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REVIEW

# Impact of viral and bacterial infections in coronary artery disease patients

Hem Chandra Jha, Aruna Mittal

Hem Chandra Jha, Aruna Mittal, National Institute of Pathology-ICMR, New Delhi 110029, India
Hem Chandra Jha, Department of Microbiology, University of Pennsylvania, Philadelphia, PA 19104, United States
Author contributions: Jha HC, Mittal A solely contributed to this paper.
Correspondence to: Aruna Mittal, Consultant, National Institute of Pathology-ICMR, New Delhi 110029, India. amittal_iop@yahoo.com
Telephone: +91-11-26198402 Fax: +91-11-2619801
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## Abstract

Atherosclerosis is becoming an alarming disease for the existence of healthy human beings in the 21st century. There are a growing number of agents, either modernized life style generated, competitive work culture related or infection with some bacterial or viral agents, documented every year. These infectious agents do not have proper diagnostics or detection availability in many poor and developing countries. Hence, as active medical researchers, we summarize some aspects of infectious agents and their related mechanisms in this review which may be beneficial for new beginners in this field and update awareness in the field of cardiovascular biology.



**Key words:** *Chlamydia pneumoniae*; *Helicobacter pylori*; *Cytomegalovirus*; Cytokines; Diagnostics

**Core tip:** This paper describes the association of atherosclerosis with different infectious agents, specifically *Chlamydia pneumoniae* (*C. pneumoniae*), *Helicobacter pylori*, Herpes viruses and periodontal pathogens. There are many other bacteria and viruses, as well as life style related factors described and cited in this review. The manuscript also emphasizes how *C. pneumoniae* is modulating the human immune system with mimicking some antigenic proteins of the host. Overall, this report helps in the field of cardiac biology to explore associated risk factors in more detail.

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## INTRODUCTION

There are numerous studies supporting the association of coronary artery disease with many infectious agents, including bacteria and viruses[1-8]. Several bacterial pathogens have been reported to trigger the inflammation of atherosclerosis, including *Chlamydia pneumoniae* (*C. pneumoniae*)[7,9,10], *Helicobacter pylori* (*H. pylori*)[11,12], *Chryseomonas sp*[13], *Veillonella sp*[13], *Streptococcus sp*[13], *Aggregatibacter actinomycetemcomitans*[14], *Porphyromonas gingivalis*[15], *Prevotella intermedia*[16], *Prevotella nigrescens*[17], *Tannerella forsythia*[18], *Ruminococcus enterotype*[19], *Enterobacter hormaechei*[20] and periodontal pathogens[21]. Similarly, many viruses are known to be associated with atherosclerosis, namely *cytomegalovirus* (CMV)[22,23], *herpesvirus*[24], *hepatitis A*[25], B[26] and C viruses[27], *Epstein-Barr virus*[28] and *Herpes simplex virus* I and II[29]. Thus, it would be important to know in which circumstances bacterial and viral infections activate heart disease mechanistically.

## REVIEW OF THE LITERATURE

Increasing the risk of heart disease is a major cause of concern. In 2008, 30% of all global death was attributed to cardiovascular diseases[30]. It is also estimated that by 2030, over 23 million people will die from cardiovascular

diseases annually[30]. The incidence rate of atherosclerotic symptoms is increasing exponentially year by year[31]. There are numerous factors involved in the causation of atherosclerosis. Some researchers strongly classify it as a life style disease, including body mass weight, smoking, heavy alcohol intake, sedentary life style, blood pressure, elevated levels of cholesterol and bad lipids, reduced levels of good lipids and a stressful life[32-38]. Many studies have found a significant association of atherosclerosis with genetics or as hereditary[39], with close blood relatives suffering from heart attack, diabetes or hypertension[8,40,41]. Moreover, mainly from last decades, various studies were conducted on the association of heart disease with infectious agents. Many types of specimens, including blood samples, PBMCs and specific tissue sites were evaluated for the establishment of infection with atherosclerosis[42]. To date, there are hundreds of research studies using ELISA, standard PCR, real time quantitative PCR, cell culture, immunohistochemistry and immunocytochemistry methods to find a relevant and authentic answer for the association between infectious agents with atherosclerosis[6-8,43-49]. Although some controversy exists in this field in order to completely accept the direct association between infectious agents with atherosclerosis, there is no question of the enhanced presence of infectious agents in atherosclerosis or accelerated progression of atherosclerosis in the presence of infectious agents. To date, some well established infectious agents, like bacteria and viruses, *C. pneumoniae*, *H. pylori* and *cytomegalovirus,* were observed in a number of studies and explained the etiology of disease causation in detail[50-53].

