REVIEW

# *Chlamydia pneumoniae* and atherosclerosis

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**Abstract**

***Objective*—To review the literature for evidence that chronic infection with *Chlamydia pneumoniae* is associated with atherosclerosis and acute coronary syndromes.**

***Data sources*—MEDLINE and Institute of Science and Information bibliographic databases were searched at the end of September 1998. Indexing terms used were chlamydi*, heart, coronary, and atherosclerosis. Serological and pathological studies published as papers in any language since 1988 or abstracts since 1997 were selected.**

***Data extraction*—It was assumed that chronic *C pneumoniae* infection is characterised by the presence of both specific IgG and IgA, and serological studies were examined for associations that fulfilled these criteria. Pathological studies were also reviewed for evidence that the presence of *C pneumoniae* in diseased vessels is associated with the severity and extent of atherosclerosis.**

***Data synthesis*—The majority of serological studies have shown an association between *C pneumoniae* and atherosclerosis. However, the number of cases in studies that have reported a positive association when using strict criteria for chronic infection is similar to the number of cases in studies which found no association. Nevertheless, the organism is widely found in atherosclerotic vessels, although it may not be at all diseased sites and is not confined to the most severe lesions. Rabbit models and preliminary antibiotic trials suggest that the organism might exacerbate atherosclerosis.**

***Conclusion*—More evidence is required before *C pneumoniae* can be accepted as playing a role in atherosclerosis. Although use of antibiotics in routine practice is not justified, large scale trials in progress will help to elucidate the role of *C pneumoniae*.**

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The organism now known as *Chlamydia pneumoniae* was first isolated in 1965 in Taiwan. It was subsequently recognised to be a cause of acute respiratory disease[1] giving rise to the acronym TWAR (Taiwan acute respiratory) agent. Chlamydia are unique, obligate, intracellular bacterial pathogens of eukaryotic cells. As they are difficult organisms to culture, much knowledge about *C pneumoniae* infections has come from serological studies, many of which, since 1988, have shown an association between *C pneumoniae* infection and atherosclerosis. However, association does not prove causality and, unfortunately, serological distinction between past and current infection is difficult.

In a general population, infection was absent in children under 5 years, attaining a peak incidence of 9.2% in those aged 5–10 years before falling to 1.5% over the age of 20.[2] By the age of 20 years, prevalence of specific IgG has already reached 50%, persisting or even increasing with age.[3–5] Seroprevalence is proportional to the product of annual incidence and the duration of seropositivity following infection. As specific IgG antibodies are thought to disappear about three years following primary *C pneumoniae* infection,[6] an annual incidence of 1.5% should result in a prevalence of 4.5% rather than the observed 50%. One possibility is that there is a high prevalence of chronic infection driving a persistent specific IgG response. This suggests that the optimal time to eradicate *C pneumoniae* infection is around the age of 20 years, when half the population is seropositive and after which the risk of reinfection is relatively low. However, epidemics do occur[7 8] and IgG titres probably decay more slowly than previously thought. Of 90 students followed up for up to five years, only those with an initial low titre of 1:16 had a geometric mean titre of less than this at five years.[6] Therefore, a high seroprevalence might indicate a population characterised not by chronic infection needing treatment but by a high past exposure.

The problem is how to prove persisting infection against a background of persisting antibody. In primary respiratory infection, the predominant IgM response is followed by a delayed IgG and a delayed, weak, or absent IgA response. Adult infections are thought to be mainly reinfections characterised by specific IgG and IgA antibody responses without changes in IgM.[9] Thus, accurate detection of acute infection requires paired samples taken four to six weeks apart and the demonstration of a threefold or more rising titre. Serological criteria for chronic infection are more controversial but persistently raised specific IgA and

IgG is generally accepted as an indication of chronic infection, since IgA is thought to have a much shorter half life than IgG. These uncertainties partly explain why different authors have used different criteria for seropositivity. The picture is further complicated by reports of acute infection without an antibody response,[10 11] and that few studies of antibody response have used culture and antigen or DNA detection as absolute criteria of current infection. Compounding these problems, serology uses crude, whole *C pneumoniae* antigens, containing epitopes potentially cross reactive with antibodies to other *Chlamydia* species,[12] to other Gram negative bacteria,[13] or even to human heat shock protein as has been described for *Chlamydia trachomatis*.[14] Atherosclerosis is known to be associated with the presence of antibody to human heat shock protein,[15] and the possible confounding effects of such antibody has not been determined in any serological study of *C pneumoniae* and heart disease.

