

# Increased risk of prosthetic joint infection associated with esophago-gastro-duodenoscopy with biopsy

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**Background** There are no prospective data regarding the risk of prosthetic joint infection following routine gastrointestinal endoscopic procedures. We wanted to determine the risk of prosthetic hip or knee infection following gastrointestinal endoscopic procedures in patients with joint arthroplasty.

**Methods** We conducted a prospective, single-center, case-control study at a single, tertiary-care referral center. Cases were defined as adult patients hospitalized for prosthetic joint infection of the hip or knee between December 1, 2001 and May 31, 2006. Controls were adult patients with hip or knee arthroplasties but without a diagnosis of joint infection, hospitalized during the same time period at the same orthopedic hospital. The main outcome measure was the odds ratio (OR) of prosthetic joint infection after gastrointestinal endoscopic procedures performed within 2 years before admission.

**Results** 339 cases and 339 controls were included in the study. Of these, 70 cases (21%) cases and 82 controls (24%) had undergone a gastrointestinal endoscopic procedure in the preceding 2 years. Among gastrointestinal procedures that were assessed, esophago-gastro-duodenoscopy (EGD) with biopsy was associated with an increased risk of prosthetic joint infection (OR = 3, 95% CI: 1.1–7). In a multivariable analysis adjusting for sex, age, joint age, immunosuppression, BMI, presence of wound drain, prior arthroplasty, malignancy, ASA score, and prothrombin time, the OR for infection after EGD with biopsy was 4 (95% CI: 1.5–10).

**Interpretation** EGD with biopsy was associated with an increased risk of prosthetic joint infection in patients with hip or knee arthroplasties. This association will need to be confirmed in other epidemiological studies and adequately powered prospective clinical trials prior to recommending antibiotic prophylaxis in these patients.

undergoing joint arthroplasties and gastrointestinal (GI) endoscopic procedures (Kurtz et al. 2007). Prosthetic joint infections (PJIs) occur in less than 2.5% of total hip and knee arthroplasties (Tattevin et al. 1999). They can occur early from local bacterial invasion (perioperative contamination or post-operative wound infection) or late from joint seeding secondary to bacteremia (Zimmerli et al. 2004). GI endoscopic procedures, including both esophago-gastro-duodenoscopy (EGD) and colonoscopy, are frequently associated with transient bacteremia probably secondary to microbial translocation of the gut into the bloodstream, and could therefore be associated with increased risk of PJI (LeFrock et al. 1973, Botoman and Surawicz 1986, Low et al. 1987, Deacon et al. 1996).

Despite the high frequency of transient bacteremia in patients undergoing GI endoscopy, there have been at least 20 published case reports of PJI in patients who had recently undergone these procedures (Triesenberg et al. 1992, Vanderhooft and Robinson 1994, Schlaeffer et al. 1996, Cornelius et al. 2003). The practice guidelines for the use of antimicrobial prophylaxis for gastrointestinal endoscopic procedures by the American Society of Gastrointestinal Endoscopy (ASGE) do not recommend routine prophylactic antibiotic use in patients with joint arthroplasties (Banerjee et al. 2008). However, the actual risk of developing PJI after GI endoscopy is unknown, as there have been no large comparative studies to evaluate the potential outcome.

We wanted to determine the risk of developing PJI after GI endoscopic procedures in a large, prospective, single-center case-control study. The exposure of interest was assessed by evaluating the prevalence of having undergone GI endoscopy within the preceding 2 years in cases of patients admitted for hip or knee PJI, and compared to control patients as defined below. An association, if demonstrated, could prompt reconsideration of the recommendation of administered antibiotic prophylaxis before endoscopic procedures.

