AGE-DEPENDENT ASSOCIATIONS OF ACUTE VASCULAR EVENTS WITH PRIOR ANTIBIOTIC PRESCRIPTIONS: IMPLICATIONS FOR TREATMENT TRIALS OF *CHLAMYDIA*-ASSOCIATED ATHEROSCLEROSIS

Hahn, David L.,*[1] and Werner, Nina L.[2]

[1]Dean Medical Center, [2]Dean Health Plan and [2]Dean Foundation, Madison, WI

INTRODUCTION

Chlamydia pneumoniae infection of vascular endothelium has been associated with the atherosclerotic process [1]. Two pilot randomized studies of antibiotic administration in patients with atherosclerosis have been published recently and longer term followup in larger numbers of patients are planned [2, 3]. One of us (DLH) became concerned about a potential risk of acute vascular events following antibiotic administration that could have implications for antibiotic treatment trials in atherosclerosis.

Case reports

Two males (ages 77 and 75) were treated with antibiotics (case 1 received doxycycline, 100 mg twice daily for 4 weeks; case 2 received azithromycin, 1000 mg once weekly for 6 weeks) for chronic asthmatic bronchitis and both improved after treatment. At the conclusion of 4 weeks of doxycycline treatment, case 1 was hospitalized for stroke symptoms and died unexpectedly of an autopsy-proven ruptured abdominal aortic aneurysm and ulcerative atherosclerosis. Two months after finishing azithromycin treatment, case 2 had a mild stroke from which he made a complete recovery. During hospitalization he was found to have bilateral moderate to severe carotid artery stenosis. Both patients were seroreactive against *C. pneumoniae* (IgG titers of 1:128 and 1:1024, respectively). Polymerase chain reaction (PCR) testing of atheroma material derived from an elective abdominal aortic aneurysm resection prior to antibiotic treatment in case 2 was positive for *C. pneumoniae* (Lee Ann Campbell, personal communication).

We hypothesized that antibiotics could destabilize atherosclerotic plaque by release of breakdown products of killed chlamydia organisms, analogous to the immunopathologic reaction reported following penicillin treatment for syphilis (Jarisch-Herxheimer reaction) [4]. The purpose of this study was to determine whether hospitalization for acute vascular events was associated with antibiotic prescriptions within the preceding six months in a defined clinical population.

METHODS

We utilized the database of a health maintenance organization (HMO), located in south central Wisconsin, that contained clinical and pharmaceutical data for 160,194 enrollees as of January 1, 1996. The HMO database contained records of hospitalizations, diagnoses and all pharmaceutical prescriptions billed to the HMO. HMO contracts covered the cost of prescriptions (minus a copayment) for all patients under age 65 and for 90% of patients over age 65. Pharmacists were also asked to report medications not billed to the HMO, but no data were available to

verify compliance with this request. Only patients continuously enrolled during the study period (June 1, 1995 to December 31, 1996) were eligible for analysis.

Cases were defined as all patients with a hospitalization in 1996 for an acute vascular event, defined as any one of the following diagnoses and ICD-9 codes: unstable angina, 411.1; acute myocardial infarction (AMI), 410.xx; transient ischemic attack (TIA), 435.9; occlusion or stenosis of precerebral artery (OCC/STEN), 433.xx; cerebrovascular accident (CVA), 434.xx,436; and ruptured abdominal aortic aneurysm (AAA), 441.xx. Distribution (%) of case diagnoses was: angina (38.3%), AMI (25.3%), TIA (11.4%), CVA (21.2%), OCC/STEN (2.0%), AAA (1.7%). Only the first qualifying hospitalization in 1996 was recorded.

Up to 4 controls per case were matched by sex and year of birth from the remaining HMO enrollees with continuous coverage. In analyses of time period between prescription and hospitalization for vascular event, controls were assigned the admission date of their matched case. Of 980 total cases, 671 could be matched with 4 controls each, 43 with 3 controls, 83 with 2 controls, 157 with one control and 26 could not be matched due to an insufficient number of unaffected elderly HMO members (total 3,136 controls).

All antibiotic prescriptions (ABX) in the six month (182 day) time period before the hospital admission date for the acute vascular event (for cases) and the proxy admission date (for controls) were recorded for the following antibiotic classes (AHFS code): beta-lactams (08:12.06, 08:12.07, 08:12.16), macrolides (08:12.12), tetracyclines (08:12.24), quinolones (08:22), sulfonamides (08:24) and miscellaneous anti-infectives (08:40). Overall, 1631 prescriptions were recorded for 877 (21.3%) of the 4116 cases and controls (one prescription for 505 patients, two prescriptions for 199 and three or more for 173).

Univariate statistics used were the Chi-square test and Fishers Exact test for categorical variables. Logistic regression was used to control for confounding and to test for interactions. ANOVA was used to test significant differences for continuous variables. $P < .05$ was regarded as significant.

RESULTS

Antibiotics were prescribed less frequently in summer months (19% of prescriptions) compared to other seasons (26% to 29%). Young adults were much more likely to have been prescribed an antibiotic than were the elderly (27% of 30 year-olds v 5% of 90 year-olds, P for trend<.0001). There were no differences in prescribing rate between the sexes, nor was there a significant variation in monthly hospitalization rate for acute vascular events throughout 1996.

Sex distributions for cases and controls were similar (60.6% and 62.7% male, respectively, P=NS). Cases were somewhat older than controls (70.3 and 66.6 years, respectively, P<.0001). Youngest and oldest cases and controls were 31 and 32, and 98 and 96 years, respectively.

