LEADING ARTICLE

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Inflammation, Infection and Atherosclerosis

Do Antibacterials Have a Role in the Therapy of Coronary Artery Disease?

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Abstract

Since the recent publication of 3 studies on the use of antibacterials in patients with coronary artery disease (CAD), there has been a phenomenal interest in the role of infection in the genesis of CAD. It is now generally accepted that inflammation accompanies atherosclerosis from its initiation to the evolution of end-events. Inflammation may occur in response to traditional risk factors, such as hyperlipidaemia, smoking and diabetes mellitus. There is a recent resurgence of the concept that inflammation may have an infectious basis. This concept is based on the identification of microorganisms in the atherosclerotic plaque and seropositivity. The data on eradication of the offending organism with antibiotics and prevention of atherosclerosis-related events have, however, been inconsistent. This may reflect lack of precise understanding of steps leading to atherosclerosis and the evolution of acute ischaemic events. Further work in this area may help identify subsets of patient populations within which infection may play a causative role in the genesis of CAD. Targeted therapy then may be considered logical.

Atherosclerosis is still the major cause of morbidity and mortality in the US and Europe, despite a major decline in mortality from coronary artery disease (CAD) over the last 2 decades in the Western Hemisphere.[1,2] Several risk factors, such as dyslipidaemia, smoking, hypertension and diabetes mellitus, have been identified and correlated with the presence of CAD. Control of the these risk factors in the general population is thought to have contributed at least in part to the decrease in mortality and morbidity.[3-5] However, the mortality and morbidity in other areas, such as Asia, continues to increase,[6] suggesting that 'traditional' risk factors alone cannot explain the atherosclerotic process. Since the traditional risk factors explain the occurrence of CAD events only in a small number of patients, several new risk factors, such as hyperhomocysteinaemia, elevated lipoprotein A [Lp(a)], excess iron load in the body, imbalance between oxidant-antioxidant species, and genetic predisposition, have been considered as contributors to atherosclerosis.[7-11] In this article, we discuss the evidence for another putative risk factor, infection and the ensuing inflammation, in the pathogenesis of CAD, and the possible role of antibacterials in the treatment of CAD.

1. Atherosclerosis Is An Inflammatory Disease

Many experimental and clinical studies have

provided evidence for the presence of ongoing inflammation in atherosclerosis.[12-14] The earliest lesion of atherosclerosis, the so-called fatty streak, is purely an inflammatory lesion. It consists mainly of monocyte-derived macrophages and T lymphocytes.[15] Factors such as elevated and oxidatively modified low density lipoprotein (LDL) cholesterol, free radicals, cigarette smoke, hypertension, diabetes mellitus, genetic alterations, elevated plasma homocysteine concentrations and infectious organisms, activate the endothelium and facilitate leucocyte deposition. Release of growth factors from inflammatory cells stimulates migration and proliferation of smooth muscle cells. As the process of atherosclerosis proceeds, the complex lesion over time becomes covered with a fibrous cap that overlies a core of lipid and necrotic tissue. Whereas the integrity of this fibrous cap is responsible for the stability of the atherosclerotic plaque,[16-18] sustained inflammation may cause instability of the plaque. Cytokines released by inflammatory cells play a key role in the regulation of the stability of this plaque.[19,20] Cytokines also regulate the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and selectins, which are crucial in the recruitment of leucocytes to the lesion and further growth of smooth muscle cells.[19-21]

Activated T cells in human atheroma secrete the lymphokine interferon (IFN)γ, an inhibitor of the production of the interstitial form of collagen. There is evidence connecting activated T cells and their products to plaque rupture. Van der Wal et al.[22] in autopsy studies found that T cells and macrophages predominate at the site of coronary artery plaque rupture. These authors also noted that smooth muscle cells and leucocytes express high levels of transplantation antigen HLA-DRα, an indicator of the state of activation of smooth muscle cells. Only IFNγ can induce the expression of HLA-DRα in cultures of human vascular smooth muscle cells.[21]

