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Original Contribution

Antibiotic Use and Risk of Multiple Sclerosis

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Some reports suggest that bacteria, including *Chlamydophila pneumoniae*, could be involved in the etiology of multiple sclerosis. If that is true, persons who used antibiotics active against these bacteria, compared with nonusers, might be at lower risk of multiple sclerosis. Using a 1993–2000 case-control study nested in the United Kingdom–based General Practice Research Database cohort, the authors identified 163 multiple sclerosis cases who were followed up for at least 3 years before their first symptoms (the index date). Up to 10 controls matched to the cases by age, sex, general practice, and time in the cohort were selected. Exposure to antibiotics was assessed through computerized medical records. Overall antibiotic use or use of antibiotics against *C. pneumoniae* was not associated with multiple sclerosis risk. However, use of penicillins in the 3 years before the index date decreased the risk of developing a first attack of multiple sclerosis (odds ratio = 0.5, 95% confidence interval: 0.3, 0.9 for those who used penicillins for $\geq$15 days compared with no use). In conclusion, use of antibiotics active against *C. pneumoniae* was not associated with a decreased risk of short-term multiple sclerosis. The observed lower risk of multiple sclerosis for penicillin users needs to be confirmed in other populations.

anti-bacterial agents; *Chlamydophila pneumoniae*; multiple sclerosis; prospective studies

Abbreviations: CI, confidence interval; GPRD, General Practice Research Database; MS, multiple sclerosis; OR, odds ratio.

The etiology of multiple sclerosis (MS), an inflammatory demyelinating disease affecting the central nervous system, remains unknown (1). Some bacterial agents, most notably *Chlamydophila* (previously *Chlamydia*) *pneumoniae*, have been proposed as possible etiologic agents for MS. Epidemiologic studies of a link between *C. pneumoniae* infection and MS risk have yielded conflicting results (2–9) that may be explained by methodological differences (10).

Some bacterial infections, including *C. pneumoniae*, often follow a mild or even asymptomatic clinical course, and they may go by undiagnosed and untreated (11). If a causal relation between a particular bacterial infection and MS indeed exists, then it is conceivable that persons who have been treated, for whatever indication, with antibiotics active against that bacteria might be at a lower risk of developing MS than those who have not received such antibiotic treatment. For example, a lower risk of MS for those treated with macrolides, tetracyclines, or quinolones would provide indirect evidence for an association between *C. pneumoniae* infection and MS. This indirect approach to the study of bacterial infections as potential contributors to the risk of chronic disease has been previously applied to evaluate risk factors for myocardial infarction and stroke (12, 13).

In the present study, we investigated the association between the use of each class of antibiotics and the risk of MS in a prospectively followed British population.

MATERIALS AND METHODS

Study population

The General Practice Research Database (GPRD) contains prospective health information on over 3 million Britons

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who are enrolled with selected general practitioners (14). These physicians have been trained to record their patients' medical and demographic information in a standard manner and have agreed to supply it anonymously for research purposes. In addition, practices used in this study agree to collaborate in specific research projects by providing photocopies of their patients' paper medical records after personal identifiers have been removed. Drug prescriptions were computer generated by the physicians and were automatically recorded in the database by using a coded drug dictionary based on that of the United Kingdom Prescription Pricing Authority. Medical diagnoses were entered by using a classification system compatible with the *International Classification of Diseases*, Ninth Revision. This computerized information has been found to be of satisfactory quality for drug safety studies (15, 16).

Case ascertainment

The assessment of incident cases of MS in the GPRD has been described previously (17). Briefly, we identified persons with a new diagnosis of MS (*International Classification of Diseases*, Ninth Revision, code 340.0) recorded in the GPRD between January 1, 1993, and December 31, 2000. We then requested photocopies of all their MS-related medical records available in the general practitioner's office, including laboratory results, specialist referrals, and hospital discharges. Two physicians independently reviewed the paper medical records and classified participants as MS, possible MS, or no MS cases according to standardized criteria (18, 19). The date of first symptoms was assigned according to criteria proposed by Poser (20). This review confirmed 438 (61.4 percent) of the 713 persons identified as potential cases. Reasons to exclude the other 275 participants were that 1) they were prevalent MS cases ($n = 83$, diagnosed before January 1, 1993), 2) they had a diagnosis of possible MS ($n = 59$), 3) their medical records could not be obtained because of transfer into another practice ($n = 71$) or death of the participant ($n = 10$), or 4) they did not have MS ($n = 52$). Ninety-eight percent of the confirmed cases had been diagnosed by a neurologist, and 85 percent of the diagnoses were supported by magnetic resonance imaging.

