This is the accepted manuscript of the article, which has
been published in **Clinical microbiology and infection** .
2019, vol25 (8), 1021-1025.

# The effect of preoperative oral antibiotic use on the risk of periprosthetic joint infection after primary knee or hip replacement: a retrospective study with a 1-year follow up

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## Abstract

### Objectives

Antibiotics are used for various reasons before elective joint replacement surgery. The aim of this study was to investigate patients' use of oral antibiotics before joint replacement surgery and how this affects the risk for periprosthetic joint infection (PJI).

### Methods

Patients having a primary hip or knee replacement in a tertiary care hospital between September 2002 and December 2013 were identified (n=23 171). Information on oral antibiotic courses purchased 90 days preoperatively and patients' chronic diseases was gathered. Patients with a PJI in a one-year follow-up period were identified. The association between antibiotic use and PJI was examined using a multivariable logistic regression model that included other factors possibly associated with the risk of infection.

### Results

158 (0.68%) cases of PJI were identified. 4 106 (18%) joint replacement operations were preceded by at least one course of antibiotics. The incidence of PJI for patients with preoperative use of oral antibiotics was 0.29% (12/4 106), whereas for patients without antibiotic use it was 0.77% (146/19 065). A preoperative antibiotic course was associated with a reduced risk for subsequent PJI in the univariate (OR 0.38, 95% CI 0.21 – 0.69) and multivariable model (OR 0.40, 95% CI 0.22–0.73).

### Conclusions

The use of oral antibiotics before elective joint replacement surgery is common and has a potential effect on the subsequent risk for PJI. Nevertheless, indiscriminate use of antibiotics before elective joint replacement surgery cannot be recommended, even though treatment of active infections remains an important way to prevent surgical site infections.

## Introduction

Periprosthetic joint infection (PJI) is a catastrophic complication of joint replacement surgery (1). Therefore, it is essential that adequate preventive measures are taken before any elective joint replacement operation.

Active infections, including skin and urinary tract infections, at the time of operation are considered as potential risk factors for subsequent surgical site infection (SSI). Their treatment has been recommended by the international consensus statement on PJIs (2). Furthermore, active preoperative screening and treatment of dental infections is recommended (2-4).

Staphylococcal skin and nasal colonization is common among patients before elective joint replacement (5,6). Thus, even without the presence of active infection, preoperative decolonization may reduce the incidence of SSIs caused by *Staphylococcus aureus* (6-9). The use of oral antibiotics can reduce carriage of *S.aureus* (10), but it has been suggested that oral antibiotics may not reach sufficient nasal concentrations for effective decolonization. Therefore, they are recommended for decolonization of methicillin-resistant *S.aureus* (MRSA) only in conjunction with topical agents (11,12).

Although perioperative intravenous antibiotics have a well-established role in the prevention of SSIs related to joint replacement surgery (13,14), no studies have been conducted on the use of preoperative oral antibiotic before joint replacement surgery and its effect on the risk for subsequent SSI or PJI. The aim of this study was to investigate patients' use of preoperative antibiotics and how this affects the risk for PJI in a one-year follow-up.

## Methods

This retrospective study was performed in the Coxa Hospital for Joint Replacement, Tampere, Finland. Patients, who had undergone an elective primary hip or knee replacement between

September 2002 and December 2013, were identified from the local prospective joint replacement database. Patient consent is not required in retrospective studies like this, according to the Finnish national legislation. If more than one primary joint replacement was performed on a patient during the study period, each operation was considered separately. During the years 2002–2007 patients considered to have high risk for MRSA carriage were screened for MRSA. From 2008 onwards all patients were screened for MRSA on admission, but not for methicillin-sensitive *S.aureus* (15). Routine preoperative skin and nasal decolonization was not in use during the study period. All patients had a preoperative visit to the operating hospital within two months before the joint replacement operation, this included routine laboratory tests and a clinical check-up. Preoperative urine samples were routinely taken and 25% of the patients with bacteriuria received antibiotics (16). A single dose of cefuroxime was used as perioperative antibiotic prophylaxis. If this was contraindicated, clindamycin or vancomycin was used. Known MRSA-carriers received cefuroxime and vancomycin. Cemented prostheses were fixed with gentamicin-impregnated bone cement.