Pathological studies have generally shown that *C pneumoniae* is more common in atherosclerotic than control blood vessels. However, such studies do not show whether infection preceded or followed the development of

*Table 1 Studies investigating the serological association between C pneumoniae and atherosclerosis*

| | | *Association with†* | | | |
|---|---|---|---|---|---|
| *Study* | *Case control** | *IgG* | *IgA* | *ICs* | *Diagnostic antibody titre‡* |
| *Prospective studies* | | | | | |
| Saikku (1992)[19] | 103 *v* 103<br>Cardiac death or MI | 2.2 (1.1– 4.5) 2.6 (1.2–5.2)<br>6 months before event but not 5 years before | | | IgG ⩾ 128 and/or IC or IgA ⩾ 64 and/or IC |
| Miettinen (1996)[20] | 162 *v* 636 (NIDDM)<br>40 *v* 1155 (No DM)<br>Cardiac death or MI | 32% *v* 15%.<br>2.44 (0.98–6.08)<br>Only in non-diabetic men in East Finland | | | IgG ⩾ 128 and IgA ⩾ 40 |
| Ossewaarde (1998)[29] | 54 *v* 108<br>Cardiac death or MI or angina | 52% *v* 34%<br>2.8 (1.3–5.8) | No | No | ELISA |
| Nieto (1997)[30] | 256 *v* 550<br>Cardiac death, MI or revascularisation | No | | | IgG ⩾ 64 |
| Siscovick (1998)[31] | 100 *v* 183<br>Cardiac death or MI | No | | | Not stated (abstract) |
| *Cross sectional studies* | | | | | |
| Diedrichs (1997)[21] | 131 *v* 63<br>CA | 66% *v* 48% | 44% *v* 22% | | |
| Halme (1997)[22] | 93 *v* 115<br>CA | 100% *v* 61% (in men only) | | No | IgG ⩾ 128 and/or IgA ⩾ 40 |
| Saikku (1988)[23] | 70 *v* 41<br>MI or stable angina | 49% *v* 15%<br>5.5 (2.1–14.7) | 41% *v* 10% | | IgG ⩾ 128 IgA ⩾ 32 |
| Cook (1998)[24] | 176 *v* 1518<br>CVA | Acute infection 13.6% *v* 5.7%<br>4.2 (2.5–7.1)<br>Chronic infection 32.4% *v* 12.7%<br>4.4 (3–6.5) | | | IgG ⩾ 512 or 4 fold IgG rise or IgM ⩾ 8<br>IgG ⩾ 64 and ⩽ 256 or IgA ⩾ 8 |
| Mazzoli (1998)[25] | 29 *v* 74<br>MI | 82% *v* 34% | 71% *v* 14.9% | | |
| Dahlen (1995)[32] | 60 *v* 60 | 93.3% *v* 78.3%<br>3.56 (1–16.1) | No | | IgG ⩾ 32<br>IgA ⩾ 16 |
| Mendall (1995)[33] | 100 *v* 64<br>CA | 22% *v* 5%<br>7.4 (1.7–33.1) | No | | IgG ⩾ 64<br>IgA not stated |
| Blasi (1997)[28] | 61 *v* 61<br>MI | 57% *v* 30%<br>3.2 (1.5–6.8) | No | | IgG ⩾ 16<br>IgA ⩾ 16 |
| Thom (1991)[34] | 461 *v* 95<br>CA | 22% *v* 13%<br>2 (1–4) | | | IgG ⩾ 64 |
| Thom (1992)[35] | 171 *v* 120<br>CA | 67% *v* 56%<br>2.6 (1.4–4.8) | | | IgG ⩾ 8 |
| Melnick (1993)[36] | 326 matched pairs.<br>Carotid doppler | 73% *v* 63%<br>2 (1.2–3.4) | | | IgG ⩾ 8 |
| Patel (1995)[37] | 83 *v* 305<br>Rose questionaire, ECG | 30% *v* 18%<br>2.25 (1.1–4.6) | | | IgG ⩾ 64 |
| Thomas (1997)[38] | 83 *v* 93<br>MI/IHD | 71.1% *v* 31.2%<br>5.4 (2.7–10.9) | | | IgG ⩾ 16 |
| Toss (1998)[39] | 256 *v* 190<br>Unstable angina | Seroprevalence not reported | 36% *v* 19%. | | IgG ⩾ 16<br>IgA ⩾ 64 |
| Wimmer (1996)[40] | 58 *v* 52<br>CVA | No | 47% *v* 23%<br>1.7 (1.1–2.7) | 24% *v* 8%<br>2 (1.1–3.8) | IgG ⩾ 32<br>IgA ⩾ 16 |
| Leinonen (1990)[16] | 42 *v* 41<br>MI | No | No | 57% *v* 12%<br>10 (3–29) | IgG ⩾ 128<br>IgA ⩾ 32 |
| Leinonen (1994)[17] | 95 *v* 139<br>MI | No | No | 58% *v* 26%<br>4 (2–7) | IgG ⩾ 32 and ⩽ 128<br>IgA ⩾ 8 and ⩽ 32 |
| Weiss (1996)[18] | 65 *v* 28<br>CA | No | No | | All titres considered |
| Kark (1997)[26] | 302 *v* 486<br>MI | No | No | No | All titres considered |
| Boman (1998)[27] | 101 *v* 52 | No | No | | |
| Linnanmaki (1993)[41] | 46 *v* 46<br>CA | No | | 41% *v* 15%<br>4 (1.4–11) | IgG ⩾ 32 |
| Anderson (1998)[42] | 124 *v* 97<br>CA | No | | | IgG ⩾ 16 |