Of the 438 cases, 282 experienced their first symptoms after their first computer-recorded medical information was collected. To ensure at least 3 years of exposure information, our primary analysis included only the 163 cases for whom at least 3 years of information was available in the GPRD before the date of first symptoms.

Study design

We conducted a case-control study nested in the GPRD cohort. Cases were defined as patients with a confirmed diagnosis of MS between January 1, 1993, and December 31, 2000, and at least 3 years of continuous recording in the GPRD before their first symptoms. Up to 10 controls per case were selected, matched by age (± 1 year), sex, general practice, and date of joining the practice (± 1 year). Controls had to be alive, had to be free of an MS diagnosis, had to have information present in the database at the date of first symptoms in their corresponding case (the index date), and had to have at least 3 years of continuous recording in the database before the index date.

Exposure assessment

The information on antibiotic prescriptions before the index date was extracted from the computerized medical records. These records include only those antibiotics prescribed by the general practitioner but not those possibly administered during hospital admissions. For each antibiotic prescription, we obtained duration of use, dosage, and type. We determined the indication for treatment (respiratory infection, genitourinary infection, ear infection, oral and periodontal infection, skin and soft tissue infection, acne/rosacea, other infections) by examining the medical diagnosis associated with each prescription in the computerized record. Information about duration, dosage, and indication was missing for 6.0 percent, 5.1 percent, and 6.6 percent of the prescriptions, respectively. For prescriptions for which duration of use was unknown, we used the median duration of the corresponding antibiotic type, but analyses restricted to prescriptions of known duration yielded similar estimates (data not shown). Antibiotics were classified as penicillins, cephalosporins, tetracyclines, macrolides, or others (quinolones, sulfonamides, trimethoprim, etc.). We also created a category for antibiotics active against *C. pneumoniae* that included tetracyclines, macrolides, and quinolones.

The main exposure was total number of days of antibiotic use in the 3 years before the index date. For penicillins, we also determined whether prescriptions were high dose ($>$750 mg/day for amoxicillin and amoxicillin/clavulanic acid; $>$1,000 mg/day for ampicillin, dicloxacillin, floxacillin, penicillin V, and pivampicillin; and $>$1,600 mg/day for bacampicillin).

Statistical analysis

We used conditional logistic regression to estimate odds ratios and their 95 percent confidence intervals adjusted for matched factors and total number of prescriptions for antibiotics other than the type included in the model. Under our design, the odds ratio is a consistent estimator of the incidence rate ratio of MS for exposed versus unexposed subjects.

To assess whether the association between antibiotic use and risk of MS varied according to age, sex, calendar time, or clinical course, we created interaction terms based on the number of antibiotic prescriptions and age ($<$40, $\geq$40 years), sex, and clinical course at onset (relapsing-remitting, progressive). The p value for interaction was computed from the log-likelihood ratio test comparing models with and without the interaction term.

We repeated the analyses by including cases and controls independently of their time in the cohort, including possible cases, or considering alternate exposure windows (2 years and 5 years before the index date). In this paper, statements about statistical significance refer to the conventional (and arbitrary) 0.05 cutoff.

TABLE 1. Characteristics of cases and controls* studied to assess the association between antibiotic use and risk of multiple sclerosis, General Practice Research Database, United Kingdom, 1993–2000†

	Multiple sclerosis cases ($n = 163$)	Controls ($n = 1,523$)
Age (years)		
Mean (standard deviation)	36.2 (9.5)	36.3 (9.5)
<30	31.3	30.8
30–39	33.7	34.1
40–49	25.8	25.4
≥50	9.2	9.7
Ever smoker	44.4	39.8
Course of the disease		
Relapsing-remitting at onset	90.8	
Relapsing-remitting	79.8	
Secondary progressive	11.0	
Primary progressive	9.2	
First symptoms		
Optic neuritis/diplopia	25.8	
Sensory symptoms	49.1	
Motor deficit/weakness	17.2	
Ataxia/dysarthria/limb incoordination	20.2	

* Of the 1,604 controls originally selected, data on 81 were effectively excluded from the matched analysis because the cases to whom they were matched did not fulfill the inclusion criteria.

† All values are expressed as percentages unless otherwise specified.

