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Systemic Antibiotics and Tooth Loss in Periodontal Disease

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Abstract

Systemic antibiotics have been recommended for the treatment of destructive periodontal disease. Our goal was to relate antibiotic use for medical or dental reasons to subsequent tooth loss in a cohort of 12,631 persons with destructive periodontal disease. After adjustment for age, smoking, and other confounders, the dispensing of antibiotics for 1-13 days, 14-20 days, or 21 or more days was not associated with reduced tooth loss [Adjusted rate ratio (RR) = 1.0; 95% Confidence Interval (CI) = 0.8-1.1; RR = 1.2; 95% CI = 0.9-1.4, and RR =1.2, 95% CI =1.0-1.3, respectively]. Numerous subgroup analyses were consistent with these overall null findings, with two exceptions: Longer courses of tetracyclines were associated with reduced tooth loss among persons receiving periodontal care, and penicillin was associated with reduced tooth loss among persons with more severe disease. Long-term, larger randomized trials are needed to provide evidence that antibiotics reduce tooth loss when used in the management of destructive periodontal disease.

Keywords

antimicrobials; systemic antibiotics; tooth loss; cohort study

INTRODUCTION

The hypothesis that destructive periodontal disease is an infection has prompted extensive research on identifying causative micro-organisms and the potential role of antimicrobials and antibiotics to improve outcomes by reducing putative pathogens in the oral flora and modulating the host response to inflammation. Several classes of antibiotics have been evaluated in clinical studies, and systematic reviews have indicated that systemic antibiotics for the treatment of destructive periodontal disease resulted in short-term improvements in clinical attachment and probing levels (Herrera *et al*., 2002; Haffajee *et al*., 2003). No studies have been identified reporting on the effects of systemic antimicrobials on true endpoints, such as tooth loss (Herrera *et al*., 2002). The aim of this study is to examine the association between systemic antibiotic use and the incidence of tooth loss.

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MATERIALS & METHODS

Design and Data Sources

We conducted a retrospective cohort study of 12,631 Health Maintenance Organization (HMO) members with destructive periodontal disease, 45 to 61 yrs old in 1999, who had complete medical, dental, and prescription drug coverage between 1996 and 2002. The participants had been diagnosed with early, moderate, or advanced chronic periodontal disease by a general dentist or a periodontist during 1999-2002. The study protocol was approved by the institutional review boards of the two research organizations involved in the study.

Outcome: Tooth Loss

For each individual, the number of teeth lost in each year was determined by the presence of standardized dental extraction codes in the dental services utilization database: simple, additional, and emergency extraction, and surgical removal of an erupted tooth. We calculated tooth loss rates by dividing the number of teeth lost by the number of person-years of follow-up. The number of tooth-years of follow-up could not be calculated, because the number of teeth at baseline was not available. We evaluated tooth loss rates in the period from January 1, 1999, to December 31, 2002.

Main Exposure: Antibiotic Use

Primary Definitions of Antibiotic Use—The number of days of antibiotics dispensed during the first three years of the study for medical or dental reasons was categorized as (a) no use, (b) 1 to 13 days, (c) 14 to 20 days, or (d) 21 or more days. The categories were chosen to reflect the possible prescription patterns of physicians and dentists, *i.e.*, antibiotics filled for 1 to 13 days, representing one course of the prescribed antibiotics, 14-20 days, representing two courses, and 21 or more days, representing three or more courses. For this analysis, the focus was on the number of days, and not on whether the antibiotic was used on consecutive days or was spread over the three-year period (*e.g.*, 21 days of continuous use was identical to three 7-day courses). The analysis was performed for any antibiotic use and for the following antibiotic classes: penicillins, clindamycin, tetracyclines, metronidazole, and macrolides. Antibiotic utilization was related to tooth loss rates in the 4th and subsequent years (long-term effects). These definitions and analysis have been our standard approach and were not a *post hoc* data-driven decision (Cunha-Cruz *et al*., 2006; Saver *et al*., 2007).

