CLINICAL UPDATE

Chlamydia pneumoniae and cardiovascular disease

Mikkel M Larsen, Birgitte Moern, Andrew Fuller, Paul L Andersen and Lars J Ostergaard

ABSTRACT

- *Chlamydia pneumoniae* has been detected in atherosclerotic plaques, while seropositivity to this organism confers a slightly increased risk of coronary events.
- However, no aetiological link has been established; a major difficulty when investigating this link is the lack of a gold standard for diagnosing chronic vessel infection.
- The outcomes of case–control studies and prospective trials of macrolides in treatment and prevention of cardiovascular disease have been ambiguous but suggest a short-term preventive effect. Whether this is due to the antimicrobial or anti-inflammatory activity of the macrolides is unknown.
- Larger and longer prospective trials currently under way may provide better insight into the association of *C. pneumoniae* with cardiovascular disease.
- At present, there is no justification for treating cardiovascular disease with antibiotics.

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WHETHER CARDIOVASCULAR DISEASE is an infectious disease is not clear. A number of infectious agents have been implicated, including *Helicobacter pylori*, cytomegalovirus and periodontal bacteria, but by far the most studied is *Chlamydia pneumoniae*. During the past decade, the role of this organism in development of atherosclerosis, coronary heart disease (CHD) and stroke has been extensively explored, and associations with other vascular diseases, such as abdominal aortic aneurysm, have been proposed. Linking *C. pneumoniae* with the development or outcome of cardiovascular disease would have a substantial effect on antibiotic use. Indeed, a 1999 survey found that up to 4% of physicians in the United States had recommended treating cardiovascular disease with antibiotics.[1] As inappropriate use of antibiotics will affect the development of antibiotic resistance, it is crucial to assess the evidence. This review focuses on the relationship between *C. pneumoniae* and vascular disease and the evidence on antibiotic therapy for cardiovascular conditions.

Serological evidence

In 1988, Saikku and colleagues reported serological evidence of an association between *C. pneumoniae* infection and acute myocardial infarction.[2] Since then, numerous studies have examined the relationship between raised *C. pneumoniae* antibody titres and vascular disease. A review in 1997 identified 18 case–control studies with 2700 cases. Most studies reported an odds ratio (OR) of 2 or more, suggesting a real association between serological markers of *C. pneumoniae* infection and vascular disease.[3] More recent meta-analysis of 16 prospective case–control studies reported a weak association between raised *C. pneumoniae* IgA titres and CHD (OR, 1.25; 95% CI, 1.03–1.53), and a non-significant association between raised IgG titres and CHD (OR, 1.15; 95% CI, 0.97–1.36).[4,5]

However, a major difficulty in interpreting these results is the lack of a gold standard for diagnosing chronic *C. pneumoniae* infection of blood vessels. The gold standard for acute *C. pneumoniae* infection is the microimmunofluorescence test — an IgM titre greater than 1:16 or a fourfold rise in IgG titre is considered diagnostic. While persistently raised IgG and IgA titres have been proposed as criteria for chronic infection, there are no uniform cutoff titres to define seropositivity, and it is unclear whether seropositivity reflects chronic, or merely past, infection.[6] In addition, the microimmunofluorescence test is technically challenging, and may be replaced by new enzyme-linked immunosorbent assays.[7]

Furthermore, smoking is an independent risk factor for *C. pneumoniae* seropositivity. There may also be a positive correlation between *C. pneumoniae* seropositivity and a serum lipid profile associated with an increased risk of atherosclerosis, and between seropositivity and essential hypertension.[8-10]

The role of seroepidemiology thus remains controversial. Although seropositivity established a link between *C. pneumoniae* and atherosclerosis, it seems unlikely that serological tests alone will identify individuals at high risk for atherosclerosis.