Cells within the atherosclerotic plaque also express genes encoding matrix degrading enzymes, such as the collagenolytic enzyme matrix metalloproteinase (MMP)-1.[23] Thus, degradation of the fibrous cap could result from a decrease in interstitial collagen mediated by IFNγ and from the action of metalloproteinases.[21,23] The activation of monocytes and macrophages in the atheroma increases the production of tissue factor procoagulant and other prothrombotic factors, which collectively increase the potential for thrombogenesis. The colocalisation of CD4+ T cells and macrophages in atherosclerotic lesions, the abundant expression of HLA class II molecules and the expression of the leucocyte stimulatory molecule CD-40 and its ligand (CD40L) indicate a contribution of cell-mediated immunity to atherogenesis.[24] It is now abundantly clear that thrombotic episodes occur repeatedly in atherosclerotic arteries and the thrombi spontaneously dissolve. The reperfused artery and myocardium often show deposition of acute inflammatory cells, which may be the basis of acceleration of atherosclerosis in ischaemic-reperfused regions. These observations, mostly from experimental work, collectively suggest that atherosclerosis is an inflammatory disease that involves an intimate interaction between blood vessel and circulatory cells (fig. 1).

2. Clinical Markers of Inflammation in Coronary Artery Disease

The markers of inflammation identified in patients with CAD are summarised in table I. Studies performed almost 2 decades ago suggested that total leucocyte count correlates with the extent and severity of coronary atherosclerosis.[25-27] The initial leucocyte count in acute myocardial infarction

Table I. Markers of inflammation in clinical coronary artery disease

Increased total leucocyte count in blood
Increased neutrophil chemotaxis, and leukotriene B_4 and elastase release
Increased lymphocyte activation (increased procoagulant activity) *in vitro*
Elevated C-reactive protein and amyloid A levels in serum
Increased circulating levels of leucocyte adhesion molecules
Accumulation of inflammatory cells (T lymphocytes and monocytes/macrophages) in the atherosclerotic regions.
Collection of large number of inflammatory cells in the shoulder region of vulnerable plague

