# Antibiotics against *Chlamydia pneumoniae* and prognosis after acute myocardial infarction

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**Background** There is mounting pathologic and immunologic evidence that *Chlamydia pneumoniae* plays a role in the atherogenic pathway. However, very few clinical studies have supported these findings.

**Methods** Using the administrative data of all patients ≥65 years of age who had an acute myocardial infarction (AMI) in Quebec between 1991 and 1995 (n = 26,195), we studied the relationship between the intake of antichlamydial antibiotics and post-AMI prognosis. Three groups were compared: patients exposed to (1) antichlamydial antibiotics, (2) sulfa-derivative antibiotics, to which *C pneumoniae* is not sensitive, and (3) neither of the above classes of antibiotics. Two periods of antibiotic exposure were explored: (1) during the first 3 months after AMI and (2) during the 6 months before AMI.

**Results** Patients in the 3 exposure groups were similar except for a slightly lower proportion of men in the sulfa-derivative antibiotics group. Among all patients who were exposed during the 3 months after AMI and who survived at least 3 months, the 1-year mortality rate was similar across the 3 groups (10.1%, 11.1%, and 10.4% for the antichlamydial, sulfa-derivative, and nonexposed group, respectively) but favored the antichlamydial group at 2 years (15.9%, 23.0%, and 20.0%). In adjusted survival analysis, patients in the sulfa-derivative and nonexposed groups were slightly more likely to die than patients in the antichlamydial group (relative risk [RR], 1.38; 95% confidence interval [CI], 1.04 to 1.82 and 1.29; 95% CI, 1.05 to 1.59, respectively). Among individuals treated during the 6 months before AMI, the adjusted risk of dying was similar in the sulfa-derivative and nonexposed groups compared with the antichlamydial group (RR 1.03, 95% CI 0.90 to 1.18 and 1.08, 95% CI 0.99 to 1.19, respectively).

**Conclusions** Exposure to antichlamydial antibiotics during the 3 months after AMI is associated with a small survival benefit, whereas exposure during the 6 months before AMI does not affect survival. (Am Heart J 2002;143:294-300.)

There is evidence to suggest that atherosclerosis is an inflammatory disease.[1] The lesions of atherosclerosis are believed to represent a series of highly specific cellular and molecular responses akin to an inflammatory reaction. Infectious microorganisms such as *Chlamydia pneumoniae* and herpes viruses are among several factors that may induce and promote inflammation and thereby atherogenesis. However, clinical evidence to support the role of an infectious agent in this process is limited.

*C pneumoniae* organisms have been found in atheromatous lesions of the coronary arteries[2-6] and in thoracic aorta specimens.[7] Seroepidemiologic case control studies reveal that patients with AMI are more likely to have antibodies against *C pneumoniae*,[8,9] but prospective cohort studies show conflicting serologic data.[10-16] A recent large clinical case control study has shown that patients exposed to an antibiotic to which *C pneumoniae* organisms are sensitive were less likely to sustain a cardiac event in the months after their exposure to that antibiotic.[17,18] Finally, evidence of a treatment effect is sparse. A few small randomized clinical trials of antibiotic treatment for *C pneumoniae* in patients with evidence of coronary artery disease[19-22] have suggested a potential relationship between infection and atherosclerosis. In spite of these various sources supporting the role of *C pneumoniae* in the atherogenic process, further data are required before antibiotics can be prescribed for the primary or secondary prevention of coronary artery disease.

In this study, we investigate the relationship between exposure to antibiotics to which *C pneumoniae* is sensitive and prognosis after AMI. We analyzed the administrative information of all patients ≥65 years old who underwent a first AMI between 1991 and 1995 in Quebec, Canada.

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# Methods

## Identification of study population

The identification of patients with AMI and information on their medical care were obtained from the Quebec government administrative databases. Annual cohorts of patients undergoing AMI were constructed by use of longitudinal data files of hospital admissions from January 1, 1991, to December 31, 1995. The hospital discharge summary database records provide universal information on hospital admissions, because all citizens and legal residents in the province benefit from full coverage health insurance. With these data, we identified patients for inclusion in the AMI cohort on the basis of a hospitalization for a main diagnosis of AMI (ICD9 code 410). To maximize the comparability of the groups, only first AMIs were included by ascertaining the absence of a code for AMI during the 3 years before the AMI admission. We also used this discharge database to identify admissions that followed the index AMI for diagnoses such as recurrent AMI. For each of these diagnoses, we chronologically ordered the related admissions and recorded their duration. In this analysis, we included only patients with AMI between 1991 and 1995 who were ≥65 years of age at the time of their first AMI.