In an aging population, increasing numbers of patients are

## Methods

### Setting and subjects

A description of the study setting and cohorts has been outlined in a recent publication (Berbari et al. date 2010) that assessed the risk of PJI associated with dental procedures. Briefly, the study was conducted at a single, tertiary-care referral center in Rochester, MN. Possible study participants were assessed from consecutive patients admitted to the inpatient orthopedic hospital service of the Mayo Clinic, Rochester MN, from December 1, 2001 through May 31, 2006. Case patients were defined as those with a diagnosis of prosthetic hip or knee infection who were hospitalized at the Mayo Clinic. Control patients were those with a prosthetic hip or knee who were hospitalized by an orthopedic service for a non-infectious reason during the same time period. Frequency matching was performed between case and control patients on the location of hip or knee arthroplasty. Not all index arthroplasties were performed at our institution, so periprocedural prophylactic measures differed.

Written informed consent to participate in the study was obtained from all subjects, and the study was approved by the Institutional Review Board of the Mayo Clinic (IRB #PR927-01-03, 10/24/2007).

### Data collection

Structured forms were used to interview patients and to abstract relevant clinical data from local and external medical records, including details of GI endoscopic procedures performed within 2 years of entry into the study. If patients reported having an endoscopic procedure, the procedure reports were then requested from the primary care physician's office. GI endoscopic procedures included in the analysis included EGD with or without biopsy, flexible sigmoidoscopy with or without biopsy, colonoscopy with or without biopsy, and EGD with esophageal dilation. None of the patients had undergone esophageal variceal banding or sclerotherapy, endoscopic ultrasound (EUS), or endoscopic retrograde cholangiopancreatography (ERCP).

A prosthetic hip or knee infection was defined as same microorganism being isolated from 2 or more cultures from joint or periprosthetic fluid specimens, the presence of acute inflammation consistent with infection on pathological examination, the presence of a cutaneous sinus tract communicating with the prosthesis, or the presence of purulence in a joint space as determined by the surgeon (Berbari et al. 2010). The presence of previously defined risk factors for the development of PJI were assessed (Berbari et al. 1998, Zimmerli et al. 2004).

The microbiological evaluation of PJIs was done according to Clinical and Laboratory Standards Institute (CLSI) techniques used in the clinical microbiological facilities of the Mayo Clinic. If the joint arthroplasty occurred less than 2 years before study entry, details of GI endoscopic proce-

dures were obtained retrospectively back to the date of the arthroplasty.

### Statistics

The main risk factor of interest in the study was whether the study subjects had undergone any GI endoscopic procedure up to 2 years before they entered the study. Other variables assessed for association with PJI are shown in Table 1. Logistic regression was used to assess variables for association with the odds of PJI. Multivariable models included covariates with a univariate  $p$ -value  $\leq 0.1$ , including sex, age, joint age, immunosuppression, BMI, presence of wound drain, prior arthroplasty, malignancy, ASA score, and prothrombin time as potential confounders based on the clinician's judgment. All the tests were 2-sided and  $p$ -values less than 0.05 were considered statistically significant. Statistical analysis was performed using SAS software version 9.0.

## Results

There were 339 case patients with prosthetic hip or knee infection, and 339 controls were enrolled. Cases and controls were similar regarding age, sex, and proportion of hip and knee arthroplasties. Cases were more likely than controls to be diabetic, immunocompromised, to have had a prior operation on the index joint, and to have had a prior arthroplasty on the index joint. Cases had a shorter joint age than controls (Table 1). Of the 339 case patients, 259 (74%) had a diagnosis of PJI established within 10 days before or after study entry. Reasons for admission for the control subjects included need for an arthroplasty at a site distant from the index arthroplasty (57%), need for aseptic revision of the index arthroplasty (38%), and need for some other orthopedic procedure(s) (5%).