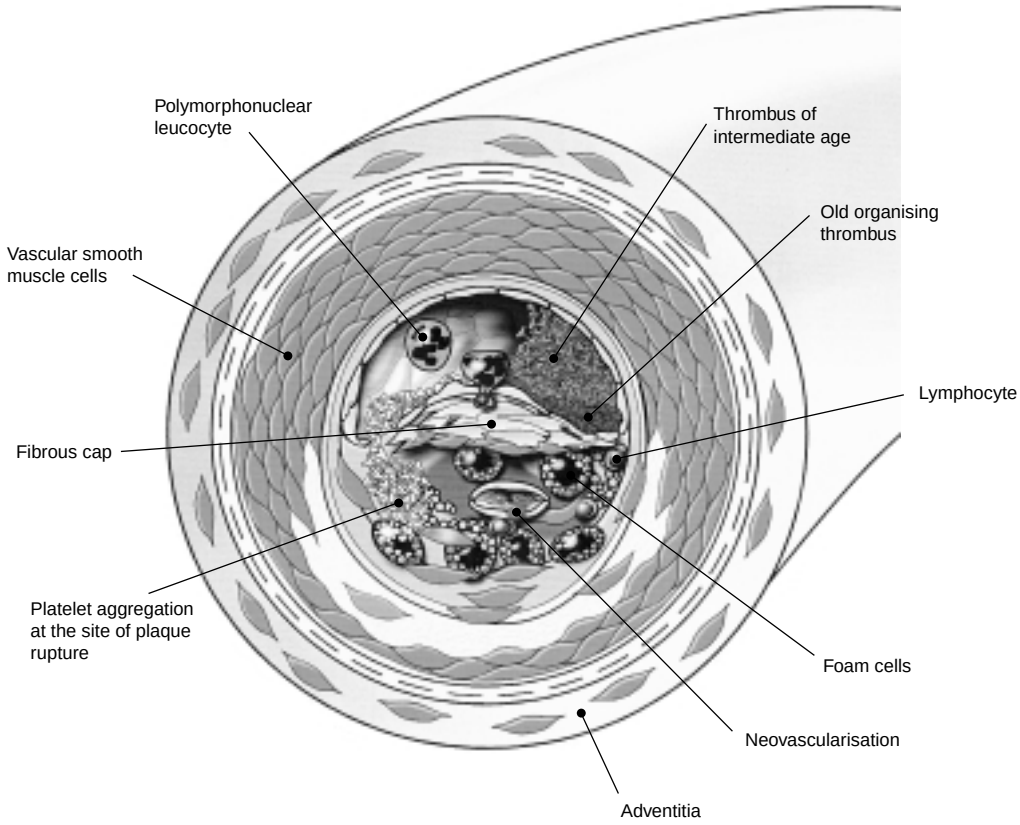

Fig. 1. Role of inflammation in atherosclerosis. After the initiation of endothelial activation, monocytes adhere, penetrate through the intercellular junction, and transform into macrophages and foam cells after incorporating the oxidised form of low density lipoprotein (LDL). The inflammatory cells release cytokines, which attract more inflammatory cells into the atherosclerotic area. Inflammatory cells release reactive oxygen species and growth factors. The vulnerable plaque is characterised by accumulation of a large number of inflammatory cells in the shoulder region of the plaque. Acute myocardial ischaemia is a result of thrombus formation, and reperfusion is characterised by neutrophil accumulation.

(MI) independently predicts the frequency of early ventricular fibrillation. Other studies showed enhanced chemotactic response of neutrophils and increased leukotriene B_4 generation in patients with stable angina.[28,29] Patients with unstable angina and acute MI have increased neutrophil elastase release. Neri Serneri et al.[30] showed that peripheral blood lymphocytes from patients with unstable angina also are activated and express significant procoagulant activity. Our group[31] measured circulating levels of ICAM-1 released from activated endothelial cells and L-selectin shed into the blood from activated leucocytes in a population of patients with CAD. We found higher levels of circulating ICAM-1 in patients with CAD, with the highest levels in patients with acute ischaemic syndromes.

Two recent clinical studies demonstrated the role of inflammation in CAD. Liuzzo et al.[32] reported that C-reactive protein and serum amyloid A protein were elevated in most patients with unstable angina pectoris and recent MI. The serum level of C-reactive protein may be an independent significant predictive factor in future MI and isch-

aemic stroke.[33] Recently, Biasucci et al.[34] have emphasised the presence of inflammatory component in patients with unstable angina. They showed that the magnitude of the immune response correlates with the clinical outcome. These studies clearly demonstrate that inflammation is an ongoing process in CAD, and its exacerbation may lead to acute coronary syndromes.

Although these studies do not provide the aetiology of inflammation, these observations definitely suggest that unstable angina may be a process triggered by acute inflammation in response to one or more stimuli.

3. Role of Infection in Human Atherosclerosis

It has recently been proposed that inflammation may be triggered by an infectious pathogen, and acute exacerbation of the infectious process may relate to the pathogenesis of atherosclerosis and acute coronary syndromes.[12,35,36] Despite all the recent emphasis and press attention, the infectious basis of atherosclerosis was initially formulated more than 100 years ago,[37,38] and since then occasional reports have correlated infections with atherosclerosis.[39-41] Infectious agents are important inflammatory stimuli that can initiate and maintain the atherosclerotic process. The histopathology of atherosclerotic lesions indeed suggests a correlation of some infections with progression of CAD. A number of pathogens have been thought to be involved in coronary atherosclerosis, and these include viruses (cytomegalovirus and herpes simplex) and bacteria (*Chlamydia pneumoniae* and *Helicobacter pylori*).[39-52]

