Antibiotics in Primary Prevention of Stroke in the Elderly

Paul Brassard, MD, MSc; Chantal Bourgault, PhD; James Brophy, MD, PhD; Abbas Kezouh, PhD; Samy Suissa, PhD

**Background and Purpose**—An increasing number of reports have linked infections to atherosclerosis and thrombosis. Thus, use of antibiotics may lower the risk of developing cerebrovascular disease. We investigated whether antibiotic use is associated with the risk of stroke in elderly individuals treated for hypertension.

**Methods**—A cohort of 29,937 elderly subjects initiating antihypertensive therapy between 1982 and 1995 was formed from the Quebec healthcare insurance database. A nested case-control design was used in which each subject hospitalized with a primary discharge diagnosis of stroke between 1987 and 1995 was matched on calendar time to 5 randomly selected controls from the cohort. Conditional logistic regression was used to estimate odds ratios of stroke after adjustment for predisposing factors.

**Results**—We identified 1888 cases and 9440 controls. The overall adjusted odds ratio for current antibiotic use was 0.80 (95% confidence interval, 0.63 to 1.01), and that for recent use was 0.81 (95% confidence interval, 0.70 to 0.94). Penicillin was the only individual antibiotic class that showed a protective association across different time windows. No significant association was found between stroke risk and the use of fluoroquinolones, macrolides, tetracyclines, or cephalosporins.

**Conclusions**—Although no clear, consistent associations between overall antibiotic use and cerebrovascular disease could be found, an intriguing association between penicillin use and stroke should be explored further. *(Stroke. 2003;34:e163-e167.)*

Key Words: antibiotics • atherosclerosis • case-control studies • infection • primary prevention • stroke

An increasing number of reports are linking infections to atherosclerosis and thrombosis. The proposed mechanisms are their common interaction with the inflammatory process, involving endothelial injury, macrophage transformation, and perhaps antigenic mimicry. An intriguing hypothesis sees arteriosclerosis as a chronic inflammatory condition with a possible treatable infective component that may be responsible either for disease initiation or progression or as a precipitating event contributing to plaque rupture resulting in acute ischemic events. Under that assumption, subjects treated with antibiotics may be at lower risk of developing clinical manifestations such as cerebrovascular disease than untreated subjects.

To test this hypothesis, we evaluated the effect of antibiotic use, regardless of the clinical indication or specific antibacterial activity, in the primary prevention of stroke in a general population of elderly patients initiating pharmacological treatment for hypertension.

**Methods**

**Sources of Data**

This study was conducted through the use of the computerized administrative databases of the Quebec Health Ministry (Régie de l’Assurance Maladie du Québec [RAMQ]), developed in the context of the universal insurance program provided to the elderly population of the Province of Quebec. Information for each outpatient prescription includes the nature, quantity, strength, and dosage of the drug, as well as the dispensing date and prescribed duration of the prescription. The RAMQ databases also provide data on all medical services offered to the study population. Data on admission and discharge dates for all hospitalizations, along with up to 9 discharge diagnoses coded using the ninth revision of the *International Classification of Diseases* (ICD-9), are available from the hospital discharge database. The coding accuracy of discharge diagnoses in these databases has previously been shown.

**Study Design**

A case-control analysis of a cohort of newly diagnosed hypertensive patients was conducted, with cases defined as any hospitalization with a primary discharge diagnosis of stroke (ICD-9 code, 430 to 438). Admission date for stroke was labeled the index date. For each stroke hospitalization, a risk set of all subjects with the same month and year of cohort entry and still at risk for an event at the case’s index date was identified. Five controls, selected at random within these risk sets through incidence-density sampling, were matched to each case accordingly. A detailed description of the cohort is available.

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Results of this study were presented at the 17th International Conference on Pharmacoepidemiology, Toronto, Canada, August 23–26, 2001.

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Drug Exposure
Exposure history for antibiotics was available for up to 14 years before the index date. Because the latency period for stroke in relation to antibiotic use is not known, several a priori–defined time windows were used to document exposure: current (within 30 days of index date), recent (within 30 days to 1 year), and past (>1 year before) use. The prespecified hierarchy assignment order for simultaneous exposure to >1 of these time windows was the following: current>recent>past use. For each of these time windows, indicator variables were created for any antibiotic class (our primary analysis) and each individual antibiotic class (fluoroquinolones, tetracyclines, macrolides, cephalosporins, penicillins, and others) and compared with no antibiotic use.