The courses of antibiotics (identified based on their ATC codes (17), see web-only Supplementary Table S1) purchased by the patients within 90 days before the joint replacement were identified from the prescription register of the Social Insurance Institution of Finland. The type of antibiotic and the date of purchase were recorded. Antibiotics are not available without a prescription in Finland and all purchases are recorded in this nationwide prescription register. Antibiotics given for in-patients could not be identified.

Patients with a valid entitlement to reimbursement for certain chronic diseases (diabetes, rheumatic diseases, hypertension, chronic heart failure, chronic coronary disease, arrhythmias, chronic lung disease, Parkinson's disease, epilepsy, Alzheimer's disease, psychotic disorders, haematological and solid malignancies) at the time of the joint replacement were identified from the reimbursement register of the Social Insurance Institution of Finland (see a more detailed description in a previous study of the same study population (16)). For the analyses, chronic heart failure, chronic coronary

disease and arrhythmias were grouped together, as were Parkinson's disease, epilepsy, Alzheimer's disease and psychotic disorders.

The weight and height of patients were retrieved from the local prospective joint replacement database to calculate body mass indexes (BMIs). The data on the types of prostheses, municipality of residence and indication of surgery was also gathered from the database. MRSA carriers were identified from the official database of carriers of multidrug resistant microbes in Pirkanmaa Health District.

Cases of infection were identified from prospective post-discharge surveillance data gathered by an infection control nurse according to the Centers for Disease Control and Prevention criteria (18) and National Nosocomial Infection Surveillance system methodology adapted for Finland (19). The primary outcome was the occurrence of PJI. The occurrence of any surgical site infection (superficial or deep incisional infection or PJI) was considered as a secondary outcome. Infection cases recorded between September 2002 and December 2014 were identified in order to have a 1-year follow up period for all operated joints. Microbiological data on the pathogens causing PJIs were collected from the electronic records of the microbiology laboratory.

## Statistical analysis

All data analyses and management were performed using SPSS for Windows 23.0 statistical software package.

Categorical variables were compared with $\chi^2$ test and continuous variables (age) with Student's independent-samples t-test. P-value <0.05 was considered statistically significant.

The association between preoperative antibiotic use and the outcome (PJIs and all infections separately) was examined using logistic regression with univariate analysis, and odds ratios and 95% confidence intervals (CI) were calculated. Then, a multivariable model was developed in order to consider possible confounding factors.Patients' gender, operated joint, age, BMI, use of cement in

the operation, indication for surgery (arthrosis, rheumatic disease, previous trauma and other reasons) and chronic diseases (chronic heart disease, chronic lung disease, diabetes, hypertension, malignancy, neurological or psychiatric disorder and rheumatic disease) were all included in the model. Patients with the use of antibiotics with potential activity against staphylococcal species (i.e. amoxicillin-clavulanate, cephalosporins, clindamycin, flucloxacillin, fluoroquinolones, macrolides, tetracyclines, trimethoprim and trimethoprim/sulfamethoxazole) (20) were examined separately.

## Results

In total, there were 23 171 primary joint replacements performed for 17 562 patients. Table 1 shows the general characteristics of the study population. During the one-year follow-up, 158 PJIs occurred in the study population (incidence 0.68%). Overall, 490 surgical site infections (2.11% of the study population) were identified.

4 106 (18%) of the joint replacement operations were preceded by one or more courses of oral antibiotics within 90 days before the operation. In 989 (4.3% of the study population) cases there were two or more antibiotic courses. The distribution of the time difference between the joint replacement surgery and the date of purchase of the antibiotic course closest to the operation is shown in Figure 1. The median number of days between the joint replacement and the antibiotic course was 30. The most commonly used antibiotics were first generation cephalosporins, penicillin and pivmecillinam (Table 2). In total, there were 5 741 packages of antibiotics purchased preoperatively, giving an antibiotic consumption of 2.75 packages per 1000 patients per day.