3.1 Cytomegalovirus and Herpes Simplex Virus

Cytomegalovirus (CMV) has been frequently associated with atherosclerosis.[44,45] High levels of antibody titres against CMV have been described in patients with restenosis after coronary interventions[42] as well as in patients with CAD compared with controls.[51] High levels of antibody titres have also been demonstrated in patients with transplantation atherosclerosis.[43] Human endothelial cells infected with herpes simplex virus (HSV) demonstrate thrombin formation and increased adherence of platelets[52] and granulocytes.[53] Many other studies have documented the presence of CMV or HSV in human atheroma.[54-59]

CMV induces major histocompatibility class I antigen expression in human aortic muscle cell.[58] Transfection with this virus also causes expression of genes for several cytokines.[59] The failure to culture infectious viral particles from the atherosclerotic lesion is probably due to the 'hit and run' mechanism of HSV-mediated disease,[60] which implies that these viruses provoke the disease, but do not persist in the lesion. These studies support the observation of Fabricant et al.[39] on the role of these viruses in atherosclerosis. Recently, the Atherosclerosis Risk In Communities (ARIC) study[61] documented a significant correlation between carotid intima-medial thickness and the level of anti-CMV antibodies. However, no correlation of carotid atherosclerosis with antibodies against HSV type I or type II antigen was identified.[62] A negative correlation has been reported in other studies as well.[63]

3.2 *Helicobacter pylori*

There have been some reports relating *H. pylori* to the pathogenesis of atherosclerosis[64] as well as with serum lipid levels.[65] However, most studies have failed to show any association between *H. pylori* serology and carotid or coronary atherosclerosis.[66] A meta-analysis[67] of 18 studies failed to show any correlation of seropositivity against *H. pylori* with the presence or extent of coronary heart disease. Recent evidence, however, suggests that the more virulent strain bearing the cytotoxin-associated gene A (CagA) may be relevant in atherosclerosis through low grade, persistent inflammatory stimulation.[68]

3.3 *Chlamydia pneumoniae*

Chlamydia spp. are Gram-negative bacteria that cause human infectious disease. There are 3 different species of *Chlamydia*: (i) *C. trachomatis*, which

causes eye disease and sexually transmitted disease; (ii) *C. psittaci*, which infects birds and causes a human form of pneumonitis; and (iii) *C. pneumoniae*, which causes upper respiratory infections. There is only one immunotype, named TWAR, and this term is now used synonymously with *C. pneumoniae*. Many studies support the hypothesis of *C. pneumoniae* as the most probable infectious agent associated with human atherosclerosis. These experimental and clinical studies are summarised here.

3.3.1 Experimental Data

Fryer et al.[69] showed that *C. pneumoniae* can infect cultured human vascular endothelial cells and stimulate a 4-fold increase in the expression of tissue factor and platelet adhesion, thus providing a link between infection with *C. pneumoniae* and procoagulant activity. Gaydos et al.,[70] Wyrick and Brunridge[71] and Godzik et al.[72] showed that *Chlamydia* can replicate and maintain infection in human macrophages, endothelial cells and aortic smooth muscle cells. Fong et al.[73] showed replication of *C. pneumoniae* in a rabbit model. Moazed et al.[74] examined the relation of infection with *C. pneumonia* with atherosclerosis in 2 different animal models: apolipoprotein E–deficient transgenic mice, which spontaneously develop atherosclerosis, and C57 BL/6T mice, which only develop atherosclerosis on an atherogenic diet. After intranasal inoculation, *C. pneumoniae* was persistently identified in atherosclerotic lesions of the aorta by polymerase chain reaction (PCR) and immunohistochemistry. Elevated antibody titres [immunoglobin (Ig)G] lasted for up to 12 weeks. Muhlestein et al.[75] injected rabbits with *C. pneumoniae* or saline, and randomly assigned them to azithromycin or placebo for 2 months. Maximal intimal thickness of the aorta at 3 months was increased 3-fold in infected untreated animals, while it was normal in uninfected or treated infected animals. A recent carefully conducted study shows that high cholesterol levels provide a milieu for the growth of *C. pneumoniae* and development of atherosclerosis in a rabbit model.[76]

