological follow-up of treated acute Q fever. Landais *et al.* advocate IFA serological testing at 3 months and 6 months after acute illness.[34] Phase 1 IgG titres greater than 800 serve as a trigger for trans-oesophageal echocardiogram (TOE) and PCR testing on serum, irrespective of the presence or absence of clinical symptoms. Limonard *et al.* argue that in the recovery period following acute disease, an IgG titre >800 on IFA is not uncommon.[9] It was observed that none of their subset of patients with IgG titres >800 developed a clinical picture consistent with chronic Q fever endocarditis. Given the ever-pressing considerations of resource allocation, he raises the impracticality and cost of screening echocardiograms in the absence of a clinical compatible illness. A modified flow diagram is shown (Fig. 3).

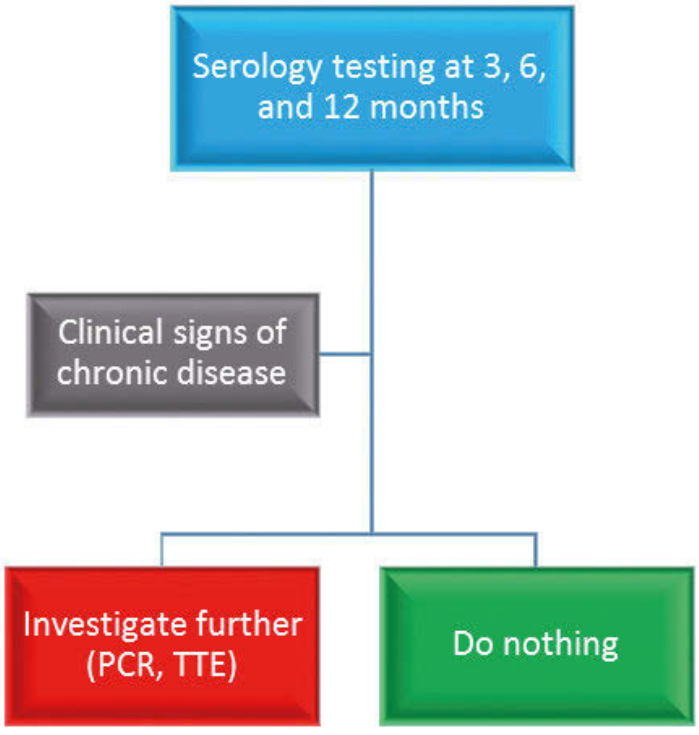


**Figure 3.** Algorithm for serological follow up in Q fever (modified from Limonard *et al.*[9])

## Conclusion

Q fever can give rise to a protean clinical illness. Our patient became critically ill with multi-organ involvement. We report a very rare case of presumed Q fever cholecystitis and coexisting pneumonia, and only the second report of positive PCR in gallbladder tissue. One must recognise that the positive PCR in this case may in fact represent the systemic nature of the disease. Furthermore, it is clear that there exists a gap in knowledge of the clinical spectrum of disease in contemporary Australia. This warrants further investigation. Last, serological follow up remains a perturbing issue with no clear consensus guidelines on a national or global level.

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