The incidence of PJI for patients with preoperative oral antibiotic use was 0.29% (12/4 106), whereas for patients without antibiotics the incidence was 0.77% (146/19 065). A preoperative oral antibiotic

course was associated with a decreased risk for subsequent PJI (OR 0.58, 95% CI 0.21–0.69). After adjusting for potential confounding factors in the multivariable model, the risk for PJI for patients with preoperative antibiotic use was still statistically significantly lower (OR 0.40, 95% CI 0.22–0.73).

141 The results were similar when antibiotic use within 30 days was considered: the incidence of PJI was
142 0.19% (4/2 066) for patients with antibiotic use and 0.73% (154/21 105) for patients without
143 antibiotics (OR 0.26, 95% CI 0.10–0.71, in the univariate and OR 0.24, 95% CI 0.08–0.77, in the
144 multivariable analysis) .

145 Of the twelve cases of PJI with preoperative oral antibiotic use, six were classified as early infections,
146 occurring within 30 days from the joint replacement. Overall, 34% (54/158) of the PJIs were early
147 infections. The causative organism for the PJI with preoperative oral antibiotic use could be identified
148 in five cases: in two cases it was *Staphylococcus aureus*, in two cases a coagulase-negative
149 staphylococcus and one case was polymicrobial (a coagulase-negative staphylococcus and
150 *Enterococcus faecalis*) (see Supplementary Table S2). The remaining cases (7/12, 58%) were culture-
151 negative. On the other hand, 16% (23/146) of the PJIs in patients without antibiotic use were culture-
152 negative.

153 When also superficial infection cases were included in the analysis, preoperative antibiotic use did
154 not have an effect on the overall risk for surgical site infection: the incidence was 1.90% (78/4 106)
155 for patients with antibiotic use and 2.16% (412/19 065) for patients without antibiotic use (OR 0.88,
156 95% CI 0.69–1.12).

157 No single antibiotic agent or antibiotic group reduced the risk for PJI statistically significantly (Table
158 2). However, when compared with patients without the use of pre-operative oral antibiotics, the risk
159 for PJI was lower for patients with anti-staphylococcal antibiotics (OR 0.34, 95% CI 0.16–0.72), but
160 not for patients with the use of other antibiotics (OR 0.46, 95% CI 0.19–1.13).

161 A lower incidence of PJI for patients with antibiotic use was observed also when the analyses were
162 repeated in the subgroups of hip and knee joint replacements (separately), operations with and
163 without the use of cement, patients with osteoarthritis as the indication for surgery and the year
164 when the surgery was conducted (see Supplementary Table S3). Statistically significant differences,
165 however, were not observed in all cases due to insufficient statistical power.

## Discussion

This large study shows that the use of oral antibiotics before elective joint replacement surgery is common. Also, the use of antibiotics preoperatively is associated with and may have an effect on the subsequent risk for periprosthetic joint infection.

In this study population, almost one fifth of the patients with elective joint replacement had received oral antibiotics within three months before surgery. The use of oral antibiotics prior to joint replacement surgery has hardly been studied. In a Swedish study by Stefansdottir et al. (5), 25% of the patients coming for elective joint replacement had received antibiotics within six months before surgery, a number comparable to the present study. This study indicates that patients with elective joint replacement seem to receive more antibiotics than the general population. According to the data published by European Centre for Disease Prevention and Control, the overall antibiotic consumption in Finland has been about 2 packages per 1000 inhabitants per day in the recent years (21), whereas in this study the number was 2.75 packages per 1000 patients per day.