3.3.2 Human Studies

Many reports link *C. pneumoniae* with acute coronary syndromes. The first serological evidence of an association between *C. pneumoniae* and CAD was presented by Saikku et al.[47] They examined serum samples from 40 male patients with acute MI, 30 male patients with chronic CAD and 41 controls. 68% of patients with acute MI and 50% of patients with chronic CAD had elevated IgG (>1/128) or IgA (>1/32) titres or both against *C. pneumoniae*. Only 17% of the control group had high titres. Although the early work showed a preponderance of reports on *Chlamydia* seropositivity in CAD patients, more recent reports tend to refute this observation. We have recently studied patients with CAD from 3 different countries (Italy, US and Sweden), and found that the presence of elevated antibody titres (IgG and IgA) against *C. pneumoniae* were seen in a relatively small number of patients and did not show a correlation with the extent or severity of CAD.[77]

Sophisticated techniques such as PCR, electron microscopy, immunostaining, and culture of the organism have also been used to look for the presence of infection with *Chlamydia*. Many of these studies support the concept that infection with *Chlamydia* may be associated with the genesis of atherosclerosis in the early stages.[78-82] For example, Shor et al.[82] detected *C. pneumoniae* in fatty streaks and atheromathous lesions in 7 autopsy cases. Kuo et al.[78] and Campbell et al.[79] demonstrated the presence of *C. pneumoniae* in the coronary arteries of young adults. Muhlestein et al.[83] reported immunofluorescence positivity in 79% of 24 coronary artery specimens taken from patients with CAD. Some negative reports have also appeared in the literature,[84-86] and the absence of *Chlamydia* positivity may be a reflection of the method used to identify the bacteria. Positivity for *C. pneumoniae* was found by PCR and immunochemistry in the atherosclerotic tissues in patients from the ARIC study.[50]

Discrepancy in data on vessel wall infection between various studies can be explained by the degree of sensitivity of the test employed as well as

the quality and type of specimen examined.[86] We have recently examined the association of *C. pneumoniae* with coronary atherosclerosis in 60 consecutive autopsy cases.[87] 32 of 42 cases with severe atherosclerosis were positive on immunoperoxidase staining compared with 1 of 18 with mild atherosclerosis ($p < 0.001$). We also studied HLA-DR genotypes in these patients. Interestingly, 48% of cases of severe atherosclerosis were positive for HLA-class II genotypes 13, 15 or 17 in cardiac smooth muscle compared with 19% of cases with mild atherosclerosis. Similar results have been reported by Dahlen et al.[88,89] These observations collectively indicate an association of *C. pneumoniae* and atherosclerosis only in some genetically prone individuals.

4. Which Pathogen is Associated With Atherosclerosis?

The association between CMV, HSV or *H. pylori* and atherosclerosis does not fulfil the Koch's criteria that should be met to link an infectious agent with the production of the disease.[90,91] Evidence for *C. pneumoniae*, thus far, presents the strongest association with human atherosclerosis. On the basis of seroepidemiological, pathological and laboratory data, this agent fulfils many of Koch's criteria to be considered a pathogen in the genesis of atherosclerosis. In essence, *C. pneumoniae* has been isolated from human atherosclerotic plaques;[78-83] this agent can be identified in the atheroma by culture or directly by microscopy;[92,93] and lastly, on transfer to a susceptible host, this agent causes the disease.[75]