### Antibiotic use

To describe the drug treatment patterns for these patients with AMI, we used the Quebec drug claims database. This administrative database contains records on outpatient drug prescriptions for all individuals ≥65 years of age and older and for welfare recipients.

At the time of the study, these patients had all their outpatient medications paid for by the provincial government. A patient who was given a prescription by a physician and presented the latter to a pharmacist could receive the drug immediately without any copayment. There was no incentive for patients to pay for medication out of pocket. Drugs given during hospitalization are not covered under this plan. The cost of these drugs is absorbed by hospital budgets. It is possible that some patients may have received these antibiotics while hospitalized. However, if they were admitted because of a *C pneumoniae*–related infection, they would likely be discharged receiving an oral form of the antibiotic to finish the course of treatment on an outpatient basis. Such a prescription would then be captured in the outpatient drug database.

### Vital status

To assess the vital status of the patients with AMI, we used both the discharge and physicians' claims databases. The all-cause mortality variable in the discharge database was coded if and only if a patient died within the hospital setting, whereas the physicians' claims database mortality variable is built on death certification that can occur out of hospital. This latter variable is constructed by comparing vital status information provided by the Quebec institutions that manage pensions and car insurance. Therefore a date of death exists in the physicians' claims database if and only if those two institutions agreed on mortality of one individual. In addition to these mortality variables, there is a code in the physicians' claims database for death certification and the date of the latest treatment received. Using every source of information to document mortality rates, we ascertained the vital status in 99.75% of the patients with AMI in our database. Average follow-up was 2.4 years.

### Exposure groups and time of exposure

For this study, we identified three groups of antibiotic users. One group included patients who were prescribed antibiotics to which *C pneumoniae* is sensitive: tetracyclines, macrolides, or quinolones (n = 5511). A second group included individuals treated with sulfa-derivative antibiotics to which *C pneumoniae* organisms are not sensitive (n = 3099). This group was constructed to identify a group who might be subjected to the same selection process as the antichlamydial group. Finally, a third group included patients treated with neither of the above classes of antibiotics but possibly with other types of antibiotics to which *C pneumoniae* is not sensitive or no antibiotics at all (n = 13,937). To isolate the antichlamydial effect, patients exposed to both antichlamydial antibiotics and sulfa-derivative antibiotics were excluded from the analysis (n = 3648). Thus all patients in the cohort were divided according to their exposure history at any time between 1991 and 1995.

We then identified two different times of exposure to antibiotics in relation to the index AMI: (1) exposure during the first 3 months after AMI among patients who survived at least 3 months after AMI to assess possible early protective effects of antichlamydial antibiotics and (2) exposure during the 6 months before AMI to investigate whether antibiotics could have a plaque-stabilizing effect and to assess whether, even among individuals with AMI, those exposed before have a better course after AMI. For exposure during the 3 months after AMI, we excluded patients who were exposed during the 6-month period preceding AMI and for exposure during the 6 months before AMI, we excluded individuals who were also exposed during the first 6 months after AMI. The cutoff of 3 and 6 months were arbitrarily chosen to ensure adequate sample size.

### Statistical analysis

Kaplan-Meier methods were used to construct cumulative survival curves for the 3 exposure groups by time of exposure. Cox proportional hazards models were developed to explore the effects of baseline variables on the estimated effects of antibiotic exposure.