## C. PNEUMONIAE

*C. pneumoniae* is an intracellular obligatory bacteria which causes upper and lower respiratory tract infections[54]. Other than respiratory disease, *C. pneumoniae* has been found to be associated with heart disease, Alzheimer's disease, multiple sclerosis, lung cancer and arthritis[55-59]. 95% of the population is exposed to *C. pneumoniae* in their life time; however, this exposure is asymptomatic while in contact with *C. pneumoniae* frequently and exposure to some other co-activator of *C. pneumoniae* infection triggers the establishment of infection and chronicity of disease pathogenesis[60]. There are numerous tissue or body organelles involved in the acceleration of *C. pneumoniae* infection[61,62]. Correct diagnosis of infectious agents is always in question and many methodological improvements have been made in this aspect[63,64]. To date, nested PCR or quantitative probe based real time PCR methods have been largely updated in this field[7,65,66]. 16S rRNA and major outer membrane protein have been found to be critical for identification on PCR based methods[7,67,68]. Moreover, immunoglobulin based screening also has significance and capability for the predication of disease occurrence in existing non-symptomatic and close relative populations of patients[41]. In many studies, *C. pneumoniae* specific immunoglobulin IgA has been found to be more predictive and robustly observed compared to IgG in the serum of coronary artery disease patients[8,69,70], while some studies reported it vice versa as well[71]. In response to *C. pneumoniae* infection, many host immune responses are manipulated or aggravated to counter the effect of bacterial pathogens and stop the progression of disease, while at the same time, this smart bacteria also activates host signaling by mimicking some of the key proteins, starting to accelerate disease progression[49,72,73]. These host-pathogen responses are very complex and many studies find some narrative result which suggests the hypothetical model for the infection progression due to *C. pneumoniae*[74]. Moreover, details are needed to explore this field to prevent infection of the human population from these kinds of opportunistic pathogens.

## H. PYLORI

*H. pylori* is known to be an active initiator of gastric carcinoma[75]. Moreover, the presence of *H. pylori* has been found to be associated significantly in atheromatous plaque[76]. In our study, we found significant *H. pylori* IgA antibody titer in CAD patients compared to controls and levels of H. pylori IgG were also high[8]. Furthermore, we also detected *H. pylori* DNA in atheromatous plaque by using quantitative real time PCR[6]. There are many other reports also suggesting the active involvement of H. pylori in the development of atherosclerosis[11,77,78]. However, it is important to know in which circumstances this bacterium activates oncogenesis and heart disease.

## CMV

CMV is an important pathogenic virus which causes many chronic diseases, such as cancer and atherosclerosis[79-82]. There is growing evidence supporting the synergistic effect of infectious agents in the progression of heart disease[50,83]. In our antibody titer detection assay and PCR assay, we found higher positivity for CMV in CAD patients compared to controls[6]. However, there is lots of space where we can identify the initiator organism or activator organism among many infections which may alter the immune response of systems.

## HUMAN HERPES VIRUSES

Evidence suggests that human herpes viruses have a potential link to arterial injury[83]. This hypothesis is proven in animal model studies, as well as a clinical epidemiological association between herpes viral infection and accelerated arteriosclerosis[84]. Studies suggested that eight members of the herpes virus family member may infect humans[85]. *Herpes simplex virus*-1 (HSV-1), *herpes simplex virus*-2 (HSV-2), *Epstein-Barr virus* (EBV) and CMV are widespread in the general population; they are primary candidates for investigations into viruses related to ath-