*Number of cases and controls in final analysis and diagnosis of cases.
†Percentage of cases and controls who are seropositive or who have immune complexes (ICs). Odds ratio and 95% confidence interval. Adjusted figures are shown where reported by the authors.
‡Microimmunofluorescence test unless indicated
CA, coronary arteriograms; CVA, cerebrovascular accident; MI, myocardial infarction; IHD, ischaemic heart disease; NIDDM, non-insulin dependent diabetes mellitus; DM, diabetes mellitus; ELISA, enzyme linked immunosorbent assay.

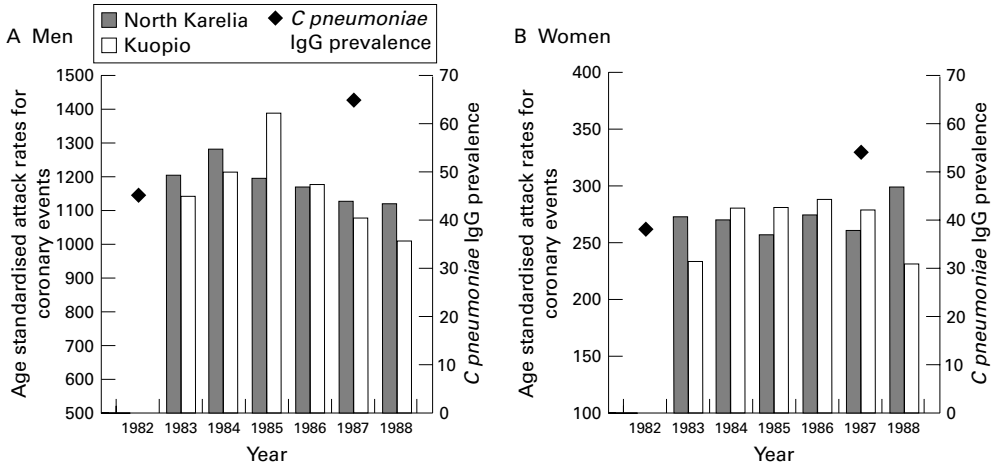


*Figure 1 Age standardised attack rates per 100 000 population in men (A) and women (B) for coronary events (definite and probable myocardial infarction and coronary deaths) in two regions of east Finland and prevalence of C pneumoniae IgG.*

atherosclerosis. Nevertheless, it might be expected that the distribution of *C pneumoniae* should be related either to the extent or severity of atherosclerosis.