# Results

## Patient characteristics

Depending on the time of exposure, the number of individuals in the 3 exposure groups differed (Table I). Overall, the median age of the 3 exposure groups were similar regardless of the time of the exposure. The proportion of men was slightly lower in the sulfa-derivative compared with the antichlamydial and nonexposed groups probably because women in this age group often get treated for urinary tract infections with sulfa-derivative antibiotics. The prevalence of diabetes mellitus was slightly lower in the nonexposed group compared with the other 2 groups. Length of hospital stay

**Table I.** Characteristics of study patients according to time and type of exposure

| | Time of exposure | | | | | |
|---|---|---|---|---|---|---|
| | During the 3 months after AMI | | | During the 6 months before AMI | | |
| **Exposure group** | **Anti-chlamydial antibiotics** | **Sulfa-derivative antibiotics** | **Non-exposed** | **Anti-chlamydial antibiotics** | **Sulfa-derivative antibiotics** | **Non-exposed** |
| No. of patients | 556 | 425 | 8184 | 1178 | 687 | 11,072 |
| Age (y) | | | | | | |
| Median | 74 | 76 | 73 | 75 | 76 | 75 |
| IQR | (69, 80) | (70, 81) | (68, 79) | (70, 80) | (70, 81) | (69, 80) |
| Sex (% male) | 54.9 | 46.8 | 57.5 | 52.2 | 45.9 | 54.2 |
| Diabetes mellitus (%) | 25.5 | 24.5 | 19.8 | 23.7 | 25.2 | 20.4 |
| LOS (d) | | | | | | |
| Median | 11 | 11 | 11 | 10 | 11 | 10 |
| IQR | (8,18) | (9,16) | (8,16) | (7,16) | (7,16) | (6,15) |
| Heart medications (% at 30 days after AMI) | | | | | | |
| Beta blockers | 36.9 | 38.4 | 44.5 | 30.3 | 28.7 | 31.7 |
| ACE inhibitors | 35.3 | 40.5 | 32 | 26.7 | 26.8 | 23.9 |
| Heart procedures (% at 30 days after AMI) | | | | | | |
| Catheterization | 19.8 | 14.4 | 18.3 | 16 | 15 | 14.1 |
| Angioplasty (PTCA) | 6.3 | 4.9 | 5.8 | 4.8 | 4.1 | 4.6 |
| Bypass (CABG) | 4.5 | 3.8 | 2.5 | 1.8 | 1.5 | 1.9 |
| Revascularization (PTCA or CABG) | 10.8 | 8.7 | 8.2 | 6.1 | 5.5 | 6.4 |

*IQR,* Interquartile range; *LOS,* length of stay; *ACE,* angiotension converting enzyme.

for the treatment of the index AMI was similar across exposure groups. There were small treatment differences across groups in terms of the heart medications and procedures received after AMI that could have potentially affected post-AMI outcomes (Table I). For example, the nonexposed group was prescribed slightly more beta blockers and angiotensin-converting enzyme inhibitors whereas the antichlamydial group was slightly more likely to undergo a revascularization procedure after AMI. However, these proportions were not adjusted for the differences in age and sex distribution across groups.

### Outcomes

The cumulative incidences of death and recurrent AMI across all comparison groups are shown in Table II. For individuals exposed during the first 3 months after AMI, the unadjusted 1-year mortality rate was similar across all exposure groups (10.1%, 11.1%, and 10.4% for the antichlamydial, sulfa-derivative, and nonexposed group, respectively), although with time, a survival benefit became apparent in the antichlamydial group (Figure 1). The unadjusted 2-year mortality rate was as follows: 15.9%, 23.0%, and 20.0% for the antichlamydial, sulfa-derivative, and nonexposed group, respectively). In contrast, rates of recurrent AMI were similar across comparison groups (Table II, Figure 2).

Taking into account the differences in age and sex distribution, as well as treatment after AMI (use of heart medications and revascularization), we performed a Cox proportional hazards survival analysis (Table III). For the period of exposure during the first 3 months after AMI, patients were more likely to die in the sulfa-derivative and nonexposed groups compared with patients in the antichlamydial group, suggesting a small survival benefit of antichlamydial antibiotics after AMI (relative risk [RR], 1.38; 95% confidence interval [CI], 1.04 to 1.82 and 1.29; 95% CI, 1.05 to 1.59, respectively). Adjustment for treatment differences and for an age/group interaction did not significantly alter the magnitude, direction or precision of the estimates. For the period of exposure during the 6 months after AMI, there was no mortality or recurrent AMI differences across the 3 groups after adjustment for age, sex and treatment differences (Table III, Figures 3 and 4).

