

Antibiotics in the Prevention and Treatment of Coronary Heart Disease

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Seroepidemiology, pathology, and animal studies provide evidence for a possible association between *Chlamydia pneumoniae* infections and atherosclerosis, coronary heart disease, and myocardial infarction. If this association exists, then exposure to certain antibiotics may positively affect the clinical course after an acute ischemic cardiac event (secondary prevention) and affect the risk of developing a first-time myocardial infarction (primary prevention). Preliminary evidence from clinical trials suggests that treatment with new macrolide antibiotics may improve outcome after ischemic events, and evidence from a large case-control analysis indicates that exposure to tetracyclines or quinolones may reduce the risk of developing a first-time myocardial infarction. However, antibiotics for the treatment or prevention of ischemic heart disease must not be recommended yet. This review of published studies briefly summarizes the currently available literature on the effects of antibiotics on the risk of developing coronary heart disease and myocardial infarction.

The well-documented risk factors for atherosclerosis, coronary heart disease (CHD), and myocardial infarction (MI) (e.g. hyperlipidemia, hypertension, obesity, lack of physical exercise, smoking) do not sufficiently account for all new cases of MI. Thus, the search for additional risk factors that may play a role in the etiology of atherosclerosis and ischemic heart disease is important since ischemic heart disease is a major cause for morbidity and mortality in industrialized countries [1, 2].

Chlamydia pneumoniae was first detected in the 1960s, and ~15 years ago it was isolated from respiratory tissue and identified as a respiratory pathogen [3, 4]. The first report about a high prevalence of elevated antibody titers against this bacterium in subjects with MI [5] raised speculations about a possible causal involvement of *C. pneumoniae* infections in the etiology of atherosclerosis, CHD, and MI. The majority of a large number of seroepidemiology studies [6–13] added evidence to the increasing body of literature suggesting a possible relationship of *C. pneumoniae* infections to the pathophysiology of atherosclerosis and subsequent ischemic heart disease. This association, however, was not found in all studies: Three US-based analyses failed to show an association between serum antibody (IgG) and subsequent cardiac events [14–16]. In these studies, baseline IgG titers for subjects who developed CHD during follow-up were compared with those for control subjects. In

contrast, research on human pathology samples [17–26] and animal models [27–30] provided further evidence that infections with *C. pneumoniae* may play a role in the etiology of atherosclerosis and ischemic heart disease.

In a public health context, a risk factor for a disease needs to be sufficiently strong and prevalent to substantially contribute to the etiology of a disease. *C. pneumoniae* has been shown to be frequently involved in respiratory tract infections in all age groups, with its most likely mode of spread being respiratory secretions [31–35]. In industrialized countries, the prevalence of elevated antibody titers against *C. pneumoniae* as a marker for previous infections with this agent is between 50%–70% in a middle-aged population [33, 36]. Many subjects acquire a first infection in childhood, and reinfections with *C. pneumoniae* during adult life are common [33]. The presence of *C. pneumoniae* in subjectively healthy, asymptomatic subjects is not uncommon [37, 38]. Respiratory infections with *C. pneumoniae* are commonly characterized by a mild, self-limiting clinical course [36, 39], which often does not warrant medical attention. The main symptoms of such chest infections are mild fever, hoarseness, and cough. Due to their mild clinical course, it can be assumed that many respiratory tract infections with *C. pneumoniae* are not treated with antibiotics and that such infections could, therefore, become chronic.

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The Possible Role of Antibiotics for CHD and MI

If a causal association between bacterial infections with *C. pneumoniae* and the risk of developing CHD and MI indeed exists, one would expect that exposure to certain antibiotics may reduce the risk of developing ischemic cardiovascular dis-

eases. The treatment of choice for the eradication of *C. pneumoniae* is not well established. In vitro studies have been done to assess inhibitory concentrations for the elimination of bacteria, but information from in vivo studies in humans is scarce. Information from in vivo studies would be important because pharmacokinetic properties of antibiotics (i.e., the capability of penetrating infected tissue) play an important role in successfully treating infections in vivo.