Pathological mechanisms

The pathological mechanisms underlying the proposed atherogenic effect of *C. pneumoniae* can be viewed in the light of atherosclerotic plaque development. Initially, fatty streaks form in arterial walls through the accumulation of low-density lipoprotein (LDL) particles within the subendothelium. This leads to recruitment of lymphocytes and monocytes, which differentiate into macrophages and sub-

Research Unit Q, Department of Infectious Diseases, Aarhus University Hospital, Skejby Sygehus, Denmark.
Mikkel M Larsen, BSc, Research Assistant; **Birgitte Moern,** MD, PhD, Consultant; **Paul L Andersen,** MD, DMSc, Medical Director; **Lars J Ostergaard,** PhD, DMSc, Medical Director.
Infectious Disease Unit, Alfred Hospital, Prahran, VIC.
Andrew Fuller, FRACP, Consultant.
Reprints: Mr Mikkel M Larsen, Research Unit Q, Department of Infectious Diseases, Aarhus University Hospital, Skejby Sygehus, 8200 AARHUS N, Denmark. MLQ@sks.aaa.dk

1: Completed placebo-controlled trials of macrolide antibiotics in patients with vascular disease

Study	Subjects	Treatment	Clinical outcome	Change in immunological markers
Cardiovascular events				
Gupta et al[28]	213	1 or 2 courses of azithromycin 500 mg once daily for 3 days	Fourfold higher risk of cardiovascular events in placebo group.	Reduced titres of *C. pneumoniae* IgG in intervention group.
ACADEMIC[29]	302	Azithromycin 500 mg once daily for 3 days, then 500 mg once weekly for 3 months	No difference in incident cardiovascular disease.	No effect on *C. pneumoniae* IgG and IgA titres. Reduced levels of C-reactive protein, interleukin (IL)-1 and IL-6 in intervention group.
ROXIS[30]	202	Roxithromycin 150 mg twice daily for 30 days	Reduction in incident cardiovascular events after 30 days. No effect after 90 or 180 days.	No effect on *C. pneumoniae* IgG titres. Reduced levels of C-reactive protein in intervention group.
Other inflammatory vascular disease				
ISAR-3[31]	1010	Roxithromycin 300 mg once daily for 28 days	Protective effect of macrolide treatment on coronary restenosis in people with high *C. pneumoniae* antibody titres; adverse effect in those with low titres.	Not investigated.
Vammen et al[32]	92	Roxithromycin 300 mg once daily for 28 days	Reduced abdominal aortic aneurysm expansion rate in intervention group.	No effect on *C. pneumoniae* IgA titres.

sequently develop into foam cells. Later in life, smooth muscle cells derived from the media of the artery wall migrate to the subendothelium and form a fibrous cap around the foam cells. This cap is continuously degraded and replaced under the influence of the inflammatory cells within. Plaque rupture and thrombus formation is a very common underlying cause of CHD and stroke.

Risk factors for atherosclerosis are multiple, and include a high-fat diet, raised LDL levels, raised blood pressure, smoking, lack of exercise and hereditary factors.[11]

The role of *C. pneumoniae* must be elucidated within this context. *C. pneumoniae* causes respiratory disease, and serological studies reveal that more than half the adult population worldwide has been infected. Most seroconverters for *C. pneumoniae* are found at ages five to nine years, the same age that fatty streaks begin to form. Chlamydiae are notorious for establishing chronic infections that resist treatment.[12] In-vitro studies have shown that *C. pneumoniae* can grow in macrophages, endothelial cells and vascular smooth muscle cells.[13] Some investigators have isolated viable chlamydia from atherosclerotic tissue, but others have not been able to replicate this finding.[14] Furthermore, some studies have detected *C. pneumoniae* in atheromatous tissues through techniques including polymerase chain reaction (PCR) and immunocytochemistry.[15] The detection rate was about 50% overall, varying from zero to 100%. In contrast, detection rates in normal arterial tissue were about 1%.[15] However, PCR detection does not seem completely reliable. For example, a study comparing detection rates between laboratories found that three of 16 control samples negative for *C. pneumoniae* were rated positive by PCR analysis, while, at low *C. pneumoniae* concentrations, only three of 16 positive control samples were rated as positive.[16] Despite these problems, the aforementioned studies suggest that *C. pneumoniae* may establish infection in vascular tissue. This infection could, if chronic, provide the antigen for chronic inflammation.