## Discussion

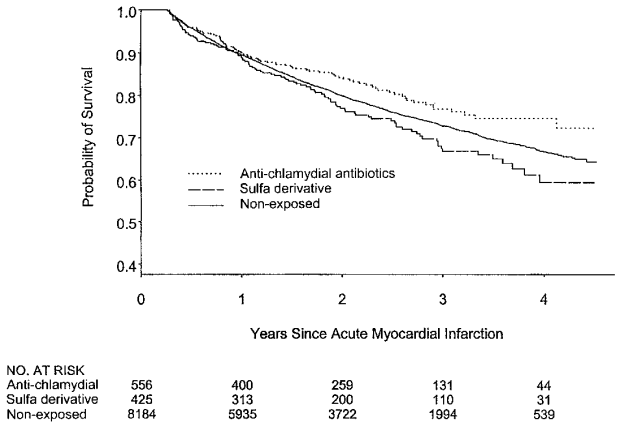
In this study of close to 30,000 patients with a first AMI, we found that patients exposed to antichlamydial antibiotics during the first 3 months after AMI have an improved prognosis compared with patients exposed to other antibiotics. However, exposure during the 6 months before AMI had no impact on prognosis. Given the low magnitude of the effect size, prevention or treatment of AMI with antibiotics against *C pneumo-*

**Table II.** Differences in mortality and recurrent acute myocardial infarction between study groups by time of exposure

| | Time of exposure | | | | | |
|---|---|---|---|---|---|---|
| | During the 3 months after AMI | | | During the 6 months before AMI | | |
| | Anti-chlamydial antibiotics | Sulfa-derivative antibiotics | Non-exposed | Anti-chlamydial antibiotics | Sulfa-derivative antibiotics | Non-exposed |
| Mortality % (95% CI*) | | | | | | |
| 1 year | 10.1 | 11.1 (-3.0-5.3) | 10.4 (-2.4-3.1) | 35.1 | 38.0 (-1.0-8.2) | 38.8 (0.6-6.3) |
| 2 years | 15.9 | 23.0 (1.4-12.8) | 20.0 (0.7-7.8) | 41.5 | 44.4 (-2.2-7.5) | 47.3 (0.4-6.6) |
| Recurrent AMI % (95% CI) | | | | | | |
| 1 year | 10.9 | 11.9 (-3.1-5.2) | 10.9 (-2.6-3.0) | 10.1 | 10.2 (-2.9-4.5) | 9.0 (-2.8-1.9) |
| 2 years | 13.5 | 17.2 (-1.4-8.8) | 14.9 (-1.9-4.5) | 12 | 11.0 (-4.4-3.8) | 11.1 (-1.8-3.5) |

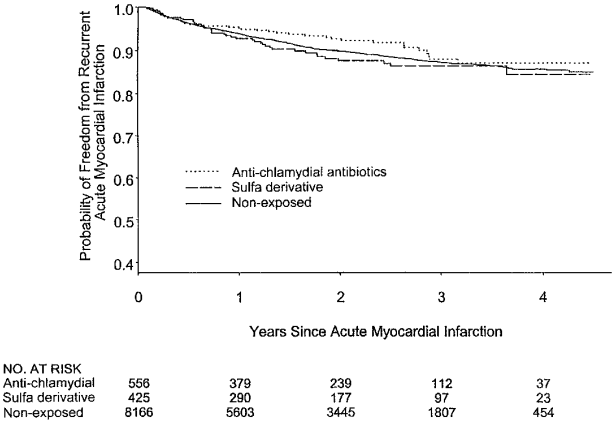
*CI,* Confidence interval around the difference in mortality between the groups.
The antichlamydial antibiotic group is the reference category.

**Figure 1**




Kaplan-Meier analysis of probability of survival among non-exposed, sulfa-derivative, and antichlamydial groups with exposure during first 3 months after acute myocardial infarction.

**Figure 2**




Kaplan-Meier analysis of probability of freedom from recurrent acute myocardial infarction among nonexposed, sulfa-derivative, and antichlamydial groups with exposure during 3 months after acute myocardial infarction.

*niae* infection does not appear to be warranted at this point. However, a large randomized trial is certainly indicated.