## Data sources and data extraction

Serological and pathological studies published as papers in any language since 1988 or as abstracts since 1997 were searched for using the MEDLINE and Institute of Science and Information bibliographic databases. The search was completed at the end of September 1998. Indexing terms used were chlamydi* and heart, chlamydi* and coronary, and chlamydi* and atherosclerosis.

Information abstracted from serological studies included how many immunoglobulin classes were detected for and whether an association with atherosclerosis was found. Pathological studies were examined for information on the extent and distribution of *C pneumoniae* in subjects with atherosclerosis.

## Serological studies of *C pneumoniae* and atherosclerosis

Table 1 shows that 21 of 27[16–42] studies that have investigated *C pneumoniae* and atherosclerosis have reported some sort of positive serological association. However, although all studies measured IgG, only three prospective and 15 cross sectional studies measured IgA. Of the cross sectional studies, five found an association with both immunoglobulins, three with IgG alone, and two with IgA alone. Five studies found no association with either immunoglobulin, although three of these did show an association with circulating chlamydial immune complexes.[16 17 40] Therefore, the serological evidence that chronic rather than past *C pneumoniae* infection is associated with atherosclerosis is not compelling. In fact, the number of cases in studies which found a positive association with both immunoglobulins[19–25] is similar to that in studies which found no association with either,[16–18 20 26 27] although controls were numerically far greater in the former group (642 and 3069 *v* 767 and 1382). People with chronic debilitating diseases including heart failure are predisposed to respiratory tract infections and this may be one reason why people with coronary artery disease are more likely to have experienced *C pneumoniae* infection. Controlling for known confounding factors such as smoking has not always been adequate,[43] and it is not known whether there is an association of *C pneumoniae* with heart failure. Of the five prospective studies, three reported a positive association but two of these depended on subset analysis. In one study, seropositivity was associated with coronary events six months but not five years before an event,[19] while in the other an association was seen in non-diabetic men in east but not west Finland and not in diabetic men.[20]

Acute infections are easier to diagnose and four studies investigated whether antibody titre rises were associated with acute vascular events such as myocardial infarction and cerebrovascular accident. Cook and colleagues[24] found an association with cerebrovascular accidents while Saikku and colleagues[23] found an association between rising IgM titres to chlamydial group lipopolysaccharide and myocardial infarction. Blasi and colleagues[28] found that 20% of patients with myocardial infarction had a rise in IgG but the proportion in the control group was unknown. No association was seen in the fourth study.[16] Therefore, there is some evidence that acute infection is associated with acute vascular events. If this is true, the incidence of such events should increase during epidemics. East Finland has one of the highest coronary mortality rates in the world but there has been a gradual decrease since the 1970s because of a primary prevention programme. East Finland has also contributed to the World Health Organisation monitoring of trends and determinants in cardiovascular disease (WHO MONICA) project,[44] and serum samples from this project have been tested to estimate the population prevalence of *C pneumoniae*.[5] Figure 1 shows the attack rates of coronary events in two regions of east Finland and the seroprevalence of *C pneumoniae*. It can be seen that in the epidemic year of 1987, acute coronary events did not increase.

### Pathological studies of *C pneumoniae* in blood vessels

Techniques such as immunocytochemistry (ICC), the polymerase chain reaction (PCR), and culture have provided direct evidence that *C pneumoniae* localises to blood vessels. Generally, ICC finds more evidence for *C pneumoniae* than PCR but it is not known whether this is because of better sensitivity or worse specificity. It is notoriously difficult to obtain perfect ICC with severe atherosclerosis and the concern is that antibodies used in ICC cross react with components of atherosclerotic tissue. However, atherosclerotic tissue is known to contain inhibitors of PCR. These uncertainties make it difficult to estimate the prevalence of *C pneumoniae* in blood vessels, especially as specimens positive by one technique were not necessarily positive by another.[45] Culture of *C pneumoniae* from blood vessels is technically challenging and had only been managed on two occasions[46 47] until recently when, following multiple serial passage, the organism was isolated from 11 of 70 atheromatous samples.[48]

Histological evidence of atherosclerosis is ubiquitous[49] and 11 of 25 studies[18 45–48 50–69] did not have control vessels (table 2). Only three studies had controls completely matched for age, origin of tissue, and tests used to detect for *C pneumoniae*. Even then, control arteries either had histological evidence of early atherosclerosis,[50] or came from arteries where adjacent segments had disease.[51] For the other studies, control vessels tended to be numerically smaller and obtained at necropsy from younger subjects.