Adjustment Factors and Statistical Analyses
Cases of stroke were contrasted to controls regarding antibiotic use through multivariate conditional logistic regressions to account for the effect of matching. Hospital diagnoses or the use of prescribed medications at any time during follow-up was used to identify the following potential confounders: diabetes, prior coronary heart disease, cardiac arrhythmias (including atrial fibrillation), cardiomyopathy (including congestive heart failure), hyperlipidemia, and use of anticoagulants, corticosteroids, aspirin, and nonsteroidal anti-inflammatory drugs. We adjusted for all these factors in the analyses.

Data are not available on smoking status in these administrative databases. We attempted to circumvent the unavailability of such data by using a surrogate measure of the long-term complication of smoking composed of theophylline use or any hospitalization for pulmonary diseases. This measure was included in the multivariate analyses.

Adjusted odds ratios (ORs), approximations to the rate ratios, and 95% confidence intervals (CIs) are presented throughout this article.

Results
Among a total of 29,937 subjects, we identified 1888 cases of stroke and 9440 matched controls (Table 1). On average, cases and controls were followed up for 5 years (median, 5 years; range, 1 day to 12.6 years) from cohort entry to index date. Table 2 shows the associations of antibiotics and risk of stroke in the various time windows. Any antibiotic use showed a protective association that attenuates with time. Only recent use showed a statistically significant association between antibiotic use and stroke. As for individual antibiotic classes, only penicillin showed a consistent and significant association with the occurrence of stroke in a population-based study of elderly hypertensive subjects.

Other studies have examined whether antibiotics effective against specific bacteria such as Chlamydia pneumoniae (fluoroquinolones, macrolides, or tetracyclines), regardless of their clinical indications, could lead to a decreased risk of ischemic events such as myocardial infarction. These studies have shown conflicting results. Our own experience failed to demonstrate a consistent protective association across antibiotic classes, although a nonsignificant protective trend diminishing with time was observed for antibiotics with antichlamydial activity (OR, 0.68; 95% CI, 0.46 to 1.00 for use in the previous 3 months; OR, 0.80; 95% CI, 0.58 to 1.11 for use in the previous 6 months).5 In contrast, only 1 prior study has examined the putative association between antibiotic use and the occurrence of ischemic stroke, with no significant associations. One reason for the negative result might be related to the particularly long period between their defined exposure and stroke outcome (mean time, 646 days).

A number of limitations pertaining to our study should be kept in mind. First, antibiotic use is only an indirect marker of the presence of infection, on which we have no clinical or serological data and which thus cannot be directly linked to the occurrence of stroke. We are also uncertain about patient compliance because actual antibiotic intake was not measured.

Because information on important risk factors is sometimes lacking, observational studies such as this one are

<table>
<thead>
<tr>
<th>Antibiotics, n (%)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 1282 (68)</td>
<td>4521 (48)</td>
<td></td>
</tr>
<tr>
<td>Prior coronary heart disease 822 (44)</td>
<td>3683 (39)</td>
<td></td>
</tr>
<tr>
<td>Diabetes 350 (19)</td>
<td>999 (11)</td>
<td></td>
</tr>
<tr>
<td>Anti-arrhythmics 95 (5)</td>
<td>178 (2)</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy 591 (31)</td>
<td>1994 (21)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia 137 (7)</td>
<td>805 (9)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary disease 58 (3)</td>
<td>268 (3)</td>
<td></td>
</tr>
<tr>
<td>Anticoagulotherapy 197 (10)</td>
<td>465 (5)</td>
<td></td>
</tr>
</tbody>
</table>

NSAIDs indicates nonsteroidal anti-inflammatory drugs. Any time during follow-up.
especially sensitive to confounding and systematic biases. Smoking is one potentially important confounder of the association between antibiotic use and stroke, and unfortunately, no direct information relating to individual smoking habits is available in the Quebec administrative databases. Because it would be reasonable to think that smokers are more likely to be dispensed antibiotics, which are indicated, among other things, for exacerbation of chronic bronchitis, insufficient correction of cigarette use could bias our study results by decreasing any measured protective effect of antibiotics. Another potential confounding factor not controlled for in the present study was socioeconomic status. Because infectious diseases could be unequally distributed among different socioeconomic categories, antibiotic use could thus vary accordingly.