Alternative Definitions of Antibiotic Use—Short-term effects of antibiotic use on tooth loss were defined as the risk of tooth loss within one year after the receipt of antibiotic prescriptions during any year of the study (in contrast to our primary definition of use in the initial three-year period). For any antibiotic use and the 5 classes of antibiotics, we examined the number of days on antibiotics during any one year (0, 1-13, 14-20, or 21 or more days). Antibiotic use during any three-year period was also evaluated for tooth loss in the following year and yielded qualitatively similar results (results not presented).

Statistical Analyses

We used chi-square tests to compare baseline characteristics with number of days of antibiotic use during the first three-year period. We used negative binomial regression models with robust standard errors to estimate rate ratios and differences of the number of teeth lost in any given year in relation to the time on antibiotics, controlling for potential confounding variables (see Table 1 for definitions). The effects of specific periodontal treatments will be evaluated in another study report. The negative binomial model was chosen due to evidence of overdispersion and better model fit (*i.e.*, smaller differences between observed and predicted observations) as compared with other count models.

We performed subgroup analyses of the primary definitions of antibiotic use by restricting the analyses to participants undergoing periodontal treatment during the first three-year period, participants with moderate to advanced periodontal disease, and participants classified as active smokers. We tested interactions between these variables and antibiotic use by comparing the likelihood ratios of models with and without the interaction terms (Type 3 analysis in proc genmod). All reported p-values are based on two-sided tests. Analyses were performed with StataSE, version 8 and SAS, version 9.1 software.

RESULTS

Of the 12,631 participants, 3643 (29%) did not fill any antibiotic prescription during the first 3 yrs of the study; 2858 (23%) filled prescriptions for 1-13 days; 1633 (13%) for 14-20 days; and 4497 (36%) for 21 or more days (Table 1).

Primary Measures of Antibiotic Use

Antibiotic use for 1-13 days and for 14-20 days during the first three-year period was not associated with subsequent tooth loss [rate ratio (RR) = 1.0; 95% confidence interval (CI) = 0.8, 1.1 and RR = 1.2; 95% CI = 0.9-1.4, respectively], compared with no antibiotic use. Antibiotic use for 21 days or more was associated with a 20% (95% CI = 1.0, 1.3) increased tooth loss rate, compared with no antibiotic use. A linear trend of increased tooth loss rate was observed ($p < 0.05$). The adjusted rate for 21+ days on antibiotics was 1.5 teeth *per* 100 persons (95% CI = 0.3-2.7) higher than the adjusted rate for no antibiotic use. The rate ratios and differences in tooth loss rates associated with diabetes, current smoking, caries treatment, periodontal status, and tooth loss during baseline were higher than those associated with antibiotic use. High use of preventive dental treatment was associated with decreased tooth loss (Table 2).

Before adjustment, tetracyclines were associated with a 20% reduced tooth loss rate (95%CI = 0.6-1.0). After adjustment for potential confounding factors, penicillin, metronidazole, tetracyclines, and macrolides used during the first 3 yrs were not associated with subsequent tooth loss. Relative to no clindamycin use, 1-13 days on clindamycin was associated with a 70% increased risk of tooth loss (95% CI = 1.3, 2.2), and a linear trend for increased tooth loss rate was observed ($p < 0.05$) (Table 3).

Subgroup Analyses of the Primary Measures of Antibiotic Use

When analyses were restricted to participants undergoing periodontal treatment, any antibiotic use was not associated with decreased tooth loss rate, nor were the specific classes penicillins, clindamycin, metronidazole, and macrolides. At least 21 days of tetracyclines was associated with a 60% decreased tooth loss risk (RR = 0.4; 95%CI = 0.3-0.7), and a linear trend was present ($p < 0.05$). No interactions were observed between antibiotics and periodontal treatment, except for tetracyclines ($p < 0.05$) (Table 4).

When analyses were restricted to participants with moderate or advanced periodontal disease, both 21+ days of antibiotics and 21+ days of penicillins were associated with a 20% decreased tooth loss rate (95%CI = 0.7-1.0 and 0.6-1.0, respectively), after adjustment for confounding. Other specific classes were not associated with tooth loss among participants with moderate or advanced periodontal disease. Interactions between periodontal status and antibiotics were statistically significant for any antibiotics, penicillins, clindamycin, and macrolides ($p < 0.05$) (Table 4).