The enthusiasm for implicating these pathogens in CAD was dampened by the results of analysis of several studies. For example, in a recent population-based, case-control study, Danesh et al.[94] showed that after adjustment for age, gender, smoking, indicators of socioeconomic status and standard risk factors, the odds ratio (95% confidence intervals) for CAD patients to have seropositivity to *H. pylori* was 1.28 (0.93 to 1.75), to CMV 1.40 (0.96 to 2.05), and to *C. pneumoniae* 0.95 (0.66 to 1.36). They also found a strong correlation between *H. pylori* and *C. pneumoniae* IgG concentrations, suggesting co-nesting of these infections.[95] These observations on seropositivity do not, however, rule out a role for *Chlamydia* or other organisms in initiating or perpetuating the atherosclerotic lesion in some genetically prone individuals, especially in those with other traditional risk factors.[12]

5. Mechanism of Infection-Induced Atherogenesis or Aggravation of Atherosclerosis

The mechanism by which *C. pneumoniae* influences atherogenesis is still poorly understood. Atherosclerosis could result from direct local infection of the vessel wall or from some of indirect effects of the infection, which are summarised here and in figure 2.

(i) Kol et al.[96] demonstrated that *C. pneumoniae* produces a large amount of heat shock protein 60 (HSP 60) during chronic persistent infection, and HSP 60 may play a role in atherogenesis. These authors found that chlamydial HSP 60 colocalises within the plaque macrophages and in human atherosclerotic lesions. This bacterial product stimulates macrophage function with release of pro-inflammatory cytokines, such as tumour necrosis factor (TNF)α and matrix signalling metalloproteinases.[23] Mayr et al.[97] recently showed that antibodies to chlamydial HSPs also induce endothelial cytotoxicity, a key event in the pathogenesis of atherosclerosis.

(ii) Repeat bacterial infection can aggravate the pre-existing infection or inflammation by enhancing T cell activation and other inflammatory responses which may cause destabilisation of the intimal fibrous cap with subsequent plaque rupture and coronary thrombosis.[36]

(iii) Kalayoglu and Byrne[98] found that intracellular *C. pneumoniae* induces macrophage foam cell formation in human atheroma. Foam cell formation markedly increases upon exposure of macrophages and LDL, suggesting that lipid accumulation is induced by deregulation of native LDL uptake or metabolism.

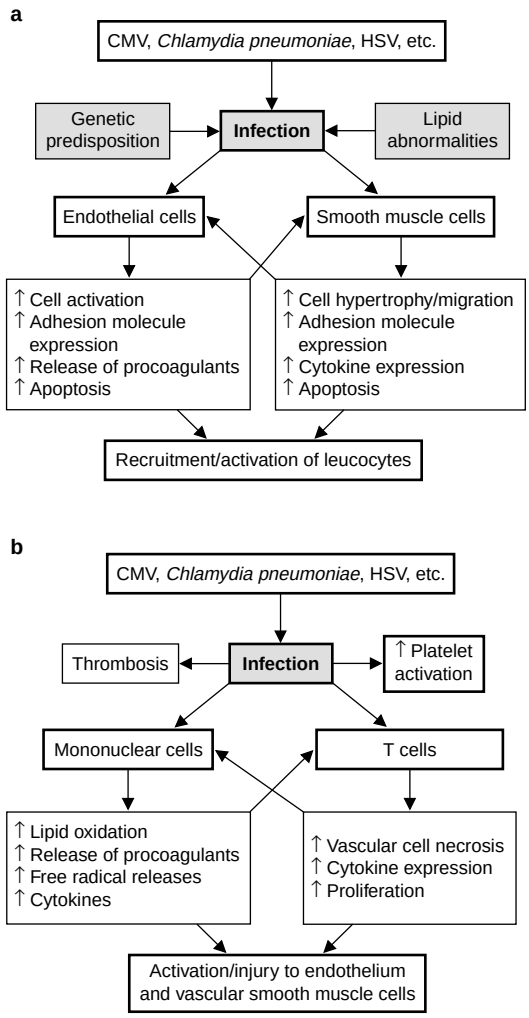

Fig. 2. Relationship between infection, inflammation and other mediators of atherosclerosis. In susceptible individuals, intracellular infection can activate endothelial and smooth muscle cells, which results in recruitment and activation of leucocytes (**a**). Infection can also activate mononuclear cells and T lymphocytes, which, via a cascade of events, activate and injure endothelial and vascular smooth muscle cells (**b**). **CMV** = cytomegalovirus; **HSV** = herpes simplex virus.