Although three studies failed to find evidence for *C pneumoniae* in atherosclerotic vessels,[18 52 53] most have found it in 15–100% of cases. In contrast, it appears to be uncommon in control vessels and only in two studies was *C pneumoniae* as prevalent in control as in diseased vessels.[54 55] In reality, it is likely that most control vessels, although macroscopically normal, did have early histological disease, which would suggest that *C pneumoniae* is more common in people with severe rather than mild atherosclerosis. There were five studies in which the severity of atherosclerosis was formally graded on a histological basis. In one, *C pneumoniae* was detected in 86% of severe compared with 6% of mild lesions using ICC.[45] However, when a subset of samples was tested by PCR, discordant results were obtained and the prevalence in non-atherosclerotic or minimally atherosclerotic lesions was said to be quite high.[70] In a necropsy study of 60 Alaskan natives who died mainly from non-cardiovascular causes (mean age 34.1 years), the Stary classification was used to grade the severity of a segment of the right coronary artery obtained from each subject.[56] Twenty two subjects were found to have *C pneumoniae* but there was no difference in the severity of their coronary artery segments compared with that of subjects without *C pneumoniae*. In total, 14 of 40 specimens with raised lesions were positive for *C pneumoniae* compared with 7 of 18 specimens with flat lesions. The main interest of this paper was the finding that a high IgG titre of $\geqslant 256$ on average eight years before death was associated with the presence of *C pneumoniae* in coronary arteries, suggesting

*Table 2 Studies investigating the presence of C pneumoniae in blood vessels*

| | | *Case and controls positive for C pneumonia** | | |
|---|---|---|---|---|
| *Study* | *Number of cases/controls* (description of case tissue)* | *PCR* | *ICC* | *Other* |
| *Controlled studies. Age, tissue, and diagnostic method matched* | | | | |
| Kuo (1995)[51] | 18 *v* 31 (coronary artery) | 17% *v* 0% | 39% *v* 0% | |
| Maass (1997)[50] | 61 *v* 39 (carotid endarterectomy) | 15% *v* 0% | | |
| Petersen (1998)[61] | 40 *v* 40 (AAA) | 35% *v* 5% | | |
| *Other controls* | | | | |
| Grayston† (1995)[62] | 5 *v* 0 (carotid endarterectomy) | 60% | 100% | |
| | 56 *v* 6 (archival or necropsy carotid specimens) | | 57% *v* 0% | |
| Ong† (1995)[55] | 32 AAA repairs *v* 6 patients with normal vascular tissue | 44% *v* 50% | 3/8 (38%) *v* not done | |
| Jackson (1997)[63] | 38 *v* 38 (vascular *v* non-vascular tissue from necropsy cases) | 16% *v* 0–8% | 24% *v* 5–11% | |
| Juvonen (1997)[64] | 12 *v* 9 (abdominal aortic aneurysm) | 6/6 *v* 0/9 | 100% *v* 0% | |
| Kuo† (1997)[65] | 23 *v* 8 (diseased femoral and popliteal arteries) | 48% *v* 0% | | 0%‡ *v* not done |
| Maass† (1998)[48] | 70 *v* 17 (coronary atherectomy, failed grafts and other vessels) | 30% *v* 0% | | 16%‡ *v* not done |
| Wong (1998)[54] | 58 *v* 58 (coronary atherectomy and failed grafts) | 39% *v* 12–30% | | |
| Shor (1992)[66] | 10 *v* 5 (coronary artery) Cases were highly selected from 1000 arteries | | 5/7 (71%) *v* 0/5 (0%) | 10/10§ *v* not done |
| Kuo (1993)[67] | 20 *v* 4 (aortic atheroma) | | 30% *v* 0% | |
| Chiu† (1997)[58] | 76 *v* 20 (carotid and aortic tissue) | | 71% *v* 0% | |
| Muhlestein† (1996)[68] | 90 coronary atherectomies 24 other controls | | | 79% *v* 4.2%¶ |
| *Studies without controls* | | | | |
| Kuo (1993)[60] | 36 (coronary artery) | 13/30 (43%) | 15/36 (42%) | 6/21§ (29%) |
| Campbell (1995)[59] | 37 (coronary atherectomy) | 32% | 45% | 2/2§ |
| Ramirez (1996)[46] | 12 (coronary artery) | 41.7% | 41.7% | 8%‡ 25%§ |
| Jackson (1997)[47] | 25 (carotid endarterectomy) | 24% | 8/16 (50%) | 4%‡ |
| Blasi (1996)[69] | 51 (AAA) | 51% | | |
| Weiss (1996)[18] | 72 (coronary atherectomies) | 1/50 (2%) | | 0/22‡§ |
| Davidson (1998)[56] | 60 (coronary artery) | 14/60 (23.3%) | 20/60 (33.3%) | |
| Bauriedel (1998)[57] | 32 (carotid and coronary arteries) | | 47% | |
| Lindholt (1998)[52] | 20 (AAA) | 0% | | |
| Paterson (1998)[53] | 30 (carotid and coronary arteries) | 0% | | |
| Saldeen (1998)[45] | 60 (coronary arteries) | | 62% | |