No consistent associations of antibiotic use and tooth loss were observed for active smokers, and interactions between smoking and antibiotics were not found (Table 4).

Alternative Measures of Antibiotic Use

For the association between antibiotic use in any year and tooth loss incidence in the following year (short-term effect), 21 or more days of any antibiotic use was associated with a 30% increased tooth loss rate (95% CI = 1.1, 1.5), 1 to 13 days of penicillin with a 30% increased rate (95%CI = 1.1-1.4), 21 or more days of penicillins with a 50% increased rate (95% CI = 1.1, 2.0), and 1 to 13 days of clindamycin use with a 60% increased rate (95%CI = 1.2-2.1).

DISCUSSION

We found no evidence in this cohort study that systemic antibiotics prescribed for medical or dental reasons were associated with a decreased tooth loss rate. Evaluation of specific antibiotic classes, such as tetracycline, metronidazole, and macrolide, similarly did not show consistent patterns for reduced tooth loss. The effects of antibiotics on tooth loss were further evaluated in groups of persons considered to be at higher risk of tooth loss. Individuals receiving periodontal treatments, individuals with more severe destructive periodontal disease, and smokers did not have a lower tooth loss rate associated with antibiotic use, except for lower tooth loss rates associated with tetracycline use among persons undergoing periodontal treatment during baseline and penicillin use among participants with moderate or advanced destructive periodontal disease.

Our findings on tooth loss conflict to some extent with the observed short-term benefits on pocket depth. The lack of a beneficial effect of antibiotics on tooth loss may be due to several reasons. Possibly, a higher tooth loss incidence among participants using antibiotics may have resulted from antibiotic use to treat acute dental conditions, such as periapical and periodontal abscesses (Newman *et al*., 2001) related to teeth requiring extraction. Participants receiving antibiotics might have differed from those not receiving antibiotics in ways not captured by the information available in this study. For example, we did not have information on socio-economic status (SES); this shortcoming may have confounded the association between antibiotics and tooth loss, since antibiotics may be prescribed more often to low-SES patients —a group already at increased risk of tooth loss. Or antibiotics may have truly no association with, or a slight adverse effect on, tooth loss. A large proportion of destructive periodontal disease cases may have a non-infectious etiology, and antibiotics would therefore show little effect when used in a non-targeted fashion (Bergström, 2004). Alternatively, the elimination of susceptible oral microorganisms may disturb the normal commensal flora and allow pathogenic oral bacteria to proliferate (Whitney *et al*., 2000; Tlaskalova-Hogenova *et al*., 2004; Loo *et al*., 2005).

Baseline dental characteristics of the participants were strongly associated with tooth loss incidence, which can be observed in the rate ratios and differences of periodontal status and tooth loss during baseline. Factors such as diabetes, smoking, and caries treatment had a stronger association with tooth loss than did antibiotics.

Overall, classes of antibiotics varied somewhat in their association with tooth loss. Tetracyclines and metronidazole were not associated with lower adjusted tooth loss rates. These antibiotic classes are frequently recommended as adjunctive periodontal therapy, due to reported reductions in the need for surgery and extraction (Loesche *et al*., 2002) and improvements in surrogate endpoints (Haffajee *et al*., 1995; Berglundh *et al*., 1998; Sigusch *et al*., 2001; Rooney *et al*., 2002; Rodrigues *et al*., 2004; Ehmke *et al*., 2005; Mombelli *et al*., 2005). Macrolides and penicillins were not associated with tooth loss, and clindamycin was associated with higher tooth loss incidence. These antibiotic classes are frequently used to treat acute dental conditions that might reflect unsalvageable teeth (Newman *et al*., 2001).