Very few studies have assessed the clinical impact of the intake of antichlamydial antibiotics on after AMI prognosis. Our retrospective cohort study allowed the evaluation of the effects of exposure to antichlamydial antibiotics before and after AMI on survival. Because of the large number of patients in this cohort, 3 different exposure groups and 2 different times of exposure could be examined. The results of our study are consistent with that of 3 recent small clinical trials that examined the efficacy of antibiotic therapy against *C pneumoniae* after a diagnosis of coronary artery disease.

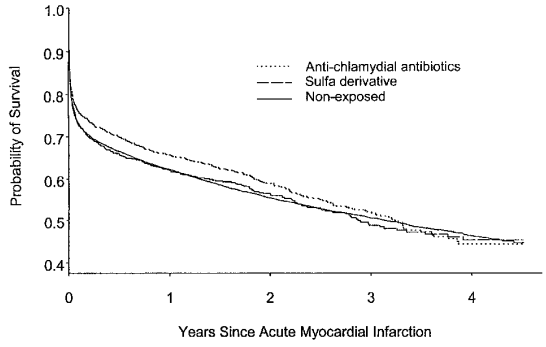
Gupta et al[20,21] randomized 60 patients with AMI who were seropositive for antichlamydial antibodies to either oral azithromycin or placebo. Although an efficacy trial, the analysis of the results focused on the strong positive relationship between anti-chlamydial antibody titers and cardiovascular events. Yet, there was a 5-fold reduction in cardiovascular events between the treatment and placebo group but because of the small size of the study, the precision of the estimate was low (odds ratio 0.2; 95% CI; 0.05 to 0.8). The randomized trial of roxithromycin in non-Q-wave coronary syndromes (ROXIS) assigned 202 patients to either roxithromycin or placebo.[19] There was a small reduction in a combined endpoint (recurrent angina, AMI,

**Table III.** Relative risks of mortality and recurrent acute myocardial infarction

| | Time of exposure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | During the 3 months after AMI | | | | During the 6 months before AMI | | | |
| | Sulfa-derivative antibiotics | | Nonexposed | | Sulfa-derivative antibiotics | | Nonexposed | |
| **Variables in model** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** |
| Mortality | | | | | | | | |
| Age, sex | 1.38 | 1.04 - 1.82 | 1.29 | 1.05 - 1.59 | 1.03 | 0.90 - 1.18 | 1.08 | 0.99 - 1.19 |
| Age, sex, age • sex | 1.38 | 1.04 - 1.82 | 1.29 | 1.05 - 1.59 | 1.03 | 0.90 - 1.18 | 1.08 | 0.99 - 1.19 |
| Age, sex, medications | 1.4 | 1.06 - 1.84 | 1.32 | 1.08 - 1.63 | 1.03 | 0.90 - 1.19 | 1.11 | 1.01 - 1.21 |
| Age, sex, revascularization | 1.37 | 1.04 - 1.81 | 1.28 | 1.04 - 1.57 | 1.03 | 0.90 - 1.18 | 1.08 | 0.99 - 1.19 |
| Recurrent AMI | | | | | | | | |
| Age, sex | 1.07 | 0.77 - 1.49 | 1.01 | 0.81 - 1.28 | 1 | 0.76 - 1.31 | 1.03 | 0.87 - 1.23 |
| Age, sex, age • sex | 1.07 | 0.78 - 1.49 | 1.01 | 0.80 - 1.28 | 1 | 0.76 - 1.32 | 1.04 | 0.87 - 1.24 |
| Age, sex, medications | 1.08 | 0.77 - 1.50 | 1.02 | 0.81 - 1.29 | 1 | 0.76 - 1.31 | 1.04 | 0.87 - 1.24 |
| Age, sex, revascularization | 1.07 | 0.77 - 1.49 | 1.02 | 0.81 - 1.28 | 0.99 | 0.75 - 1.31 | 1.03 | 0.86 - 1.23 |

*RR,* Relative risk.
The antichlamydial antibiotic group is the reference category.