Frequency of any ABX within 6 months was 183 (18.7%) of 980 for cases and 694 (22.1%) of 3136 for controls (P=.02). For patients receiving multiple ABX, the proximate ABX was defined as the prescription dispensed nearest the time of hospitalization. For cases and controls who received any antibiotic prescriptions, Table 1 presents relationships of proximate ABX to hospitalization (cases) or proxy hospitalization date (controls).

Table 1. Number of months between most recent ABX and hospitalization for an acute vascular event, no(%)

	1	2	3	4	5	6
Cases	55(30)	32(18)	30(16)	23(13)	22(12)	21(12)
Controls	191(28)	138(20)	102(15)	96(14)	88(13)	75(11)

The proportion of proximate ABXs dispensed to cases in the month prior to an acute vascular event was significantly greater than for other time periods (P for trend<.01). A similar pattern was present for the proxy hospitalization date in controls (P<.0001).

In logistic models including ABX as the sole independent predictor variable (any within 6 months, or proximate within one month of hospitalization) the odds ratio (OR) for an association of antibiotic with hospitalization was significantly less than unity, consistent with the univariate data. However, after including age and an age*ABX interaction term in the models, a significant (P<.0001) age-dependent association of ABX and hospitalization for acute vascular events was revealed. Table 2 illustrates this age-dependent association for ABX within one month of the acute vascular event.

Table 2. ABX within one month of an acute vascular event, no. with antibiotic/total (%)

Age group (y)	Cases	Controls	OR (95%confidence interval)*
<60	27/215 (13)	47/858 (6)	1.6 (1.2 to 2.0)
60-69	15/226 (7)	48/904 (5)	1.1 (.83 to 1.5)
≥70	13/539 (2)	96/1374 (7)	0.6 (.45 to .81)
P-trend	≤.0001	NS	

*adjusted for age within strata, sex and season of hospitalization

DISCUSSION

This study described patterns of antibiotic use, including associations with hospitalization for acute vascular events (mainly heart and brain attacks) in a community-based population of prepaid health plan enrollees. Younger patients were much more likely than the elderly to have received a prescription for an antibiotic. This contrast was so great that it cannot be explained by the fact that 10% of the Medicare population did not have drug benefits and might not have had prescriptions recorded in the HMO database. Perhaps younger adults have more respiratory illnesses because of greater exposure to young children or are more likely to seek or receive an antibiotic than are elderly patients who were raised in the preantibiotic era.

In univariate analyses that did not take age into account, there were slight but significant negative associations of antibiotic prescriptions with acute vascular events. When age was taken into account, significant age-dependent associations of antibiotic prescriptions with acute vascular events emerged in the multivariate analyses (Table 2). Antibiotic prescriptions had a positive association with hospitalization for an acute vascular event in patients below the age of 60 (OR 1.6) but a negative association (OR 0.6) was noted in patients 70 years of age and older. These associations were strongest for antibiotics prescribed during the month before

hospitalization and were present for both heart and brain events and for different antibiotic classes (data not shown). Clustering of antibiotic prescriptions in the (proxy) month before hospitalization was also present in controls. This observation, and the fact that associations were not limited to antibiotic classes with known *in vitro* antichlamydial activity, cast some doubt on the specificity of the findings. There was no association of antibiotic prescriptions and acute vascular events for patients 60-69 years of age.

In late syphilis, immunopathologic reactions to antibiotic treatment can be disastrous if the lesions are located in coronary arteries [4]. Thus there is a biologic precedent for the hypothesis that antibiotics could disrupt chlamydia-infected atheromatous plaques, leading to vascular accidents. Earlier "soft" plaque might be more susceptible to such antibiotic effects than later "hard" (fibrotic) plaque, leading to the age-dependent associations noted in this study. On the other hand, an equally plausible explanation for the associations found in this study is that antibiotic prescribing was a proxy for the presence of acute respiratory illnesses that have been associated with vascular accidents in several previous studies [5].

In addition to the usual problems attributed to use of an administrative database for research purposes, this analysis has several specific limitations. Low cost antibiotics (total cost less than the HMO co-pay) that were paid out of pocket by HMO enrollees with drug coverage might not have been systematically reported. Patients might not have taken medicine as prescribed and reported to the HMO. Importantly, study of conventional courses of antibiotics studied here might not apply to the type of long-term antibiotic administration contemplated in studies of *C. pneumoniae* and atherosclerosis. Last, the association of antibiotics within 30 days of an acute vascular event could be a proxy for some other cause such as an acute infection, as discussed. Nevertheless, the results reported here suggest that, in monitoring upcoming treatment trials of antibiotics in atherosclerosis, it would be prudent to age stratify adverse events so as not to miss potential significant harm affecting some subgroups of patients, as may have occurred in this study population.

REFERENCES
1. Grayston JT. Chlamydia in atherosclerosis. *Circulation*. 1993; 87: 1408-1409.
2. Gupta S, Leatham EW, Carrington D, Mendall MA, Kaske JC, Camm AJ. Elevated Chlamydia pneumoniae antibodies, cardiovascular events, and azithromycin in male survivors of myodardial infarction. *Circulation*. 1997; 96: 404-407.
3. Gurfinkel E, Bozovich G, Daroca A, Beck E, Mautner B. Randomized trial of roxithromycin in non-Q-wave coronary syndromes: ROXIS pilot study. *Lancet*. 1997; 350: 404-407.
4. Wintrobe MM, Thorne GW, Adams RD, Bennett IL, Braunwald E, Isselbacher KW, Petersdorf RG. Harrison's Principles of Internal Medicine. McGraw-Hill, p895, 1970.
5. Valtonen VV. Infection as a risk factor for infarction and atherosclerosis. *Annals of Medicine*. 1991; 23: 539-543.