Detection of *C. pneumoniae* in atherosclerotic lesions prompted research on the antigen specificity of lymphocytes within the lesions. Several studies have found that lymphocytes propagated from atherosclerotic tissue are responsive to *C. pneumoniae*, but also to other recall antigens such as tetanus toxoid and purified protein derivative. Interaction between *C. pneumoniae* and T lymphocytes and subsequent production of inflammatory cytokines, such as interferon gamma, is a proposed mechanism of plaque destabilisation.[17,18]

Development of foam cells from macrophages is a feature of atherogenesis. An in-vitro study found that exposure of human macrophages to a combination of *C. pneumoniae* and LDL induced their transformation into foam cells.[19]

Another suggested pathological mechanism is an autoimmune reaction involving bacterial heat-shock protein (HSP) with a high sequence homology to human HSP 60. The latter is an important product of cells in the arterial wall, protecting them against unfavourable conditions. Presence of antibodies directed against bacterial HSP (including chlamydial HSP) has been shown to be independently associated with prevalence of atherosclerosis, as well as with seropositivity to *C. pneumoniae*.[20]

Animal studies

Some of the more compelling arguments for an aetiological role for *C. pneumoniae* in atherosclerosis come from mouse and rabbit models. In hyperlipidaemic animals (genetically or diet induced) predisposed to develop atherosclerosis, experimental infection accelerates inflammatory progression.[21] Other studies have found inflammatory vascular changes in animals that do not normally develop atherosclerosis after single, and particularly repeated, inoculations of

2: Ongoing placebo-controlled trials of macrolide antibiotics in patients with vascular disease

Study	Subjects	Treatment
ACES[33] (Azithromycin and Coronary Events Study)	4016	Azithromycin 600 mg once weekly for 1 year
AZACS[34] (Azithromycin in Acute Coronary Syndromes)	1412	Azithromycin
CLARICOR[35] (Intervention with Clarithromycin in patients with stable coronary heart disease)	4600	Clarithromycin 500 mg once daily for 14 days
CROAATS[36] (Effects of azithromycin in *Chlamydia pneumoniae*-positive postmyocardial infarction patients)	270	Azithromycin 500 mg once daily for 3 days; treatment cycles on Days 1, 10 and 20
MARBLE[37] (Might Azithromycin Reduce Bypass List Events)	1240	Azithromycin
PROVE IT36[38] (PRavastatin Or AtorVastatin Evaluation and Infection Therapy)	4200	Pravastatin 40 mg or atorvastatin 80 mg once daily; plus gatifloxacin 400 mg once daily
STAMINA[39] (South Thames trial of Antibiotics in Myocardial INfarction and unstable Angina)	324	11-week course of azithromycin 500 mg once daily or amoxycillin 500 mg twice daily; plus metronidazole 400 mg twice daily; plus omeprazole 20 mg twice daily
WIZARD[40] (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders)	7700	Azithromycin 600 mg once daily for 3 days, then 600 mg once weekly for 11 weeks

C. pneumoniae,[22] although it has been suggested that this effect depends on high serum cholesterol levels. An actual atherogenic effect in both disease initiation and disease progression has thus been convincingly proposed in animals.[23] Whether this reflects human atherosclerotic development is unclear.

Antibiotic treatment of cardiovascular disease

Although causality has not been established between *C. pneumoniae* infection and cardiovascular disease, studies of the effects of antibiotic treatment on the disease are completed or under way. The optimal treatment regimen for *C. pneumoniae* infection has not yet been established, but the microbe is susceptible to tetracyclines and macrolides, including azithromycin and roxithromycin.[24] These newer macrolides are the most common agents used in prospective trials.

It is important when evaluating the results of these trials to consider that macrolides and tetracyclines have considerable anti-inflammatory as well as antimicrobial activity, which is a potential confounding factor.

Case–control studies

Two case–control studies have examined the relationship between antibiotic use and myocardial infarction. Jackson and colleagues found no association between use of erythromycin, tetracycline or doxycycline over a five-year period and first-time myocardial infarction.[25] However, Meier et al found that patients with myocardial infarction were less likely to have used tetracyclines or fluoroquinolones in the previous three years.[26] No correlation was seen for macrolides (the macrolide most commonly used was erythromycin). Neither study examined serological status. A more recent comparative cohort study by Ostergaard and colleagues found that use of macrolides had a protective effect on incident cardiovascular disease over a three-month period, compared with penicillin. This effect was non-significant after six months.[27] The results of these studies thus neither support nor disprove a role for *C. pneumoniae* in atherosclerosis, although it seems that the effect of macrolide treatment could be of short duration.