RESULTS

The characteristics of cases and controls are shown in table 1. The incidence of MS did not vary by overall antibiotic use or by use of antibiotics effective against *C. pneumoniae* in the 3 years before the index date (table 2).

The incidence of MS in persons who used penicillin for more than 2 weeks was half that in nonusers of penicillin (odds ratio (OR) = 0.5, 95 percent confidence interval (CI): 0.3, 0.9), with no clear association between use of penicillin for less than 2 weeks and the risk of MS. Tetracycline use for more than 1 week was also associated with a reduction in MS risk (OR = 0.5, 95 percent CI: 0.2, 1.0). Use of cephalosporins, macrolides, and other antibiotics was not associated with a reduced risk of MS.

The association of more than 2 weeks of penicillin use with a lower risk of MS did not vary significantly by sex or age, and was also observed after adjustment for smoking (OR = 0.5, 95 percent CI: 0.3, 0.9) and use of other antibiotics (OR = 0.5, 95 percent CI: 0.3, 0.8), when we included possible cases in the analysis (OR = 0.5, 95 percent CI: 0.3, 0.9) and when we did not restrict the analysis to persons for whom at least 3 years of information was available (OR = 0.5, 95 percent CI: 0.3, 0.8). The odds ratio estimates were also similar for windows of exposure other than 3 years, although the width of the confidence intervals varied. The odds ratios for penicillin use versus no use were 0.6 (95 percent CI: 0.4, 0.9) in the year before the index date, 1.1 (95 percent CI: 0.8, 1.6) 1–2 years before the index date, and 0.8 (95 percent CI: 0.5, 1.2) 2–3 years before the index date.

When we examined the use of penicillin 2 years and 5 years before the index date, the odds ratios for more than 2 weeks of penicillin use versus no use were 0.6 (95 percent CI: 0.3, 1.1) and 0.6 (95 percent CI: 0.3, 1.2), respectively. In contrast, the association between tetracycline use and MS risk was less evident when the window of exposure was either 2 years (OR = 0.5, 95 percent CI: 0.1, 1.6) or 5 years (OR = 1.3, 95 percent CI: 0.7, 2.5) before the index date.

The odds ratios of MS for those with more than 2 weeks of penicillin use compared with no use were 0.4 (95 percent CI: 0.2, 0.8) for persons with relapsing-remitting onset (145 cases) and 1.2 (95 percent CI: 0.3, 4.9) for those with a primary progressive course (18 cases), but the interaction term was not statistically significant ($p = 0.59$). The risk of MS did not clearly vary by dosage of penicillin. However, the low number of cases exposed to high-dose penicillins prevented us from drawing strong conclusions about dosage (data not shown).

Respiratory infection was the most frequent indication for use of antibiotics overall (56 percent of all prescriptions), penicillin (65 percent), cephalosporins (56 percent), tetracyclines (42 percent), and macrolides (60 percent). The association between penicillin use and MS risk was similar when we restricted the analysis to those persons whose antibiotic treatment was prompted by either a respiratory infection or another indication (table 3).

DISCUSSION

Our prospective study shows that overall use of antibiotics, and use of antibiotics active against *C. pneumoniae*, during the 3 years before the index date did not reduce the risk of developing MS in this British population. However, in all the analytical scenarios, more than 2 weeks of penicillin use was associated with a 50 percent reduction in the risk of MS. This result cannot be explained by recall bias, because the exposure information was prospectively collected before the first symptoms of disease occurred, or by bias in selection of the controls, because we used a study design that minimizes or eliminates this bias: a case-control study nested within a well-defined dynamic population.

Although we adjusted for known and suspected risk factors for MS, the presence of some residual confounding is always possible in observational studies. However, the specificity of the association with penicillin use and the consistency of the association across indications argue against a strong confounding effect. In addition, infections have been associated with higher risk of relapse of MS (21), including respiratory infections in this same population (22), and it therefore seems improbable that infections, particularly in the respiratory tract, could explain a lower risk of developing MS. Although patients' socioeconomic status can influence antibiotic prescription patterns, even in countries with universal health care such as Canada or the United Kingdom

TABLE 2. Risk of multiple sclerosis by duration of antibiotic use, General Practice Research Database, United Kingdom, 1993–2000