On the basis of available information, tetracycline antibiotics (tetracycline, oxytetracycline, minocycline) are efficacious against *C. pneumoniae*. Furthermore, new macrolides (azithromycin, roxithromycin, clarithromycin) are also highly active, while erythromycin is of uncertain efficacy against *C. pneumoniae* unless used in high doses for at least 2 weeks [40–45]. The new quinolones (e.g., grepafloxacin) are also highly efficacious against *C. pneumoniae* in vitro, but data on larger patient series are lacking. The in vitro inhibitory minimal concentrations of older quinolones (ciprofloxacin, norfloxacin) suggest some antibacterial activity in vivo. Sulfonamides and β -lactam antibiotics (penicillins, cephalosporins) are considered not to be efficacious against *C. pneumoniae* [40–45]. It must, however, be emphasized again that a comparison of the relative effectiveness of various antibiotics is difficult because efficacy in vitro does not necessarily reflect clinical efficacy in vivo.

Treatment of CHD and MI with Antibiotics

Much attention has been paid to two clinical trials that studied the effect of newer macrolide antibiotics on the short-term outcome after an acute cardiac event [46, 47]. A comparison of these studies is limited by the fact that one focused entirely on subjects with increased titers against *C. pneumoniae* antibodies, while the other included subjects who did not have elevated antibody titers against *C. pneumoniae*. Furthermore, treatment with antibiotics started early after an ischemic event in one study [46] but at various points in time after an MI in the other [47]. Both studies were rather small ($n = 220$ and 202 , respectively) and yielded results that have to be viewed as intriguing but preliminary.

Gurfinkel et al. [46] treated patients who had unstable angina pectoris or non-Q-wave MI with placebo or with roxithromycin (150 mg orally) twice a day for 30 days and analyzed the data after 1 month [46] and 90 and 180 days [48]. The primary clinical end points were cardiac ischemic death, MI, or severe recurrent ischemia during follow-up. The authors reported a statistically significant difference between the treatment and the placebo group after 30 days of follow-up: In the placebo group, there were 9 subjects with a triple end point (i.e., severe recurrent angina, plus acute MI, plus ischemic death), and in the roxithromycin group, there was only 1 subject with a triple end point ($P = .036$) [46]. Of interest, this difference was weaker after 90 days (12 subjects in the placebo group and 3 in the

roxithromycin group had triple end points, $P = .058$) and non-significant after 180 days (14 subjects in the placebo group and 7 in the roxithromycin group had triple end points, $P = .334$) [48].

Gupta et al. [47] reported the findings of a clinical trial in which they included male subjects who attended a post-MI outpatient clinic. MI survivors were stratified into three groups according to their level of IgG antibodies; subjects with the highest antibody titers ($\geq 1/64$) were treated either with placebo or with azithromycin (500 mg/day) for 3 or 6 days. There was also a significant difference between the treatment and the placebo groups in the number of recurrent adverse cardiac events after a mean follow-up of 18 months. Subjects in the placebo group who had the highest antibody titers against *C. pneumoniae* had an ~4-fold increased risk of developing recurrent cardiac ischemia, compared with subjects with no increased antibody titers against *C. pneumoniae*. Subjects in the highest antibody titer group who received treatment with azithromycin did not have an elevated risk of developing recurrent ischemia, compared with subjects with no evidence of increased antibody titers against *C. pneumoniae* (odds ratio [OR], 0.9; 95% confidence interval [95% CI], 0.2–4.6) [47].

Anderson et al. [49] randomized subjects with elevated antibody titers and CHD to receive either placebo or a 3-month course of azithromycin. There was no difference with regard to the clinical outcome (adverse ischemic cardiac events), but the treatment group had significantly lower inflammation markers (e.g. interleukin-6, C-reactive protein) than the placebo group [49].

These secondary prevention trials suggest that the newer macrolide antibiotics, azithromycin and roxithromycin, have some effect on inflammation markers or clinical outcome (or on both) after an acute ischemic cardiac event; however, these findings do not yet allow the inference that there is a causal involvement of *C. pneumoniae* in the outcome and the survival rate of CHD patients. The observed results suggest some effect of these macrolide antibiotics, but it is not clear whether this has to do with eradication of *C. pneumoniae* or with some other pharmacologic nonantibiotic effects of macrolides. Indeed, the results reported by Anderson et al. [49] and the final analysis of Gurfinkel et al. [48] provide evidence that the beneficial effects of macrolides may be of rather short duration and based on acute anti-inflammatory effects of these compounds rather than on antibiotic properties.