The incidence of PJI was lower among patients with preoperative oral antibiotic use than among patients without antibiotic use. The effect of oral antibiotic use on the risk for PJI has not been studied before and thus this finding has not been reported previously. Treatment of active infections before joint replacement surgery is recommended in the international consensus statement on PJIs (2), because there is a risk for haematogenous spread to the replaced joint postoperatively from non-treated infection sites. However, treatment of active infections should decrease the risk for PJI to the level of the general population, but not offer any additional prophylactic protection. Furthermore, active infections would probably lead to delaying the surgery.

Preoperative oral antibiotic use could possibly reduce the frequency of *Staphylococcus aureus* carriage. Supporting this view, the current study indicates that especially the use of staphylococcal antibiotics seemed to reduce the incidence for PJI. It has been estimated that 25% to 40% of the

population are nasal carriers of *Staphylococcus aureus* (6,10), and similar numbers have been found among patients with joint replacement surgery (5,8). In addition, nasal carriage of *S.aureus* is recognized as an independent risk factor for subsequent surgical site infection after joint replacement surgery (22) and different pre-operative decolonization regimens have been proposed. These include nasal mupirocin ointment with or without skin decolonization (6). In a systematic review Chen et al. found that surgical site infection rates could be reduced by 13% to 200% with decolonization-programmes (8). However, most of the studies included in the review involved only patients, who screened positive for *S.aureus*. On the other hand, Sousa et al. found in a small randomized controlled trial that decolonization was not effective in reducing the rate of PJI (23), and the international consensus statement on PJIs does not recommend universal screening and decolonization of patients undergoing joint replacement surgery (2). Unfortunately, there is no information on the rate of *S.aureus* carriage in the present study population and therefore the effect of the use of oral antibiotics on the risk of PJI in relation to the carriage rate could not be examined.

On the other hand, it has been proposed that oral antibiotics may not reach sufficient concentrations in the nares for adequate decolonization (12). Nevertheless, studies on MRSA colonization have shown that carriage of *S.aureus* outside the nasopharynx is also common (24,25), even though the role of oral antibiotics in reducing carriage in non-nasal sites is unclear. Furthermore, it is unclear for how long the potential effect of oral antibiotics in *S.aureus* decolonization could last. In a study conducted among children with skin infections and colonized by *S.aureus*, oral antibiotics reduced the carriage rate by half and this effect could be seen up to 50 days after the course of antibiotics (26).

Another possible mechanism for action for the antibiotics could be that the patients had “hidden” infections that were treated, but this seems unlikely, and for example treating bacteriuria with antibiotics has been shown to be ineffective in the prevention of PJI in the same study population (16).

There are some limitations to this study. Firstly, the indications for the antibiotics were not known, nor who had prescribed the antibiotics. The dosage of the antibiotics was also not registered, and thus antibiotic consumption rates based on defined daily doses could not be evaluated, but information on the number of pills purchased was available. Nevertheless, as all antibiotic purchases are recorded in the national register, patients' use of antibiotics could be evaluated comprehensively. Secondly, antibiotics given in hospitals could not be identified. However, it can be assumed that this number is fairly low, since the joint replacement surgery would have been most likely postponed if the patient had required treatment for an infection in a hospital setting. Thirdly, there could be a so-called "healthy patient bias", where healthier patients are more prone to take care of themselves and perhaps seek medical attention more readily, thus potentially receiving antibiotics more easily than others. However, the characteristics and distribution of chronic diseases of patients with and without antibiotic use were similar, and the effect of chronic diseases could be considered extensively. Finally, it is possible that the association between oral antibiotic use and lower risk for PJI could be caused by some unknown confounding factors that could not be identified in the analysis. Nevertheless, the effect of many known risk factors for PJI could be taken into account.