Given that dentists' prescriptions of antibiotics to treat chronic dental conditions vary greatly (Lewis *et al*., 1989; Palmer *et al*., 2000), and that evidence for specific antibiotic regimens is lacking (Loesche, 1999), we evaluated antibiotic usage in different ways. We searched for dose-response relationships, effects of repeated courses of antibiotics across time, and both short-term (one year later) and longer-term (up to 4 yrs later) effects of antibiotic use on tooth loss. In addition, several other representations of antibiotic usage, such as antibiotic duration (continuous variable), were tested. None of these analyses provided convincing evidence of a lower incidence of tooth loss among persons receiving antibiotics. When evaluating high-risk subgroups of the population, we observed similar trends, except in two circumstances. Antibiotic therapy has been recommended as a dental treatment for persons at increased risk of dental diseases (Herrera *et al*., 2002), as an adjunct to conventional periodontal therapy (Haffajee *et al*., 2003), and for smokers, because the response to conventional periodontal therapy may be compromised in these persons (Palmer *et al*., 1999). However, tooth loss rates of participants who received or did not receive antibiotic prescriptions within each of these three subgroups were not appreciably different.

The two exceptions were for longer courses of tetracyclines among persons receiving periodontal treatment and longer courses of penicillins among participants with moderate or advanced destructive periodontal disease being associated with lower tooth loss rates. The finding regarding tetracyclines is noteworthy, due to both the strength of the association and the evidence on non-antibiotic host-modulating properties of this class (Ingman *et al*., 1993). Independent confirmation of these findings in another cohort would provide a clearer picture of whether our observations were spurious or reflected real trends.

Strengths of the present study include the sample size, long-term follow-up, the ability to control for diabetes and smoking status, and the availability of comprehensive pharmacy and dental treatment information. Limitations of this study include the exclusion of subjects younger than 45 years old and the lack of information on important risk factors, such as the number of teeth at risk and the indication for the antibiotic prescriptions. This study could not assess the impact of antibiotics, such as metronidazole, in younger destructive periodontal disease patients who present with suppuration and other signs of clinical inflammation. Similarly, some have advocated that specific diagnostic testing should be done on persons with destructive periodontal disease to determine the need for antibiotics, and that antibiotics should be prescribed only to those individuals in whom a specific periodontal infection is diagnosed (Loesche *et al*., 1992,1996). With no data on diagnosis or reason for antibiotic prescription, we cannot assess whether such a targeted strategy might be effective.

In summary, systemic antibiotic use was not associated with a lower incidence of tooth loss. It is possible that our inability to identify a beneficial effect was due to a variety of biases, including confounding, selection biases, and misclassification biases. Participants treated with antibiotics may have had different numbers of teeth present at the start of this study, may have had different disease conditions, or may have had other risk factors present that actually caused their teeth to be lost more often than those participants not treated with antibiotics. Further epidemiological studies should explore the consistency of our findings, and if consistent trends emerge with respect to specific classes of antibiotics and specific risk groups, a long-term large randomized clinical trial should be planned. Meanwhile, our findings of lack of association between antibiotics and tooth loss and the growing concerns about antibiotic resistance reinforce that prescription of antibiotics for chronic destructive periodontal diseases should be made with caution.

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Table 1

Characteristics of Participants by Antibiotic Use during the First Three Years of the Study

		Antibiotic Use[1]				
		No use (n = 3643)	**1-13 days (n = 2858)**	**14-20 days (n = 1633)**	**21+ days (n = 4497)**	**Total (n = 12,631)**
Age group[2] (in yrs)	45-48	28%	29%	30%	28%	28%
	49-51	23%	23%	23%	23%	23%
	52-55	25%	25%	23%	24%	24%
	55-61	24%	23%	25%	26%	25%
Gender	Female	43%	50%	51%	59%	51%
	Male	57%	50%	49%	41%	49%
Diabetes[3]	No	91%	89%	87%	83%	87%
	Yes	9%	11%	13%	17%	13%
Anti-inflammatory use[4]	No	61%	48%	41%	33%	45%
	Yes	39%	52%	59%	67%	55%
Smoking[5]	Never	52%	52%	50%	48%	50%
	Former	24%	26%	27%	28%	26%
	Current	18%	19%	21%	23%	21%
High use of dental-preventive treatment[6]	No	53%	52%	51%	51%	52%
	Yes	47%	48%	49%	49%	48%
High use of caries treatment[7]	No	56%	50%	47%	45%	49%
	Yes	44%	50%	53%	55%	51%
Periodontal treatment[8]	No	86%	85%	83%	85%	85%
	Yes	14%	15%	17%	15%	15%
Periodontal status[9]	Mild	77%	78%	79%	82%	79%
	Moderate	20%	20%	19%	17%	19%
	Advanced	3%	2%	1%	1%	2%
Tooth loss[10]	No	90%	84%	83%	83%	85%
	1-2 teeth	9%	14%	14%	14%	13%
	3+ teeth	1%	2%	3%	3%	2%