Another limitation pertains to the study source population. Because we had incomplete information on potential strokes occurring before our study period, it might have led to a lack of comparability of cases and controls with respect to preexisting atherosclerotic disease. However, our sensitivity analysis showed no differences in our findings when patients with multiple events occurring during the study period were excluded or when hemorrhagic strokes were excluded.

In addition to possible systematic biases, one should consider the role of random error or chance in our study findings. Because no attempt was made to account for multiple testing, type I error is a possible explanation for the statistically significant associations found. The relatively small number of cases and controls found in some of the current time windows could also have hindered our ability to demonstrate significant associations.

In conclusion, no clear, consistent effect of antibiotics use was found in relation to stroke in a high-risk elderly population. Further confirmation studies for penicillin use in other populations and an evaluation of the clinical significance of this finding remain to be performed.

### TABLE 2. Risk of Stroke in Relation to Antibiotic Use and Time of Exposure

<table>
<thead>
<tr>
<th></th>
<th>Cases, n (%)</th>
<th>Controls, n (%)</th>
<th>Crude OR</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any antibiotic†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>120 (6.4)</td>
<td>598 (6.3)</td>
<td>0.99</td>
<td>0.80 (0.63–1.01)</td>
</tr>
<tr>
<td>Recent</td>
<td>558 (29.6)</td>
<td>2815 (29.8)</td>
<td>0.98</td>
<td>0.81 (0.70–0.94)</td>
</tr>
<tr>
<td>Past</td>
<td>787 (41.7)</td>
<td>3938 (41.7)</td>
<td>0.99</td>
<td>0.87 (0.75–1.00)</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>16 (0.9)</td>
<td>87 (0.9)</td>
<td>0.88</td>
<td>0.85 (0.49–1.49)</td>
</tr>
<tr>
<td>Recent</td>
<td>103 (5.5)</td>
<td>532 (5.6)</td>
<td>0.95</td>
<td>0.92 (0.73–1.16)</td>
</tr>
<tr>
<td>Past</td>
<td>165 (8.7)</td>
<td>740 (7.8)</td>
<td>1.11</td>
<td>1.08 (0.89–1.31)</td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>12 (0.6)</td>
<td>33 (0.4)</td>
<td>1.84</td>
<td>1.62 (0.79–3.31)</td>
</tr>
<tr>
<td>Recent</td>
<td>76 (4.0)</td>
<td>345 (3.7)</td>
<td>1.08</td>
<td>1.08 (0.83–1.41)</td>
</tr>
<tr>
<td>Past</td>
<td>329 (17.4)</td>
<td>1758 (18.6)</td>
<td>0.91</td>
<td>0.88 (0.77–1.02)</td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>2 (0.1)</td>
<td>27 (0.3)</td>
<td>0.37</td>
<td>0.40 (0.09–1.75)</td>
</tr>
<tr>
<td>Recent</td>
<td>52 (2.8)</td>
<td>291 (3.1)</td>
<td>0.87</td>
<td>0.88 (0.64–1.20)</td>
</tr>
<tr>
<td>Past</td>
<td>244 (12.9)</td>
<td>1243 (13.2)</td>
<td>0.96</td>
<td>0.95 (0.81–1.11)</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>18 (1.0)</td>
<td>74 (0.8)</td>
<td>1.33</td>
<td>1.30 (0.75–2.25)</td>
</tr>
<tr>
<td>Recent</td>
<td>126 (6.7)</td>
<td>536 (5.7)</td>
<td>1.26</td>
<td>1.16 (0.94–1.45)</td>
</tr>
<tr>
<td>Past</td>
<td>261 (13.8)</td>
<td>1205 (12.8)</td>
<td>1.14</td>
<td>1.06 (0.91–1.24)</td>
</tr>
<tr>
<td><strong>Penicillins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>20 (1.1)</td>
<td>156 (1.7)</td>
<td>0.60</td>
<td>0.53 (0.33–0.86)</td>
</tr>
<tr>
<td>Recent</td>
<td>231 (12.2)</td>
<td>1312 (13.9)</td>
<td>0.81</td>
<td>0.73 (0.62–0.86)</td>
</tr>
<tr>
<td>Past</td>
<td>698 (37.0)</td>
<td>3452 (37.0)</td>
<td>0.95</td>
<td>0.86 (0.77–0.97)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>58 (3.1)</td>
<td>260 (2.8)</td>
<td>1.17</td>
<td>1.05 (0.77–1.43)</td>
</tr>
<tr>
<td>Recent</td>
<td>223 (11.8)</td>
<td>1054 (11.2)</td>
<td>1.12</td>
<td>1.03 (0.87–1.23)</td>
</tr>
<tr>
<td>Past</td>
<td>599 (31.7)</td>
<td>2931 (31.1)</td>
<td>1.06</td>
<td>1.02 (0.90–1.15)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, aspirin, corticosteroids, anti-arrhythmic drugs, anticoagulant, hyperlipidemic agent use, antidiabetic medications, cardiomyopathy, prior coronary heart disease, pulmonary disease, and all antibiotic groups.
†Current (within 30 days of index date), recent (within 30 days to 1 year), and past (>1 year before) use.
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References