*In some cases, more than one specimen was obtained from each patient. In these cases and where it was possible to determine from the papers, results are expressed as positive patients per number of patients.
†Studies where control vessels did not come from age matched subjects or where control subjects were poorly described; ‡culture; §electron microscopy; ¶direct immunofluorescence.
PCR, polymerase chain reaction; ICC, immunocytochemistry; AAA, abdominal aortic aneurysm; IMA, internal mammary artery.

that chronic infection occurs. We also used the Stary grade to assess coronary atherosclerosis and found no association of severity with the presence of *C pneumoniae*.[71] Nevertheless, in another study, *C pneumoniae* was found in diseased segments of carotid artery but not in adjacent segments that were macroscopically normal but had early disease.[50] Similarly, in a study of young adults, *C pneumoniae* was more common in arteries with atheroma than in arteries with intimal thickening, but was absent in arteries that appeared normal.[51]

Few studies have examined the extent of *C pneumoniae* infection in individuals. In a postmortem study where two segments from each coronary artery were examined, we found that in patients with three vessel coronary artery disease, the organism was just as likely to be found in one as in two or three arteries.[71] Similarly, another study found that contiguous segments from diseased coronary arteries or different coronary arteries from the same subject were not all positive for *C pneumoniae*.[46]

In summary, pathological studies have shown that *C pneumoniae* is common in atherosclerotic vessels from a wide variety of sources, including those from young subjects.[51 72] This would suggest that chronic infection occurs. *C pneumoniae* may be more prevalent in severe compared with mild lesions but its distribution in an individual often does not necessarily match that of atherosclerosis. These findings suggest that *C pneumoniae* exacerbates rather than causes atherosclerosis. Thus, one study using ICC and electron microscopy reported that it was more frequently found in atherectomy samples from patients presenting with acute coronary syndrome than from patients with stable angina.[57] However, we found using PCR that *C pneumoniae* was just as likely to be found in mildly diseased lesions as in fatal plaques with acute thrombosis, rupture, or haemorrhage.[71] Also, *C pneumoniae* has been found in vessels not usually associated with atherosclerosis, such as the internal mammary artery and saphenous vein.[54 72]

## In vitro, animal, and antibiotic studies

Evidence of the potential pathogenicity of *C pneumoniae* for vasculature comes from four studies of experimental *C pneumoniae* infection in the New Zealand white rabbit.[73–76] These rabbits do not spontaneously develop atherosclerosis until a late stage, but may do so if given cholesterol supplemented diets. Such a model is useful in assessing whether *C pneumoniae* exacerbates or causes atherosclerosis. Intranasal inoculation with *C pneumoniae* in rabbits fed a normal diet was found to induce aortic inflammatory changes consistent with early atherosclerosis,[75] including foam cells,[74] in two studies but not in a third.[73] The histological changes were early and compatible with inflammation. In the largest study, in rabbits fed a diet supplemented with small amounts of cholesterol, lesion size was significantly increased in infected compared with uninfected rabbits, and these changes could be prevented by azithromycin.[76]