(iv) *Chlamydia*, as well as CMV, induces production of cytokines.[99] Many of the cytokines, as previously discussed, have a variety of actions that may induce procoagulant activity and endothelial dysfunction. Cytokines can activate neutrophils and cause release of reactive oxygen species (ROS),[100] which facilitate oxidation of LDL cholesterol, a key event in atherosclerosis. Cytokines also attract monocytes and other inflammatory cells to the area of endothelial damage. ROS also stimulate platelet activation and leucocyte chemotaxis and may participate in the formation of thrombus in the atherosclerotic narrowed coronary arteries. Cytokines influence the coagulation cascade by stimulating the formation of endogenous tissue plasminogen activator and its fast acting inhibitor, plasminogen activator inhibitor-1, resulting in thrombus formation.[100]

(v) Endothelial injury and release of cytokines decrease the synthesis of constitutive nitric oxide (NO),[101] another hallmark of atherosclerosis, and may predispose to vasospasm, platelet aggregation and thrombosis. Conversely, bacterial lipopolysaccharide is a potent stimulus for inducible NO synthetase activity,[101] leading to the formation of large amounts of NO, which can cause endothelial dysfunction and disruption followed by deposition on the vessel wall of inflammatory cells and release of growth factors.

6. Clinical Trials of Antibacterials in Coronary Artery Disease

If infection is the cause of atherosclerosis and its clinical manifestations, treatment with antibacterials should theoretically result in preventing some of the clinical manifestations of CAD.

Azithromycin is a potent azalide antibacterial which is very active against *Chlamydia* infections.[102] The first trial with azithromycin was carried out by Gupta et al.[103] in a small number of survivors of acute MI with elevated titres of IgG against *C. pneumoniae*. This trial demonstrated a significant reduction in the markers of inflammation in patients treated with azithromycin, such as monocyte macrophage tissue factor and the surface adhesion molecule CD11b. Azithromycin treatment also resulted in a significant reduction in cardiovascular events within 6 to 18 months. Subsequently, Gurfinkel et al.[104] reported similar short term efficacy in a pilot antibacterial trial from Ar-

gentina. They randomised 202 patients with unstable angina or non–Q-wave MI to the macrolide antibacterial roxithromycin 150mg twice daily or placebo for 30 days. All clinical events were reduced at 1 month in the treated patients (triple end-points 9 and 2% in the placebo and roxithromycin groups, $p < 0.03$; double end-points 4 and 0%, $p < 0.58$). Follow-up studies suggested that this favourable effect waned at 3 to 6 months. IgG titres remained unchanged, whereas C-reactive protein levels fell in both groups but more so in the roxithromycin group ($p < 0.03$).[105]

These 2 small studies led to much enthusiasm about the treatment of CAD with antibacterials. A somewhat larger study was designed and conducted by Anderson et al.[106] In this double-blind, randomised, secondary prevention study [the Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with *Chlamydia* (ACADEMIC) trial], 302 patients with serological evidence of prior *C. pneumoniae* exposure were given azithromycin 500 mg/day for 3 days and then 500 mg/week for 3 months. Antibody titres (IgG and IgA) and inflammatory markers, such as C-reactive protein, interleukin (IL)-1, IL-6 and TNFα were analysed at 3 and 6 months. Clinical end-points such as cardiovascular death, resuscitated cardiac arrest, non-fatal MI or stroke, unstable angina requiring hospitalisation and need for coronary interventions at 6 months and 2 years were also assessed. This study showed that in patients with CAD with serological evidence of prior exposure to *C. pneumoniae*, markers of inflammation improved at 6 months with azithromycin, but no differences were observed either in antibody titres or in clinical events. These results stress the need for further investigation and larger clinical trials.

