Collaborative Multidisciplinary Workshop Report: The Role of Epidemiology Studies in Determining a Possible Relationship between *Chlamydia pneumoniae* Infection and Atherothrombotic Diseases

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The Workshop Group on Epidemiology was asked to identify weaknesses of current seroepidemiology studies that examine the association of *Chlamydiae pneumoniae* with atherothrombotic diseases and to identify the potential for multidisciplinary collaborative research at various levels. The group structured this report according to the following categories: overall concept, questions, measurement needs, informative populations, trials, other proposals, and recommendations.

Overall Concept

We began by taking a broad view of the relationship between *C. pneumoniae* infection and atherothrombotic diseases. A model was used to express various components, such as determinants and characteristics of infection, possible effect modifiers, and various outcomes, both clinical and subclinical (figure 1). The model was designed to indicate significant gaps in our knowledge.

As detailed in figure 1, the first stage of the model is "preinfection," which may be influenced by host factors, environmental factors, and other determinants of infection. The second stage, "infection," may be an incident, a reinfection, or persistent (i.e., chronic active) infection. It also was noted that there might be "other factors" that influence infection, including genetic or noninfectious factors and other infections.

Another component of the model is "outcome." The initial outcome is subclinical atherosclerosis, which may or may not progress to clinical events, such as myocardial infarction, coronary heart disease death, and peripheral vascular disease. Unfortunately, most epidemiology studies have looked at the relationship of *C. pneumoniae* infection and late clinical atherothrombotic diseases, leaving a dearth of studies looking at the primary prevention of atherosclerosis, potential interactions of *C. pneumoniae* with other risk factors, and additional high-risk populations.

Questions

The workshop group began with a statement of critical epidemiologic questions that remain to be answered regarding the association between *C. pneumoniae* infection and atherosclerosis:

1. What are the determinants of incident infection with *C. pneumoniae?*
2. How do genetic factors relate to the response to infection with *C. pneumoniae?*
3. Is progression of atherosclerosis associated with persistence of infection or reinfection with *C. pneumoniae?*
4. Are there persons for whom it can be predicted that *C. pneumoniae* infection is harmful and others in whom it is not?
5. How does the natural history of *C. pneumoniae* infection relate to the natural history of atherosclerosis?

Measurement Needs

Group members generally agreed that there are a number of deficiencies in serologic and other measurements that impede further seroepidemiology studies:

1. The organisms being studied and the serologic and antigen-detection methods used need to be standardized.
2. A means is needed for differentiating incident, reactivated, and chronic infections.
3. Methods for the timing and collection of serial blood specimens must be standardized, and more quantitative serology is needed.
4. Methods for collecting peripheral blood monocytes to assess chlamydial antigens must be standardized.

Other measurements that should be included in future epi-

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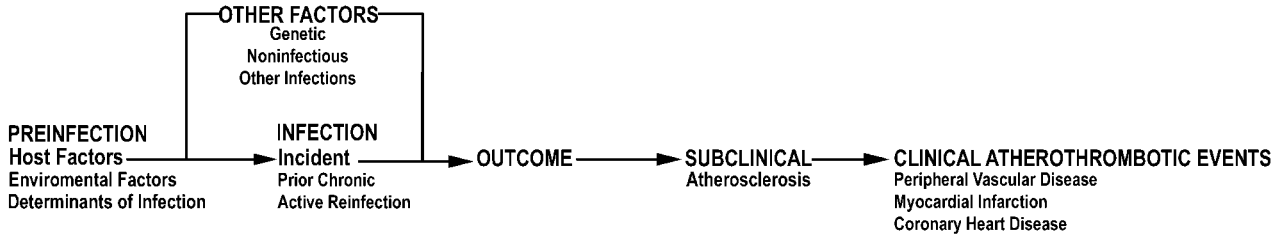

Figure 1.

demiology studies examining the association between infection with *C. pneumoniae* and atherothrombotic diseases include the following:

1. Noninvasive measurements of atherosclerosis in different vascular beds (e.g., coronary arteries, carotid arteries, adhesion factors).
2. Intermediate or surrogate markers of inflammation and adhesion molecules (e.g., inflammatory markers, acute-phase reactants, cytokines, adhesion factors).
3. Other factors potentially related to both infection and atherothrombotic diseases, such as lipids, dietary fat, and quantitative smoking measures (including measurements of early exposure to passive smoking).

Informative Populations

There was a concern that population subsets of particular interest have not been dealt with in past and current epidemiology studies. In particular, it was felt that the following population subsets should be considered in future studies:

1. Women.
2. Persons with high and low lipid levels.
3. Young adults (e.g., the Coronary Artery Risk Development in Young Adults Study) and army recruits.
4. Children and adolescents (e.g., the ongoing cohort study of childhood respiratory infections in Arizona).
5. Different ethnic groups (e.g., the Multi-Ethnic Study of Atherosclerosis).
6. Immunosuppressed persons.
7. Persons with prior chronic lung disease.

Trials

The workshop group noted that the large ongoing secondary prevention trials are excellent but do not deal comprehensively with all at-risk persons and are restricted to late stages of atherosclerosis. In particular, it was felt that there have been a deficient number of studies regarding the primary prevention of atherosclerosis, the selection of high-risk populations (as classified on the basis of evidence of chronic persistent infection), and potential interactions with other risk factors. For example, most trials are being conducted among middle-aged and older adults, while studies of younger men and women are needed to examine the effect of antibiotic treatment on the early stages of atherosclerosis.

It was also felt that both epidemiology studies and prevention trials should begin to define cohorts that would be suitable for vaccine trials in the event that a *C. pneumoniae* vaccine is developed.

Other Proposals

There was general agreement that epidemiology studies have not sufficiently dealt with analysis of multiple factors (i.e., effect modification). The problem here is that studies to date have not had large enough sample sizes to do this. The solution would be to pool data from databases from prior studies.

There was also discussion of the paradox that although most international studies showed a remarkable uniformity of past infection with *C. pneumoniae,* there did not seem to be an analogous uniformity in the prevalence of atherosclerosis in the countries under study. Some panel members felt that further international comparative studies are needed.

Recommendations

1. Further epidemiology studies regarding the association between *C. pneumoniae* and atherothrombotic diseases would benefit from a standardization of the means of measuring antibodies and antigens (see Measurement Needs section).
2. Most epidemiology studies have been done with middle-aged and older populations and in relation to clinical disease end points of atherosclerosis, such as myocardial infarction and coronary heart disease death. It is advised that epidemiology studies be extended to additional populations (see Informative Population section)
3. In regard to trials, the same concerns apply. The trials that are being conducted are primarily using middle-aged and older adults and are in relation to advanced stages of atherosclerosis, which is a logical place to start. However, future studies should extend to other populations, particularly women and younger men and women in early stages of atherosclerosis (see Trials section).