At the cellular level, recent studies indicate how *C pneumoniae* may interact with known risk factors of atherosclerosis to cause atheroma. It is clear that *C pneumoniae* is able to infect most of the cell types involved in atherogenesis, including endothelium, smooth muscle cells, and macrophages.[77] Intriguingly, a recent study found that human macrophages infected with *C pneumoniae* and incubated with low density lipoprotein were transformed into foam cells, the characteristic cells of early atheroma, within 22 hours.[78]

A key question is whether *C pneumoniae* plays a unique role in the induction of atherosclerosis. Other infectious agents, including *Helicobacter pylori*, periodontal bacteria, and cytomegalovirus, have been implicated.[43] All bacteria, including chlamydia, share highly homologous heat shock proteins (HSP) capable of inducing autoimmune antibodies in humans caused by the presence of cross reactive sites on human HSP. Macrophages in atherosclerotic lesions express high concentrations of HSP,[79] and concentrations of specific antibodies to HSP are increased in the sera of patients with atherosclerosis.[15] One possibility is that the immune response to bacterial infection generally may interact with chlamydial or human HSP in vessel walls, so exacerbating atherosclerosis. A recent study found that chlamydial and human HSP-60 co-localises in atherosclerotic lesions and that both types of HSP could induce $TNF_{\alpha}$ (tumour necrosis factor) and matrix degrading metalloproteinase activity when incubated with mouse macrophages.[80]

There have been two small antibiotic trials where patients with unstable angina or myocardial infarction were given macrolide antibiotics and were followed up.[81 82] Both reported beneficial effects in terms of reduction of further coronary events. A third study gave doxycycline to men who had had previous coronary artery bypass graft surgery.[83] No change in antibody titres or basal nitric oxide production was seen after four months of treatment. Preliminary reports from a fourth antibiotic trial reported no reduction in further coronary events.[84] Larger studies with longer follow up periods are needed; such trials are either underway or being planned. However, there is debate as to whether *C pneumoniae* can be eradicated and how long treatment should be. One study is planning to give antibiotics for a year.[85] Macrolide antibiotics have anti-inflammatory as well as antimicrobial properties and these will need to be controlled for. Pending the results of such trials, antibiotic therapy is not indicated.

## Conclusion

There is as yet no conclusive evidence that *C pneumoniae* causes atherosclerosis or precipitates acute coronary syndromes. Current knowledge about its distribution in blood vessels, animal studies, and antibiotic trials suggest that it may exacerbate atherosclerosis but these are preliminary results. There is no doubt that *C pneumoniae* is commonly found in blood vessels and it is important to discover

what the effects of infection are. It is too early to know whether antibiotics will play a role but such studies should be targeted at those who are clearly infected. Serology is an unreliable and poorly standardised surrogate for infection, failing in some studies to discriminate between those subjects with and without *C pneumoniae*.[50 58] This may be because seropositive subjects in whom *C pneumoniae* was not found had the organism at sites other than those investigated. However, it is clear that *C pneumoniae* infection may occur in the presence of low specific antibody levels.[59 60] It has been reported from Malaysia that *C pneumoniae* can be detected by PCR in serum samples,[86] although this has not been confirmed by other studies.[87] A promising possibility is the finding that *C pneumoniae* DNA can be detected in circulating white cells by PCR.[27 88] Using this technique, we have found in Southampton an association of coronary artery disease with circulating *C pneumoniae* DNA in men but not women.[83] In northern Sweden, in a population with a high seroprevalence of *C pneumoniae* antibody, a high prevalence of circulating *C pneumoniae* DNA was found in both patients and blood donors.[27]

The potential role of *C pneumoniae* and other infectious agents in coronary artery disease is an exciting and crucial area of cardiac research. Our hypothesis is that infection plays a role in only a subset of patients with coronary artery disease. Nevertheless the impact on public health could be substantial and the challenge to researchers is how to identify those patients most at risk.

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