**Figure 3**

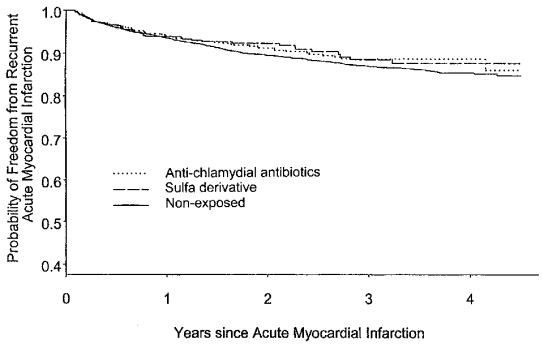



NO. AT RISK

| | | | | | |
|---|---|---|---|---|---|
| Anti-chlamydial | 1178 | 656 | 406 | 203 | 55 |
| Sulfa derivative | 687 | 375 | 247 | 130 | 56 |
| Non-exposed | 11072 | 5935 | 3722 | 1994 | 539 |

Kaplan-Meier analysis of probability of survival among nonexposed, sulfa-derivative, and antichlamydial groups with exposure during 6 months before acute myocardial infarction.

**Figure 4**




NO. AT RISK

| | | | | | |
|---|---|---|---|---|---|
| Anti-chlamydial | 880 | 613 | 372 | 177 | 45 |
| Sulfa derivative | 494 | 354 | 223 | 113 | 48 |
| Non-exposed | 7938 | 5603 | 3445 | 1807 | 454 |

Kaplan-Meier analysis of probability of freedom from recurrent acute myocardial infarction among nonexposed, sulfa-derivative, and antichlamydial groups with exposure during 6 months before acute myocardial infarction.

and death) in the treatment compared with the placebo group but because of the small study size, the events were rare. Finally, Muhlestein et al[22] randomized 302 patients with prior history of AMI, bypass, or angiographically-documented coronary artery disease who were seropositive for *C pneumoniae* to azithromycin or placebo. Cardiovascular events were rare (n = 47) and did not differ between the 2 groups. In all 3 studies, the small beneficial clinical effects were unrelated to a change in *C pneumoniae* antibody titers.

We also investigated the effect of antichlamydial exposure before the AMI to assess their potential impact on prognosis. The relationship, if any, between *C pneumoniae* and atherosclerosis is unclear. In addition to possibly contributing to initiation and progression of atherosclerosis, *C pneumoniae* may affect plaque stability either through its presence in the plaque or through mediators of inflammation.[23] We studied exposure to antichlamydial antibiotics during the 6 months before AMI and failed to show any associ-

ation. Because of our study design, we could not test whether treatment could prevent a first AMI. However, Meier et al[17] showed that exposure within only 3 years with antichlamydial antibiotics was enough to prevent AMI, suggesting that the antibiotic effect is that of a nonspecific antiinflammatory effect rather than an antiatherosclerotic one. On the other hand, because our group of patients receiving sulfa-derivative antibiotics had poorer outcome than patients receiving antichlamydial antibiotics, it is more likely that the effect is due to specific antichlamydial activity. An antibacterial effect would presumably act more in the prevention of atherosclerosis, and an exposure period of 3 years might be too short and too late.

There are several limitations to that study. The identification of patients on the basis of their exposure to antibiotics could have led to the selection of a sicker patient population. However, there is no reason to believe that patients given antibiotics for *C pneumoniae* would have a worse prognosis after AMI, thereby unmasking a beneficial effect of antibiotics treatment. The identification of a group (exposed to antibiotics to which *C pneumoniae* is not sensitive) through a similar selection process helped rule out the possibility of such a selection bias because the demographic, clinical, and outcome characteristics of these 2 groups were similar, and their mortality rate was also similar. However, given the observational nature of the study, selection bias could always explain the results even after statistical adjustments. Lastly, because our cohort was made up of patients with AMI, we could not explore the effects on antichlamydial antibiotics in preventing AMI but we investigate whether prior exposure improved prognosis post-AMI.

In conclusion, exposure to antichlamydial antibiotics during the first 3 months after AMI appears to confer a survival benefit, whereas exposure during the 6 months before AMI does not affect survival. The magnitude of the effect is too small to warrant the widespread use of antichlamydial antibiotics to prevent AMI or improve survival after AMI. However, our results support further large-scale prospective studies of *C pneumoniae* eradication for prevention and treatment of acute coronary artery syndromes.

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