There are several other major clinical trials of antibacterials underway in patients with CAD. For example, the Weekly Intervention with Zithromax® (azithromycin) Against Atherosclerosis-Related Disorders (WIZARD) trial is enrolling 3500 individuals with prior MI and *C. pneumoniae* antibody for 3 months. In this study, a 2.5-year observation is planned. The Azithromycin Coronary Events Study (ACES), sponsored by the US National Heart, Lung and Blood Institute, will include 4000 participants with evidence of CAD, irrespective of antibody status, for 1 year, with a planned 4-year observation period.

7. Limitations of Antibacterial Therapy

The interest in antibacterial therapy stemmed from early reports suggesting a causative role for *C. pneumoniae* in atherosclerosis. Therein may lie the major limitation of this strategy. As discussed in section 3.3.2, seropositivity is not an index of persistent infection.

Furthermore, the infection rate with *C. pneumoniae* in the general population is about 2 to 3% per year. Although it can be rationalised that infection could promote and maintain atherosclerosis in combination with other risk factors, and may be an important mechanism of atherogenesis in certain genetically predisposed individuals, studies based on serological markers are unlikely to yield evidence of benefit. This may also be basis of the contradictory results of preliminary studies. Treatment based on antibody titres may also be a limitation of the ACADEMIC trial. Lack of correlation between serological markers of inflammation and activity of disease suggests that routine antibacterial therapy in *all* patients with CAD or *all* patients with acute coronary syndromes is unlikely to yield beneficial effect. We believe that a cause-and-effect relationship between a single infectious agent and atherosclerosis remains unproven. We need to define the subset of patients in whom infection is the primary cause of atherogenesis, or instability of the disease, before a strong foundation for the use of antibacterials can be laid.

It is to be noted that some of the beneficial effects of macrolides in CAD may be a result of anti-inflammatory properties of these agents that are independent of their antibacterial effects.[107] This may explain the fall in C-reactive protein and other markers of inflammation in patients treated with antibacterials. Furthermore, prolonged use of antibacterials, particularly those that have a broad range of pathogen sensitivity, has significant epi-

demiological significance. Routine use of high dosages in a large population may result in antibacterial resistance, which is a major public health concern, particularly when the relationship between infection and CAD is far from proven.

8. Mosaic of Inflammation, Infection and Atherosclerosis

A large body of evidence has, in the past, supported the role of certain risk factors in the pathogenesis of atherosclerosis. Recently evidence has been presented for an infectious and/or autoimmune nature of the disease. However, one major unanswered question remains: what causes or initiates the atherosclerotic process? Traditional risk factors do not explain the atherosclerotic process in a relatively large number of patients. Furthermore, infection is not present in all patients. Lastly, it is unlikely that a group of 5 or 10 risk factors can explain the genesis of a malady that affects one-third to one-half of the world population. What is clear is that inflammation occurs in response to some kind of injury and it perpetuates the atherosclerotic process, yet it is probably not the cause of atherosclerosis. Perhaps infectious agents, in the presence of traditional risk factors, such as dyslipidaemia, can initiate the atherosclerotic process and lead to an inflammatory response. This may result in clinical CAD in genetically prone or otherwise susceptible individuals. It is futile to think that infection with an ubiquitous organism, such as *C. pneumoniae*, is the cause of atherosclerosis in all individuals, and therefore, antibacterial therapy will be useful in all CAD patients.

9. Conclusion

Atherosclerosis is a multifactorial disease. Traditional risk factors are associated with this disease in a significant number of patients. We believe that there is only a weak association between infection and the precipitation of atherosclerosis or in the acute manifestations of this complex disease entity. Further prospective large studies need to be conducted to study the association of infection with atherogenesis. If the infectious agent/s associated with atherosclerosis is/are clearly demonstrated, large studies on the treatment of the offending organism can be designed to assess the efficacy of antibacterials in a select group of patients in whom infection is the major underlying cause.

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