[1] Differences in cumulative numbers of days on antibiotics during the first three-year period were statistically significant for all characteristics of participants (Chi-square test, $p < 0.001$), except for age, high dental-preventive treatment users, and periodontal treatment users (Chi-square test, $p > 0.05$).

[2] Age of the cohort members in 1999.

[3] Diabetes status was obtained from the HMO's diabetes registry.

[4] Anti-inflammatory use refers to one or more prescription fills of non-steroidal anti-inflammatory drugs, except aspirin, during the first three-year period.

[5] Smoking status is the worst smoking status during the study. This information was not available for 367 participants.

[6] High use of dental-preventive services refers to higher than the median use of dental-preventive procedures during the first three-year period.

[7] High use of caries treatment refers to higher than the median use of restorative and endodontic procedures during the first three-year period.

[8] Periodontal treatment refers to one or more procedures related to the active and maintenance phases of the periodontal treatment during the first three-year period.

[9] Periodontal disease severity refers to the first periodontal severity code recorded in the dental utilization database.

[10] Tooth loss refers to the number of teeth extracted during the first three years of the study.

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Table 2

Association between Antibiotic Use and Other Covariates in the First 3 Years of the Study and Tooth Loss in the 4 Subsequent Years (long-term): Rates, Rate Ratios, and Rate Differences of Tooth Loss by Antibiotic and Other Covariates

		Number of Teeth Lost	Number of Person-years	Adjusted Rate (95%CI) (*per* 100)	Adjusted Rate Ratio (95%CI)[1]	Adjusted Rate Difference (95%CI) (*per* 100)[1]
Antibiotics[2,3]	No use	1724	13,706	8.5 (7.7 - 9.2)		
	1-13 days	1397	11,092	8.2 (7.4 - 9.1)	1.0 (0.8 - 1.1)	-0.2 (-1.3 - 0.9)
	14-20 days	907	6422	9.8 (8.0 - 11.7)	1.2 (0.9 - 1.4)	1.3 (-0.6 - 3.3)
	21+ days	2653	17,780	10.0 (9.1 - 10.9)	1.2[4] (1.0 - 1.3)	1.5[4] (0.3 - 2.7)
Age group	45-48	1790	13,760	8.8 (7.9 - 9.6)		
	49-51	1394	11,212	8.3 (7.5 - 9.0)	0.9 (0.8 - 1.1)	-0.5 (-1.7 - .6)
	52-55	1774	11,912	9.9 (8.7 - 11.1)	1.1 (1.0 - 1.3)	1.1 (-0.3 - 2.5)
	55-61	1723	12,116	9.6 (8.7 - 10.6)	1.1 (1.0 - 1.3)	0.9 (-0.4 - 2.1)
Gender	Female	3054	25,400	9.1 (8.5 - 9.7)		
	Male	3627	23,600	9.2 (8.4 - 9.9)	1.0 (0.9 - 1.1)	0.1 (-0.9 - 1.1)
Diabetes	No	5480	42,561	8.8 (8.3 - 9.3)		
	Yes	1201	6439	11.7 (10.1 - 13.4)	1.3[4] (1.2 - 1.5)	2.9[4] (1.2 - 4.6)
Smoking	Never	1904	25,449	7.2 (6.6 - 7.8)		
	Former	1582	13,147	9.0 (8.1 - 9.9)	1.3[4](1.1 - 1.4)	1.8[4] (0.7 - 2.9)
	Current	3195	10,404	16.4 (14.8 - 18.0)	2.3[4] (2.0 - 2.6)	9.2[4] (7.5 - 10.9)
High use of dental-preventive treatment	No	4429	25,071	11.7 (10.8 - 12.6)		
	Yes	2252	23,929	7.0 (6.5 - 7.6)	0.6[4] (0.5 - 0.7)	-4.7[4] (-5.7 - -3.7)
Periodontal treatment	No	5453	41,573	9.2 (8.7 - 9.8)		
	Yes	1228	7427	8.5 (7.5 - 9.5)	0.9 (0.8 - 1.1)	-0.7 (-1.9 - 0.4)
High use of caries treatment	No	3321	24,128	8.1 (7.5 - 8.7)		
	Yes	3360	24,872	10.2 (9.5 - 10.9)	1.3[4] (1.1 - 1.4)	2.1[4] (1.1 - 3.0)
Anti-inflammatory use	No	2760	21,797	8.9 (8.2 - 9.6)		
	Yes	3921	27,203	9.3 (8.6 - 9.9)	1.0 (0.9 - 1.2)	0.3 (-0.6 - 1.3)
Periodontal status[3]	Mild	3306	39,018	7.4 (6.9 - 7.8)		
	Moderate	2623	9116	19.3 (17.2 - 21.4)	2.6[4] (2.3 - 3.0)	11.9[4] (9.8 - 14.1)
	Advanced	752	866	51.2 (39.9 - 62.6)	7.0[4] (5.5 - 8.7)	43.9[4] (32.5 - 55.2)
Tooth loss[3]	No	4235	41,745	8.1 (7.6 - 8.6)		
	1-2 teeth	1811	6220	16.5 (14.6 - 18.4)	2.0[4] (1.8 - 2.3)	8.4[4] (6.4 - 10.3)
	3+ teeth	635	1035	27.3 (21.0 - 33.6)	3.4[4] (2.7 - 4.2)	19.2[4] (12.8 - 25.5)