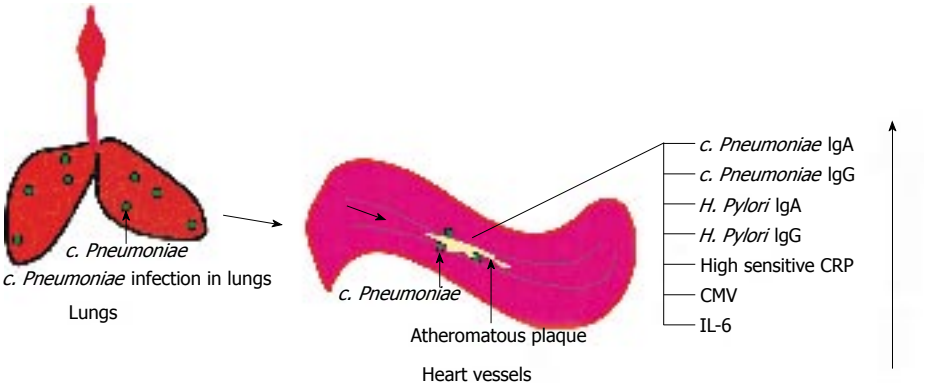


**Figure 1 A schematic representation of *Chlamydia pneumoniae* infection from lungs to heart.** IL: Interleukin-6; CMV: *Cytomegalovirus*; CRP: C-reactive protein; *c. Pneumoniae*: *Chlamydia pneumoniae*; *H. Pylori*: *Helicobacter pylori*.

erosclerosis[86].

A definite association was found for HSV-2 and subclinical coronary atherosclerosis[87]. This organism has been shown to be responsible for thrombogenic and atherogenic changes to host cells[88]. Earlier association of HSV-2 with hypertension has been reported[89]. These days, many studies emphasize the role of inflammatory pathways in atherosclerosis development[90]. Furthermore, recently Horváth *et al*[91] suggested that long-term HSV-2 infection may contribute to the development of atherosclerosis.

Many earlier studies demonstrated that only atherosclerotic tissues majorly have multiple infections[86]. Researchers also suggested that the synergistic impact of infection on atherogenesis is related to the aggregate number of pathogens infecting human beings[92]. Several serological studies demonstrated that all these pathogens (CMV, EBV, *hepatitis A virus*, HSV-1, HSV-2 and *C. pneumoniae*) are variably associated with the risk of CAD[4]. Shi *et al*[86] detected HSV-1, EBV and CMV DNA in the upper part of the non-atherosclerotic aortic wall and these viral DNA were also detected more extensively in atherosclerotic lesions compared to non-atherosclerotic tissue.

## DENTAL PATHOGENS IN ATHEROSCLEROSIS

There are several reports with an emphasis on the association of dental disease with elevated risk of myocardial infarction[93] and metabolic activity of the gut microbiota has also been shown to be related to blood pressure[94]. Several other studies also suggested an oral source for atherosclerotic plaque-associated bacteria[95,96]. *Chryseomonas sp* was present in endocarditis and all atherosclerotic plaque samples[97].

Many species, namely *Porphyromonas gingivalis*, *Tannerella forsythia* and *Actinobacillus actinomycetemcomitans,* are actively involved in periodontal disease and have been reported as a potential risk for the development of atherosclerosis[98]. Animal studies have also proven this association[99].

Beside these infectious agents, other factors that may incite vessel inflammation are oxidized low-density lipoprotein cholesterol and the metabolic syndrome, which are associated with a proinflammatory condition characterized by elevations of C-reactive protein or high sensitive C-reactive protein (hs-CRP)[100-102]. Metabolic syndrome is a cluster of abnormalities caused by elevation of multiple metabolic pathways, hyperinsulinemia, insulin resistance in body organelles, hyperglycemia, atherogenic dyslipidemia, abdominal obesity and hypertension[103-104]. In our study, we found the association of hs-CRP with elevated levels of *C. pneumoniae* IgA and H. pylori IgA[8]. We also observed higher proinflammatory cytokines interleukin-6 positively associated with hs-CRP[100]. Furthermore, our study extended the knowledge in respect of the association between C. pneumoniae IgA with Th-1, Th-2, Th-3 or adhesion molecules[101], although these markers were labeled as independent markers for CAD in our study[105]. There are many studies that suggest that Th-1 cytokines or proinflammatory cytokines are expressed earlier after *C. pneumoniae* infection followed by Th-2 kind of cytokines[106-107]; however mechanistically it moves in the case of humans is still evaded. We draw a schematic for *C. pneumoniae* in atherosclerosis (Figure 1).

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