Days of antibiotic use in the 3 years before the index date*	Cases ($n = 163$)		Controls ($n = 1,523$)		OR†,‡	95% CI†	*p* for trend	OR§	95% CI	*p* for trend
	No.	%	No.	%						
All antibiotics										
0	44	27.0	467	30.7	1	Ref.†				
1–7	44	27.0	329	21.6	1.4	0.9, 2.2				
8–14	27	16.6	222	14.6	1.3	0.8, 2.2				
15–21	17	10.4	157	10.3	1.1	0.6, 2.0				
≥22	31	19.0	348	22.8	0.9	0.6, 1.5	0.41			
Anti-*Chlamydophila* antibiotics										
0	117	71.8	1,105	72.6	1	Ref.		1	Ref.	
1–7	24	14.7	193	12.7	1.2	0.7, 1.9		1.2	0.7, 1.8	
8–14	9	5.5	87	5.7	1.0	0.5, 2.0		0.9	0.4, 1.9	
≥15	13	8.0	138	9.1	0.9	0.5, 1.6	0.71	0.8	0.5, 1.5	0.62
Penicillins										
0	77	47.2	687	45.1	1	Ref.		1	Ref.	
1–7	43	26.4	397	26.1	1.0	0.6, 1.4		1.0	0.7, 1.4	
8–14	28	17.2	183	12.0	1.3	0.8, 2.1		1.3	0.8, 2.1	
≥15	15	9.2	256	16.8	0.5	0.3, 0.9	0.07	0.5	0.3, 0.9	0.06
Cephalosporins										
0	137	84.0	1,320	86.7	1	Ref.		1	Ref.	
1–7	17	10.4	136	8.9	1.2	0.7, 2.2		1.2	0.7, 2.2	
≥8	9	5.5	67	4.4	1.4	0.6, 2.9	0.31	1.3	0.6, 2.9	0.34
Tetracyclines										
0	144	88.3	1,301	85.4	1	Ref.		1	Ref.	
1–7	11	6.7	78	5.1	1.3	0.6, 2.5		1.3	0.6, 2.5	
≥8	8	5.0	144	9.5	0.5	0.2, 1.0	0.09	0.5	0.2, 1.0	0.08
Macrolides										
0	133	81.6	1,303	85.6	1	Ref.		1	Ref.	
1–7	20	12.3	145	9.5	1.4	0.8, 2.3		1.4	0.8, 2.3	
≥8	10	6.1	75	4.9	1.3	0.7, 2.7	0.24	1.3	0.7, 2.7	0.24
Other antibiotics										
0	137	84.0	1,268	83.3	1	Ref.		1	Ref.	
1–7	11	6.7	162	10.6	0.6	0.3, 1.2		0.6	0.3, 1.2	
8–14	9	5.5	50	3.3	1.7	0.8, 3.6		1.7	0.8, 3.7	
≥15	6	3.7	43	2.8	1.3	0.5, 3.2	0.51	1.3	0.5, 3.2	0.48

* The date of first symptoms in the cases.
† OR, odds ratio; CI, confidence interval; Ref., reference.
‡ Adjusted for matching factors (age, sex, general practice, and time in the cohort).
§ Additionally adjusted for duration (days) of use of other antibiotics.

(23, 24), our study design and analysis were matched on general practice, which results in partial adjustment for socioeconomic status. Tetracycline use was also associated with a lower risk of MS in our main analysis. However, this association was based on few cases and was not robust to changes in the window of exposure, which suggests that it may be due to random variability rather than a neuroprotective effect of tetracyclines (25).

It is possible that some patients did not take the prescribed antibiotics or, while admitted to a hospital, that they received antibiotics not recorded in the database. However, because both outpatient and inpatient antibiotic prescriptions were written before the first symptoms of MS occurred, this misclassification is expected to be nondifferential and to make our estimates conservative (i.e., biased toward the null). Nondifferential misclassification could partially explain

TABLE 3. Relative incidence of multiple sclerosis by duration of penicillin use and indication, General Practice Research Database, United Kingdom, 1993–2000

Days of penicillin use	Cases		Controls		OR*,†	95% CI*	*p* for trend	OR‡	95% CI	*p* for trend
	No.	%	No.	%						
For respiratory infections§										
0	36	41.9	165	35.9	1	Ref.*		1	Ref.	
1–7	31	36.1	172	37.4	0.8	0.5, 1.3		0.8	0.5, 1.3	
8–14	14	16.3	73	15.9	0.8	0.4, 1.7		0.8	0.4, 1.7	
≥15	5	5.8	50	10.1	0.4	0.2, 1.2	0.06	0.4	0.2, 1.2	0.06
For other infections¶										
0	34	50.0	97	41.1	1	Ref.		1	Ref.	
1–7	23	33.8	101	42.8	0.6	0.3, 1.1		0.6	0.3, 1.2	
8–14	8	11.8	23	9.8	1.0	0.4, 2.7		1.1	0.4, 2.8	
≥15	3	4.4	15	6.4	0.5	0.1, 1.9	0.35	0.5	0.1, 1.9	0.38

* OR, odds ratio; CI, confidence interval; Ref., reference.

