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Commentary

The prognostic value of serological titres in chronic Q fever: treat the patient, not the laboratory data

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This commentary, based on the paper by Buijs et al. [1] in the current issue of *CMI*, discusses the importance of monitoring serological titre changes in patients with chronic Q fever. The authors evaluated phase I IgG dynamics and the association with Q fever complications and therapy failure. Contrary to common perceptions, they found no association between antibody dynamics during the patient follow-up period and various clinical outcomes. These findings challenge current practice, which puts considerable value on serological changes while monitoring the patient's response to therapy in chronic Q fever.

The CDC [2] provide recommendations for treatment and management of Q fever. They recommend monthly monitoring of *Coxiella burnetii* antibodies during early treatment and twice yearly, for a minimum of 5 years, during treatment for chronic Q fever. The recommended duration of treatment for chronic Q fever is at least 18–24 months, and until a four-fold decrease in phase I IgG titre is reached. Others support these recommendations [3,4]. Indeed, this is what most clinicians do in countries where Q fever is endemic, such as Israel and Australia. They appraise the efficacy of treatment through serological monitoring, modify treatment when no serological response has been observed and continue therapy until a stable titre <1:800 is reached for phase 1 IgG. However, a stationary and persistently high phase 1 IgG titre after 18 months of therapy is frequently encountered in individuals who appear to have recovered.

There is some evidence for basing therapy on serological monitoring. Small case series showed the slow decrease of antibody titres during treatment of Q fever infective endocarditis (IE) [5,6]. The French National Centre for Rickettsiosis reported on patients treated for chronic Q fever over 30 years. The first study compared antibiotic regimens in 32 patients with Q fever IE [7]. They reported that phase I IgG titres did not drop below 400 in the majority of cases, but the authors did not correlate serology changes with patients' clinical outcomes. The second study of 35 patients compared two antibiotic regimens and concluded in favour of doxycycline and hydroxychloroquine for Q fever IE [8]. Criteria for stopping treatment were at least 6 months without a complication, phase 1 IgG titre <1:800 and phase I IgM and IgA titres both <1/50. This target was reached earlier with doxycycline and hydroxychloroquine compared with doxycycline plus ofloxacin, and with fewer relapses.

The most recent study was a report of 104 patients with Q fever IE [9]. In this study, an association was seen between mortality at the end of follow up (1 year) and the absence of a four-fold decrease in phase I IgG and IgA titres (hazard ratio 5.69) and the persistence of phase II IgM (hazard ratio 12.08). An advantage of this retrospective cohort study was its long period of patient follow up, with a minimum of 3 years and a median of 8.3 years (range 3.1–25.8 years). A major feature of this study was the 26-year period of patient recruitment. During this period, significant changes in patient management occurred, including different treatment regimens. A large variability in phase I IgG titres at diagnosis was observed over the years (partially explained by earlier diagnosis due to increased awareness to the disease).

The present Dutch study in the current issue of *CMI* describes the largest studied cohort of patients with chronic Q fever [1]. It included 337 patients from 45 hospitals in the Netherlands over a 12-year period and involved an analysis of the dynamics of phase I IgG titre changes. Treatment, consisting of the current standard of care, doxycycline and hydroxychloroquine, was given to 93.2% of

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the patients between 2007 and 2018. The follow-up period was shorter than the French cohort (median 4.2 years). The Dutch cohort included older patients than the French cohort (mean age 68 versus 53 years), reported higher Q fever-related mortality (21% versus 10% at 5 years) and a high rate of complications. In contrast to the French study, the Dutch study did not find an association between the changes in phase I IgG titres and the occurrence of one or more Q fever complications or Q fever-related mortality (hazard ratio 1.00). In a secondary analysis, serological cure was examined as a binary variable among patients completing 1 year of therapy and all associations with complications or death were non-significant, with hazard ratios close to 1. In both studies, high IgG phase I titres at diagnosis were associated with complications and death.

It is important to emphasize the complexity of differentiating, in a retrospective study, between complications occurring because of Q fever or as the result of other underlying diseases that may be age-associated and that often exist in older patients with chronic Q fever. These are usually valvular and vascular conditions. An inherent limitation in the Dutch study was that a significant number of complications occurred in a very short time following diagnosis, even before the start of treatment. They reported that 64% of the complications (123/190) occurred before the start of treatment. To address this and to allow for the assessment of treatment effects, the authors defined a secondary outcome of adverse events (complicated, related deaths or persistent positive PCR results for blood samples) after 3 months of treatment, with similar results. There was no association between serology changes and adverse events. However, this relatively short-duration analysis might not have captured some data because of the slow kinetics of *C. burnetii* antibody changes [10,11]. Serology testing was performed in many different laboratories, using two different immunofluorescence assays kits. Immunofluorescence assay serology can give different results from one laboratory to another [12]. Furthermore, it is an operator-dependent test, even within the same laboratory. Our experience is that to appreciate serology dynamics, follow-up sera from the same patient should be tested simultaneously in the same laboratory assay run. We do not know if this practice was followed in all the centres of the Dutch study.

Clinicians managing patients with chronic Q fever face several decisions. Should increasing phase I IgG titres after 18–24 months of treatment, in clinically stable patients, lead to a therapeutic intervention (e.g. adding a third antimicrobial agent, switching treatment regimen, optimizing drug levels or surgery to remove the main focus of infection)? For stable patients with stationary titres, is it safe to stop treatment after 18–24 months? Does an increase in titres after stopping treatment indicate a relapse that requires the re-instigation of therapy? Unfortunately the answers to these questions do not come from this current study [1]. It is unlikely that any future study, comparing the outcomes of individuals with chronic Q fever guided solely by Q fever serology versus a fixed treatment duration, regardless of serology results, will ever occur in the one place. Chronic Q fever cases are too widely scattered around the world, with too few in any one centre. Nevertheless, the findings of this new study, that phase I IgG dynamics do not correlate with complications of chronic Q fever, before or after starting treatment, raise concerns that the serological response is being over-emphasized.

Being relatively uncommon, single centres, even referral centres in endemic places, encounter few patients with chronic Q fever per year, highlighting the need for international collaboration to study this disease. Differences between locations may exist with respect to the clinical manifestations, course and disease complications. The serology response could vary as a result of the antigenic epitopes of different isolates/strains of *C. burnetii.* French isolates may be different from Dutch isolates and both may be different from Australian and Israeli isolates. These and other possible differences may be missed in cohorts coming from the one country. Nevertheless, serological dynamics in the context of successful treatment of patients with chronic Q fever should continue to be evaluated, as should alternative laboratory parameters that may guide clinicians in the treatment of patients with chronic Q fever. Imaging modalities such as fluorodeoxyglucose positron emission tomography/computed tomography are often helpful to detect (or rule out) an ongoing focus of infection. A study assessing the efficacy of Q fever serology in guiding treatment to prevent complications may be feasible with an international effort. In the meanwhile, clinical treatment decisions should never rely on laboratory tests alone. Serological 'improvements' are useful (partly to relieve physician 'anxiety' about their patient's progress), but should never override proper clinical assessment. Treat the patient not the laboratory data.

Transparency declaration

NGZ has no conflicts of interest to declare. SRG is the founder and medical director of the Australian Rickettsial Reference Laboratory. The laboratory receives income from patients and the Australian Government for diagnostic testing of human samples.

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