Antibiotic Treatment of *Chlamydia pneumoniae* for Secondary Prevention of Cardiovascular Events

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Since the publication of two preliminary antibiotic treatment trials for secondary prevention of cardiovascular events in persons with coronary artery disease (CAD), there has been increased interest in the possibility that the association between *Chlamydia pneumoniae* and atherosclerosis is causal and that antibiotic treatment can have a favorable effect on the complications and outcome of the disease. The impetus for these trials was the repeated demonstration by many investigators of an association of *C pneumoniae* and atherosclerosis by both seroepidemiology and demonstration of the organism in atherosclerotic lesions. A number of antibiotic treatment trials to evaluate reduction in cardiac events are being planned or initiated in many different countries. Adequately sized and properly designed trials are both desirable and justified. Two of the difficult questions in planning such trials are the inclusion criteria for subjects and the appropriate length of treatment. In choosing the subjects, one consideration is the expected rate of end-point events: cardiovascular death, myocardial infarction (MI), and defined episodes of unstable angina. A trial with a higher event rate will require fewer subjects and a shorter observation period. The results will be applicable only to the higher-risk patient. This is exemplified by the trial in Buenos Aires in which hospitalized patients with unstable angina and non-Q-wave MI were studied. Although this is an important study that could aid many patients, evaluation of antibiotic treatment of patients with stable CAD will have even wider applicability. A surprising finding in the London study, which used stable post-MI patients, is the high rate of events observed in the 40 untreated subjects (only half of whom were randomized controls). The 28% rate in 18 months is more than twice what might be expected, even in those who had experienced an MI in the past. An event rate of 5% to 6% per year could be expected in well-managed patients with proven CAD, including but not restricted to those with previous MI.

Most trial plans call for subjects to have *C pneumoniae* antibody. I believe this is wasteful and probably misleading. It is wasteful in that instead of initiating the study with the recruitment of subjects, there is a delay to obtain the serological results and then for another contact with the patient. We and others have found that 80% to 90% of persons with CAD have *C pneumoniae* antibody. Thus, few patients would be removed from the subject pool by the antibody test.

The idea that persons with *C pneumoniae* antibody are at greater risk of cardiovascular events may be misleading. We usually think of circulating antibody as indicating protection against a disease. In this case, it is being used to indicate susceptibility, on the basis of the seroepidemiological studies. Those studies showed that persons with CAD more frequently had antibody than did those without disease. Only a few studies have evaluated in a group of persons with CAD whether those who suffered events more frequently had antibody. The results are inconclusive. In addition, several investigations have shown that some persons without antibody have *C pneumoniae* in their atheromatous lesions.

Whether *C pneumoniae* antibody (or high-titer antibody) is a useful marker needs to be determined. It is important that serum be obtained from trial subjects at the onset and at intervals during observation. If the trial is successful, the sera could be studied not only for *C pneumoniae* antibody but also for inflammatory markers (C-reactive protein and others). Such a study might identify serum markers in persons with CAD who would be most likely to benefit from antibiotic treatment. It is also possible that such measures could help determine the desired length of treatment in individuals.

The length of treatment is a most difficult question. Some plans call for very short treatment periods of 1 month or less. Knowledge of the biology of chronic chlamydia infection suggests that short periods will be inadequate for lasting benefit. The elementary body (EB) form of the organism is the infectious nonreplicating form, and it is not susceptible to the action of antibiotics. EBs may exist in the body for weeks or longer and cause new cellular infection. Although short-term treatment might kill replicating organisms in atheroma and temporarily reduce inflammation, it would be unlikely to eliminate the organism from the lesion.

Standard 1 week to 10-day antibiotic treatment of acute respiratory infection due to *C pneumoniae* may be successful, but in adults a second course of antibiotic is often needed to eliminate persistent symptoms. It is questionable whether the organism is eliminated from the body. In animal model studies, pulmonary infection can be successfully treated with antibiotics, but *C pneumoniae* can later be reactivated by cortisone treatment. Treatment of trachoma, a chronic *Chlamydia trachomatis* infection, has been discouraging. Although reinfection complicates evaluation, it is clear that long-term treatment is necessary. The same is true of the often-unsuccessful attempts to eliminate *Chlamydia psittaci* from psittacine birds. Well-controlled, persistent, long-term antibiotic treatment is necessary for success.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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In planning the appropriate length of treatment for a trial, safety both for the subjects and the community should be considered. Macrolide and azalide antibiotics have been given to patients with AIDS for 1 to 3 years with minimal side effects. Although chlamydiae have not developed antibiotic resistance, long-term antibiotic therapy could contribute to resistance in other organisms. While not ignoring the possible unfavorable effects of the therapy, taking the known facts about treating chlamydia into account, we have recommended that treatment in a trial be for 1 year. It is important that the length of treatment be adequate to determine if a favorable effect can be found. The subjects should be observed for several years after cessation of therapy to determine if any favorable effect wanes with time, suggesting that therapy should be for a longer period.

Intermittent antibiotic therapy has been used for trachoma. The theoretical basis for this regimen is that by allowing suppressed chlamydia particles to initiate growth by removing the antibiotic, the organism would become more accessible to eradication by subsequent antibiotic treatment. A possible disadvantage of this approach to treatment of organism in atherosclerotic lesions is that stimulating growth of the organism might destabilize the plaque and lead to rupture. Although this is hypothetical, continuous therapy would probably be just as effective and possibly safer.

It is unfortunate that the first reported trial suggested two things that are unlikely to be true. One is that short-term therapy can be effective, and the other is that a fall in C pneumoniae antibody titer can result from antibiotic therapy. All available evidence suggests that even vigorous antibiotic therapy does not depress the antibody response in acute chlamydia infection nor lower the titer in chronic infection.

There is reason for concern with the publicity releases accompanying the publication of the two trials. Physicians should not assume that the enthusiasm for the studies indicated that antibiotic therapy for CAD is now appropriate. It is important to reiterate, as stated by their authors, that both trials are preliminary. Only larger, properly designed trials with the subjects observed for an adequate period of time can provide confidence that a new treatment is or is not appropriate. Enthusiasm for a new treatment modality should not obscure the need for careful scientific study.

References
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