While this study indicates that preoperative antibiotic use is associated with a lower rate of PJI, even when several confounding factors were considered and subgroup analyses performed, the use of oral antibiotics as prophylaxis cannot be recommended, unless there are active infections, due to potential harms, such as the increased risk for *Clostridioides difficile* infections. Furthermore, there is a risk for an increase in the incidence of resistant bacterial strains. For example, Cheng et al. have shown that the use of non-MRSA antibiotics increases the rate of nasal MRSA carriage (27). In addition, even if used, the current study shows that the number needed to treat (NNT) with preoperative oral antibiotics to prevent one case of PJI would be high (NNT 211).

In conclusion, the use of oral antibiotics before elective joint replacement surgery is common and it may affect the subsequent risk for PJI, perhaps due to a reduced rate of *S.aureus* carriage. Further studies are needed in order to evaluate the significance of this novel result. Meanwhile, indiscriminate use of antibiotics before elective joint replacement surgery cannot be recommended, even though the treatment of active infections remains important in the prevention of surgical site infections.

## Transparency declaration

Dr Honkanen reports grants from the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital, during the conduct of the study. All authors report no other conflicts of interest.

## Acknowledgements

The authors wish to thank infection control nurse Jaana Sinkkonen for her help in gathering the data.

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Table 1. Characteristics of patients with and without preoperative oral antibiotic use

| Patient characteristic | Patients with antibiotic use (n= 4 106) | | Patients without antibiotic use (n= 19 065) | |
|---|---|---|---|---|
| | n | % | n | % |
| Male gender | 1 324 | 32 | 7 486 | 39 |
| Age, y, mean (SD) | 66 | (11) | 67 | (11) |
| Knee location | 2 383 | 58 | 10 588 | 56 |
| BMI, mean (SD) | 29.7 | (5.3) | 29.2 | (5.1) |
| Known MRSA-carrier | 16 | 0.4 | 46 | 0.2 |
| Rural living location | 493 | 12 | 2 649 | 14 |
| Chronic diseases | | | | |
| Chronic heart disease [a] | 1 577 | 38 | 6 241 | 33 |
| Chronic lung disease | 375 | 9 | 1 140 | 6 |
| Diabetes | 414 | 10 | 1 463 | 8 |
| Hypertension | 1 285 | 31 | 5 031 | 26 |
| Malignancy | 182 | 4 | 625 | 3 |
| Neurological or psychiatric disorder [b] | 180 | 4 | 687 | 4 |
| Rheumatic disease | 264 | 6 | 948 | 5 |
| Osteoarthrosis as the indication for operation | 3 740 | 91 | 17 265 | 91 |
| Use of cement in the operation | 3 123 | 76 | 14 287 | 75 |

a. Includes chronic heart failure, chronic coronary disease and arrhythmias
b. Includes Parkinson's disease, epilepsy, Alzheimer's disease and psychotic disorders

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Table 2. The numbers of primary joint replacement operations preceded by different groups of antibiotics 90 days before surgery and their effect on the risk for periprosthetic joint infection (PJI)

| Antibiotic group | Number of operations preceded by antibiotic use | | Effect of antibiotic on the risk for PJI in the univariate analysis | |
|---|---|---|---|---|
| | n | % of all operations | OR | 95% CI |
| 1st generation cephalosporins | 984 | 4.2 | 0.29 | 0.07–1.16 |
| Penicillin | 693 | 3.0 | 0.41 | 0.10–1.67 |
| Pivmecillinam | 571 | 2.5 | 0.51 | 0.13–2.05 |
| Amoxicillin | 544 | 2.3 | 0.53 | 0.13–2.15 |
| Fluoroquinolones | 500 | 2.2 | 0.58 | 0.14–2.35 |
| Tetracyclines | 424 | 1.8 | NA[a] | NA |
| Macrolides | 374 | 1.6 | 0.78 | 0.19–3.16 |
| Trimethoprim | 303 | 1.3 | NA[a] | NA |
| Amoxicillin-clavulanate | 182 | 0.8 | NA[a] | NA |
| Clindamycin | 146 | 0.6 | 1.01 | 0.14–7.23 |