† Adjusted for matching factors (age, sex, general practice, and time in the cohort) and number of infections (respiratory or other infections).

‡ Additionally adjusted for duration (days) of use of other antibiotics.

§ Data are for 86 cases and 460 controls with at least one recorded respiratory infection.

¶ Data are for 68 cases and 236 controls with at least one recorded infection in another location (no respiratory).

the lack of association of overall and anti-*Chlamydophila* antibiotic use with MS risk, but not the inverse association between penicillin use and MS risk. In fact, the indirect approach we used to test the association between bacterial infection and MS renders any observed null association between antibiotic use and MS risk not particularly informative. Null associations could be explained by having studied an irrelevant window of exposure, by the inability of the antibiotics to clear the bacterial infection in time to prevent MS, or by nondifferential misclassification of antibiotic use. In contrast, the nonnull associations detected by our approach (such as the one between penicillin use and MS risk) cannot be the result of those problems. As for a possible role of chance, the association between penicillin use and MS risk was strong, and the relative risk estimates were stable across analytical scenarios and indications for infection.

To our knowledge, only two prospective epidemiologic studies have assessed *C. pneumoniae* infection status before the development of first symptoms of MS (26). The anti-*C. pneumoniae* immunoglobulin G serum level was associated with an increased MS risk in the older cohort (Kaiser Permanente cohort, mean age at onset: 46 years) but not in the younger cohort (US Army cohort, mean age at onset: 27 years). These discrepant results would be expected if infection with *C. pneumoniae* increases the risk of MS only 1) after a long incubation period or 2) in older persons (26). Our study could not address the first explanation because the window of exposure was 3 years before symptoms began and does not support the second explanation because the association between antibiotic use and MS risk was similar for younger and older persons (data not shown).

We are unaware of previous epidemiologic studies that evaluated the association between penicillin use and MS risk, and we can only speculate about the biologic mechanisms that may explain the reduced risk of MS for penicillin users. Penicillins might decrease the risk of MS by eliminating an infectious agent, but most microorganisms that are sensitive to penicillins (e.g., spirochetes, which have been proposed as etiologic agents of MS (27)) would also be affected by macrolides and some cephalosporins. Alternatively, penicillins might have a neuroprotective effect independently of their antibacterial action (e.g., by increasing glutamate transporter expression (28), which may in turn reduce neurologic damage (29, 30)), but whether penicillins can cross the blood-brain barrier early in the pathophysiology of MS is unclear. Finally, penicillins inflict greater damage to the bacterial wall than other antibiotics do (31), which may cause a greater, or qualitatively different, exposure to bacterial antigens and, in turn, modify the immune response. Interestingly, use of penicillin, but not of other antibiotics, was also strongly associated with a lower risk of stroke in a cohort of elderly hypertensives (13). It is also worthwhile to note the different association of penicillin use with relapsing-remitting or primary progressive MS, although the small number of cases experiencing a primary progressive onset did not allow us to infer meaningful conclusions.

We could not evaluate whether more than 2 weeks of use of cephalosporins (which, like penicillins, are beta-lactam antibiotics) was associated with the risk of MS because too few persons received prescriptions for cephalosporin courses that lasted more than 2 weeks. Additionally, we could not evaluate the association between ceftriaxone, a parenteral third-generation cephalosporin that has been suggested to have a neuroprotective effect through an increase in glutamate receptor expression (28), and MS risk because most recorded cephalosporin use in our study was oral and corresponded to first- and second-generation cephalosporins (3.8 percent of cephalosporin prescriptions were

for cefixime and cefpodoxime, the only third-generation cephalosporins recorded in the database).

In conclusion, our results do not suggest that bacterial infection, and specifically infection with *C. pneumoniae*, is involved in the development of MS. The observed lower risk of MS for penicillins users, which needs to be confirmed in other populations, opens a new line of research.

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