[1] Adjusted by the other variables in the Table.

[2] Number of cumulative days of antibiotic prescriptions filled during the first three-year period.

[3] Test for linear trend: $p < 0.05$ (linear trends tested by assessment of the statistical significance of the adjusted rate ratio of the main exposures continuous variables with values representing each category).

[4] $p < 0.05$.

Table 3

Association between Classes of Antibiotics Used in the First 3 Years of the Study and Tooth Loss in the 4 Subsequent Years (long-term): Rate Ratios of Tooth Loss by Antibiotic Classes

		Number of Teeth Lost	Number of Person-years	Unadjusted Rate Ratio	Adjusted Rate Ratio[1]
Penicillins	No use	3585	28,523		
	1-13 days	1626	10,900	1.2 (1.0 - 1.4)	1.0 (0.9 - 1.1)
	14-20 days	758	4957	1.2[2] (1.0 - 1.5)	1.2 (1.0 - 1.4)
	21+ days	940	6088	1.3[2] (1.1 - 1.5)	1.1 (1.0 - 1.3)
Clindamycin[3]	No use	6518	48,709		
	1-13 days	321	1279	1.9[2] (1.4 - 2.6)	1.7[2] (1.3 - 2.2)
	14-20 days	24	256	0.7 (0.5 - 1.1)	0.7 (0.5 - 1.1)
	21+ days	46	224	1.6 (0.9 - 2.8)	1.2 (0.7 - 2.0)
Metronidazole	No use	6509	47,614		
	1-13 days	278	2284	0.9 (0.7 - 1.2)	1.0 (0.8 - 1.3)
	14-20 days	70	330	1.6 (0.9 - 2.8)	1.4 (0.8 - 2.4)
	21+ days	52	240	1.6 (0.8 - 3.5)	1.6 (0.9 - 2.8)
Tetracyclines	No use	6099	44,317		
	1-13 days	483	3092	1.2 (0.9 - 1.4)	1.1 (0.9 - 1.4)
	14-20 days	100	805	0.9 (0.6 - 1.4)	1.0 (0.7 - 1.5)
	21+ days	227	2254	0.8[2] (0.6 - 1.0)	0.9 (0.7 - 1.1)
Macrolides	No use	5551	41,195		
	1-13 days	977	6583	1.1 (0.9 - 1.3)	1.1 (0.9 - 1.3)
	14-20 days	203	1412	1.1 (0.8 - 1.5)	1.1 (0.8 - 1.5)
	21+ days	178	1278	1.1 (0.8 - 1.4)	1.0 (0.8 - 1.4)

[1] Adjusted for age (45-48; 49-51; 52-55; 55-61 yrs old), gender (male/female), smoking status (non-smoker, former smoker, or current smoker), diabetes, anti-inflammatory use, high use of dental preventives and caries treatments, periodontal treatment, periodontal disease severity (mild, moderate, or advanced periodontitis), and tooth loss during the first 3 yrs (0; 1-2; 3+ teeth).