Randomised clinical trials

A number of randomised controlled trials have investigated the potential of macrolide treatment to prevent cardiovascular disease. Some are completed (Box 1), while others are ongoing (Box 2).

Completed trials: Gupta et al enrolled 213 patients with previous myocardial infarction who were stratified on the basis of *C. pneumoniae* serology (negative, intermediate or positive).[28] The *C. pneumoniae*-positive group ($n = 60$) was randomised to receive a single or double three-day course of placebo or azithromycin. The incidence of cardiovascular events (defined as myocardial infarction, unstable angina or cardiovascular death) was significantly higher in the group of *C. pneumoniae*-positive patients who did not receive azithromycin than in the *C. pneumoniae*-negative group (OR, 4.2; 95% CI, 1.2–15.5). There was no significant difference between the *C. pneumoniae*-positive group who received azithromycin and the *C. pneumoniae*-negative group (OR, 0.9; 95% CI, 0.2–4.6). The study concluded that *C. pneumoniae*-seropositive individuals are at higher risk of myocardial infarction, and that this can be reversed by azithromycin treatment. However, as discussed above, the value of serological tests alone to predict future cardiovascular events is still questionable.

The subsequent ACADEMIC (Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia) study enrolled 302 *C. pneumoniae*-seropositive patients with previous cardiovascular disease.[29] They were randomised to receive placebo or azithromycin once weekly for three months after an initial three-day course. There was no significant reduction in the number of cardiovascular events (defined as stroke, unstable angina, unplanned coro-

nary intervention or cardiovascular death) in the azithromycin group six months or two years later (the study was designed to detect a 50% reduction).

The ROXIS (Randomised Trial of Roxithromycin in Non-Q-Wave Coronary Syndromes) trial enrolled 202 patients with unstable angina, irrespective of *C. pneumoniae* serological status.[30] Patients were randomised to receive a 30-day course of roxithromycin or placebo. At the end of treatment, the incidence of cardiovascular events was lower in the roxithromycin group than in the placebo group, a difference that seemed to fade after three months.

The ISAR-3 (Intracoronary-stenting-and-antibiotic-regimen) trial examined the effect of roxithromycin treatment for 28 days on restenosis after coronary stenting in over 1000 patients.[31] After a year of follow-up, treatment was found to protect against restenosis in patients with high *C. pneumoniae* titres, but to be associated with more frequent restenosis in seronegative individuals than in the placebo group.

Vammen and colleagues investigated the effect of 28 days' roxithromycin treatment on abdominal aortic aneurysm expansion.[32] After one year of follow-up, the expansion rate was significantly lower in the treated group than in the placebo group.

Although these studies establish a link between macrolide treatment and amelioration of vascular diseases, the underlying mechanisms are not clear. While some studies found greater benefit in *C. pneumoniae*-seropositive individuals, others did not. The lack of a standardised treatment regimen impedes study comparison, but some studies suggest that the beneficial effect of macrolide treatment on CHD may be of short duration (ie, three months).

Ongoing clinical trials: A number of large-scale intervention studies are under way, and results are anxiously awaited (Box 2). In the WIZARD (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders) study, 7700 patients with previous myocardial infarction and positive *C. pneumoniae* serology have been randomised to three months of treatment or placebo. Preliminary results suggest a possible early treatment benefit which is not sustained over time.[40] The outcomes of other studies are awaited.

Conclusion

Our knowledge of the relationship between *C. pneumoniae* and cardiovascular disease has expanded greatly. Serological evidence of infection confers a moderately increased risk of atherosclerosis. Identification of the organism and the consequent lymphocytic response in diseased vascular tissue is consistent with an infectious aetiology. Animal studies strongly support an atherogenic link. However, the clinical impact of the associations remains to be clarified. Macrolide treatment may have a short-term effect, particularly in patients with no known history of cardiovascular disease, but this effect may be due to their anti-inflammatory rather than antichlamydial activity. Ongoing trials will not be able to differentiate these effects, but will show whether antibiotics are beneficial in patients who have already had atherosclerotic events. At present, there is no justification for treating cardiovascular disease with antibiotics.

Competing interests

None identified.

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