Editorial Comment
Antibiotics and Stroke

It is sobering to consider that despite its prevalence and prominence, the cause of atherosclerosis remains unknown. In this issue of Stroke, Brassard et al have addressed its intriguing association with inflammation. If infection plays a role in the genesis of vascular events such as stroke, might antibiotics reduce their incidence?

Briefly, Brassard et al examined retrospectively a large data set of elderly hypertensive patients beginning therapy and, after adjustment for confounders, found that antibiotic use, particularly penicillin, was negatively associated with stroke. They noted a “protective association.”

Enthusiasm for a conclusion supporting a popular and intriguing hypothesis should be tempered by consideration of exactly what was done and what was found. Two principles are helpful in assessing the strength of this evidence:

First, in science, an answer cannot be more specific than the question it addresses.

Second, causation cannot be deduced from association.

With regard to the first issue, the hypothesis of the present study was that “subjects treated with antibiotics may be at lower risk of developing clinical manifestations such as cerebrovascular disease.” Of the 6 defined antibiotic groups, 3 were associated with fewer strokes, 3 with more. (Patients who had received penicillins, macrolides, and fluoroquinolones experienced somewhat fewer strokes; those receiving tetracyclines, cephalosporins, and other antibiotics experienced somewhat more.) Overall the odds ratio was 0.99 for current use, 0.98 for recent, and 0.99 for past use. Adjustment for confounders resulted in odds ratios of 0.80, 0.81, and 0.87, respectively, and a “statistically significant” negative association for penicillin administration.

Since it was statistical adjustment that resulted in the association, statistical adjustment might be responsible. A problem with retrospective studies is that one can adjust only for factors for which data are available. An overall association shown to be robust when adjusted for confounders is a good deal more persuasive than an association that appears only after statistical manipulation, particularly when the calculations are limited by the availability of data collected for another purpose.

It is unfortunate and confusing (and unnecessary) that contemporary statistical methods use the same calculations and units for predictions confirmed as for observations noticed. Confirmed predictions carry “predictive value”; they suggest that a similar maneuver, in similar patients, will have similar results. Not so with observations. All observations will be “statistically significant” given only adequate sample size. The effects are beyond the plausible range of the play of chance, or they would not have been noticed. The “statistical significance” of an observation does not reflect its predictive value.

The association of antibiotic type with stroke incidence varied a good deal, and of course one association must always be strongest. That past penicillin administration was associated with the least stroke incidence constitutes only an unexpected observation. Of course, the explanation for the association might be that penicillin protects from stroke, but in the context of this investigation, it provides only a hypothesis that might be assessed using other data. Of course, confirming the association would not establish that it was causal.

The second issue is that causality cannot be deduced from association. Although causality usually produces
association, association does not of itself imply causality. More than 20 observational studies showed that women taking hormone replacement therapy (HRT) had fewer heart attacks, yet all of the randomized trials (from which causality can be deduced) showed that HRT was associated with an increase in heart attacks. The explanation appeared to be due to either or both survivor effect (high-risk women given HRT had events prior to recruitment to the observational studies, leaving low-risk women to be observed) and association of HRT use with socioeconomic status. It is puzzling that HRT was never prescribed to raise socioeconomic status, despite a similar association and identical logic.

If a negative association between penicillin use and stroke incidence were to be confirmed with other data, causality would still not have been established. This means that “protective association” overstates the strength of the evidence. A negative association no more means that antibiotics prevent stroke than that HRT prevents heart attacks.

Notwithstanding these issues, the investigators are to be congratulated on having squeezed the available data to shed light on an important issue. But the jury remains out.

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