[2] $P < 0.05$.

[3] Test for linear trend: $p < 0.05$ (linear trends tested by assessment of the statistical significance of the adjusted rate ratio of the main exposures as continuous variables, with values representing each category).

Table 4

Subgroup Analyses of the Association between Antibiotic Use in the First 3 Years of the Study and Tooth Loss in the 4 Subsequent Years: Adjusted Rate Ratios of Tooth Loss by Antibiotic and Classes of Antibiotics

		Persons Undergoing Periodontal Treatment[1]	Persons with Moderate and Advanced Periodontal Disease	Current Smokers
All classes[2]	1-13 days	0.8 (0.6 - 1.0)	0.9 (0.7 - 1.1)	1.0 (0.8 - 1.2)
	14-20 days	0.8 (0.6 - 1.1)	1.0 (0.8 - 1.3)	0.9 (0.7 - 1.3)
	21+ days	1.0 (0.8 - 1.3)	0.8[3] (0.7 - 1.0)	1.2 (0.9 - 1.5)
Penicillins	1-13 days	0.9 (0.7 - 1.1)	0.9 (0.8 - 1.2)	1.2 (0.9 - 1.4)
	14-20 days	1.1 (0.8 - 1.5)	1.0 (0.8 - 1.3)	1.0 (0.7 - 1.5)
	21+ days	1.3 (0.9 - 1.7)	0.8[3] (0.6 - 1.0)	1.2 (0.9 - 1.6)
Clindamycin	1-13 days	1.3 (0.6 - 3.0)	1.0 (0.7 - 1.4)	1.7[3] (1.0 - 2.9)
	14-20 days	0.8 (0.4 - 1.5)	0.5 (0.3 - 1.1)	0.6 (0.3 - 1.2)
	21+ days	0.6 (0.3 - 1.5)	0.8 (0.3 - 2.0)	1.5 (0.8 - 2.8)
Metronidazole	1-13 days	1.3 (0.9 - 1.9)	1.0 (0.6 - 1.5)	0.8 (0.6 - 1.1)
	14-20 days	1.3 (0.6 - 2.9)	0.8 (0.4 - 1.5)	1.6 (0.7 - 3.5)
	21+ days	0.9 (0.2 - 4.5)	1.0 (0.3 - 3.1)	1.9 (0.9 - 4.1)
Tetracyclines	1-13 days	1.1[4] (0.8 - 1.5)	1.0 (0.8 - 1.4)	1.1 (0.8 - 1.4)
	14-20 days	0.9 (0.6 - 1.5)	0.8 (0.5 - 1.3)	1.2 (0.6 - 2.2)
	21+ days	0.4[3] (0.3 - 0.7)	0.7 (0.5 - 1.1)	1.0 (0.6 - 1.5)
Macrolides	1-13 days	0.8 (0.6 - 1.1)	1.0 (0.8 - 1.3)	1.0 (0.8 - 1.3)
	14-20 days	1.3 (0.7 - 2.3)	0.7 (0.5 - 1.0)	1.4 (0.9 - 2.4)
	21+ days	1.0 (0.6 - 1.7)	1.0 (0.7 - 1.5)	1.2 (0.7 - 1.9)

[1] Persons undergoing periodontal treatment: one or more periodontal procedures related to the active and maintenance phases of the periodontal treatment during the first three-year period.

[2] Number of cumulative days of antibiotic prescriptions filled during the first three-year period.

[3] $p < 0.05$.

[4] Test for linear trend: $p < 0.05$ (linear trends tested by assessment of the statistical significance of the adjusted rate ratio of the main exposures as continuous variables, with values representing each category).