329 a. There were no PJIs in this group

330

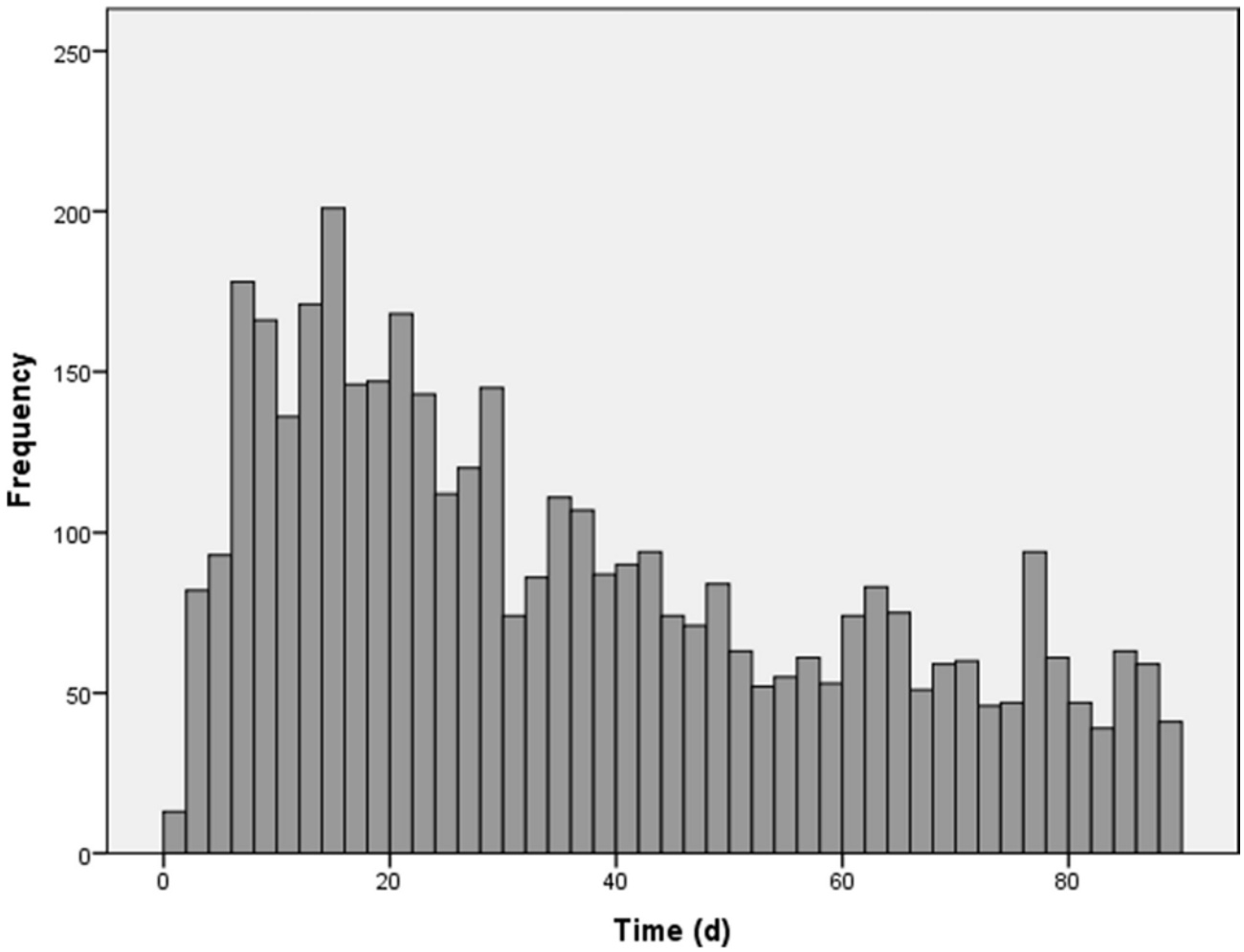


Fig. 1. The time difference (in days) between the joint replacement surgery and the date of purchase of the antibiotic course received closest to the surgery.