Some antibiotics, such as tetracyclines or macrolides, have been shown to have pharmacologic effects beyond antibacterial efficacy, such as antioxidative effects and inhibitory effects on metalloproteinases [50–52], which in turn have been shown to be involved in plaque instability and rupture. Thus, inhibition of metalloproteinases may lead to stabilization of previously unstable atherosclerotic plaque and to an improvement of the

clinical outcome of patients with unstable CHD independently of any antibacterial efficacy of these antibiotics [50–55].

Prevention of First-Time Acute MI with Antibiotics

While these randomized clinical trials [46, 47, 49] have been conducted in patients with ischemic heart disease (i.e., secondary prevention of CHD), the effect of antibiotic exposure on the risk of developing a first-time cardiac ischemic event (i.e., primary prevention) has also been explored. While such a question would be extremely difficult to study prospectively because of the large number of subjects needed and the high costs involved, it was possible to study the effect of antibiotic exposure in large retrospective case-control analyses [56, 57]. These two epidemiology studies were based on two hypotheses: (1) infections with bacteria (e.g., *C. pneumoniae*) involved in the etiology of CHD are highly prevalent, the clinical course of such an infection is often mild, and appropriate eradication is rarely done in the general population; and (2) exposure to certain antibiotics may alter the risk of developing an acute MI, regardless of the indication for the antibiotic.

Meier et al. [56] analyzed the patient records and the exposure history to certain antibiotics of 3315 cases with an acute, first-time MI and of 13,139 control subjects who were matched to cases by age, sex, calendar year, and general physician's practice attended. The database used was the large and well-documented UK-based General Practice Research Database [58–60]. The study was restricted to subjects who were free of any documented clinical risk factors (e.g., angina pectoris, hypertension, hyperlipidemia, clotting disorders, diabetes mellitus) prior to the MI. For each study subject, antibiotic exposure in the 3 years prior to the date of the MI (or the corresponding date in the matched controls) was assessed from the computerized record and categorized as follows: users of tetracyclines only, macrolides only, quinolones only, sulfonamides only, penicillins only, cephalosporins only, or mixed exposure (i.e., subjects who received prescriptions for various antibiotics across categories). The results of the multivariate conditional logistic regression analysis, adjusted for smoking status and body mass index, yielded a significant difference between the proportion of controls and MI cases using tetracyclines (OR, 0.70; 95% CI, 0.55–0.90) or quinolones (OR, 0.45; 95% CI, 0.21–0.95) in the 3 years preceding the event date. No such effect was found for macrolides (predominantly erythromycin use; OR, 0.93; 95% CI, 0.73–1.20), sulfonamides (OR, 1.01; 95% CI, 0.79–1.29), penicillins (OR, 0.94; 95% CI, 0.85–1.04), or cephalosporins (OR, 0.90; 95% CI, 0.67–1.22) [54]. Further stratification of exposure by daily tetracycline dose yielded an OR of 0.71 (95% CI, 0.55–0.91) for users of a regular dose and of 0.67 (95% CI, 0.30–1.53) for users of a high dose. Compared with non-use of antibiotics, use of one to two prescriptions for a macrolide antibiotic in the 3 years preceding the date of the MI (or the corresponding date in matched controls) resulted in an OR of

1.03 (95% CI, 0.79–1.36), and use of three or more prescriptions resulted in an OR of 0.61 (95% CI, 0.34–1.11) [56].

In a similar retrospective case-control analysis using data from a large health maintenance organization (Group Health Cooperative of Puget Sound, Seattle), Jackson et al. [57] analyzed the records of 1796 cases with an incident MI and 4882 matched controls. They did not find any evidence for a protective effect of previous use of tetracyclines or erythromycin in the primary prevention of MI. Stratification by cumulative duration of treatment did not suggest a reduced risk of developing an MI in association with increasing treatment duration (1–14, 15–28, 29+ days). No stratified analysis according to daily dose of antibiotic use was presented; this may have added relevant information because a short treatment with a high daily dose may be more effective in treating a particular infection than a longer-term, low-dose treatment.

One possible explanation for the lack of effect observed by Jackson et al. [57] may be the fact that they included MI cases with a history of cardiovascular risk factors for MI (e.g., 26% of the case patients had angina pectoris, 75% had hypertension, and 27% had diabetes mellitus), while Meier et al. [56] included only previously healthy subjects (both cases and controls) who did not have cardiovascular or metabolic diseases predisposing for MI. The elimination of subjects with preexisting risk factors allows for better detection of an isolated risk factor of interest, while it is extremely difficult to measure the effect of a single newly hypothesized risk factor of interest in a population that already has numerous clinical diseases that predispose to development of the outcome of interest [61].

However, the intriguing findings of Meier et al. [56] also need careful interpretation for various reasons even though they may fit well in the hypothesis that bacteria susceptible to tetracyclines or quinolones are involved in the etiology of acute MI (e.g., *C. pneumoniae*). The observed effect (a reduced risk of developing a first-time MI after exposure to tetracyclines or quinolones) may indeed reflect a real finding and could be due to eradication of *C. pneumoniae* from the organism or, as discussed above, due to some other pharmacologic mechanisms, such as the anti-inflammatory effect of tetracyclines [50–55].

Alternative explanations, however, may be chance or residual confounding of poorly measurable parameters, such as socioeconomic status. The term “confounding” describes a spurious association between exposure and outcome due to the presence of a third factor, which is related both to the exposure and the outcome. Socioeconomic status is a multifactorial and poorly defined potential confounder, and it has been postulated that the observed association between infections and CHD may be explained, at least in part, by confounding by socioeconomic status; thus, subjects with low socioeconomic status have independently both a higher likelihood of acquiring respiratory tract infections (e.g., through household crowding) and of developing CHD (e.g., through low-quality, fat-rich diet, or other risk factors). In the analysis of Meier et al. [56], such con-

founding would have had to selectively affect exposure to tetracyclines or quinolones but not of other antibiotics; this suggestion seems unlikely but cannot be excluded entirely.

A major limitation of both the case-control analyses of Meier et al. [56] and Jackson et al. [57] is the fact that no information was available on seroepidemiologic parameters for cases and controls. Thus, the study population is a heterogeneous mixture of subjects with or without previous exposure to *C. pneumoniae*; in addition, subjects with previous infections to *C. pneumoniae* may substantially differ with regard to the number, severity, and timing of previous infections with *C. pneumoniae*. Furthermore, subjects may have been seropositive but acquired the infection after antibiotic exposure, while other subjects may indeed have had a *C. pneumoniae* infection prior to use of an antibiotic. It would have been of major interest, but unfortunately not feasible, to include only cases and controls with known antibody titers and a known temporal sequence of infection followed by antibiotic exposure; a subanalysis of these subjects—if possible—might have further clarified the issue. In addition, for many exposed subjects the magnitude of antibiotic use may have been too small for an effect on the outcome because antibiotics have been prescribed for various indications (other than respiratory tract infections with *C. pneumoniae*) not requiring longer-term or high-dose treatment.

Conclusion

Two randomized placebo-controlled trials [46, 47] of the secondary prevention of MI and a large retrospective case-control analysis exploring the effect of antibiotic exposure as primary prevention of MI [56] yielded intriguing evidence that certain antibiotics may have an effect on atherosclerosis, CHD, and MI. However, additional large-scale clinical trials are needed to collect data on whether certain antibiotics indeed alter the course of ischemic heart disease, as indicated in these preliminary findings. Such controlled trials need to be large in size and well-targeted to particular subgroups of interest, such as subjects with elevated antibody titers who are otherwise free of major risk factors for CHD. Until there is a better understanding of the molecular mechanisms of infection-induced atherosclerosis and more direct evidence for a causal pathway, use of antibiotics in the prevention or treatment of CHD is premature and must not be recommended outside well-controlled trials.

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