The 339 cases and 339 controls had undergone 187 GI endoscopic procedures within 2 years of enrollment in the study. These procedures included colonoscopies without biopsy (33%), colonoscopies with biopsy (25%), EGDs with biopsy (14%), EGDs without biopsy (12%), flexible sigmoidoscopies without biopsy (10%), flexible sigmoidoscopies with biopsy (1%), and EGDs with esophageal dilation (5%) (Table 2). Of the case patients, 21% had undergone a GI endoscopic procedure in the 2 years prior to admission, as compared to 24% of the control patients (OR 1.0, 95%CI 0.7-1.5). However, of the individual GI endoscopic procedures, EGD with biopsy had occurred in 19 (6%) of the cases and in 8 (2%) of the controls (OR = 2.8, 95% CI: 1.1–7.1;  $p = 0.03$ ). The mean age of the prosthetic joint at the time of EGD with biopsy was similar in the cases and controls (3.9 (SD 3.8) years vs. 4.5 (SD 4.6) years)—in contrast to the difference in joint age between cases and controls in the total cohort described above. In a multivariable analysis adjusting for age, sex, joint age, immunosuppression, BMI > 40, diabetes mellitus, presence of wound drain, prior arthroplasty or other surgery, malignancy, ASA

Table 1. Clinical features of patients included in the 2 study populations

| Characteristic                         | Cases<br>(n = 339) | Controls<br>(n = 339) | OR (95% CI)                    | p-value |
|--|--------------------|-----------------------|--------------------------------|---------|
| THA / TKA                              | 164 / 175          | 164 / 175             | –                              | –       |
| Female sex, no. (%)                    | 168 (50%)          | 180 (53%)             | 0.9 (0.6–1.2)                  | 0.4     |
| Median age (range)                     | 69.5 (26–91)       | 71.4 (36–95)          | 0.94 per 5 years<br>(0.88–1.0) | 0.09    |
| Joint age in months,<br>median (range) | 16 (1 day–296)     | 50 (1.2–414)          | 0.91 per 1 year<br>(0.88–0.94) | < 0.001 |
| BMI                                    |                    |                       |                                | < 0.001 |
| < 25                                   | 76 (22%)           | 51 (15%)              | 1.0 (reference)                |         |
| 25–30                                  | 89 (26%)           | 124 (37%)             | 0.5 (0.3–0.8)                  |         |
| 31–39                                  | 113 (33%)          | 138 (41%)             | 0.5 (0.4–0.8)                  |         |
| ≥ 40                                   | 61 (18%)           | 26 (8%)               | 1.6 (0.9–2.8)                  |         |
| Diabetes mellitus                      | 69 (20%)           | 42 (12%)              | 1.8 (1.2–2.7)                  | 0.006   |
| Prior operation on index joint         | 130 (38%)          | 86 (25%)              | 1.8 (1.3–2.5)                  | < 0.001 |
| Prior arthroplasty on index joint      | 107 (32%)          | 55 (16%)              | 2.4 (1.6–3.4)                  | < 0.001 |
| Immunocompromised <sup>a</sup>         | 208 (61%)          | 149 (44%)             | 2.0 (1.5–2.8)                  | < 0.001 |

<sup>a</sup> Diagnosis of rheumatoid arthritis, diabetes mellitus, malignancy, chronic kidney disease, or current use of systemic steroids or immunosuppressive medications.

Table 2. Types of procedures performed in the 2 study populations

| Endoscopy                             | Cases    | Controls | OR (95% CI)    | p-value           |
|---------------------------------------|----------|----------|----------------|-------------------|
| Any endoscopy                         | 70 (21%) | 82 (24%) | 1.0 (0.7–1.5)  | 1.0               |
| EGD with biopsy                       | 19 (6%)  | 8 (2%)   | 2.8 (1.1–7.1)  | 0.03 <sup>a</sup> |
| EGD without biopsy                    | 13 (4%)  | 9 (3%)   | 2.0 (0.8–5.4)  | 0.2               |
| Colonoscopy with biopsy               | 20 (6%)  | 27 (8%)  | 0.8 (0.4–1.6)  | 0.5               |
| Colonoscopy without biopsy            | 28 (8%)  | 34 (10%) | 1.1 (0.6–1.9)  | 0.8               |
| Flexible sigmoidoscopy with biopsy    | 1 (0.3%) | 1 (0.3%) | 0.8 (0.1–15.2) | 0.9               |
| Flexible sigmoidoscopy without biopsy | 5 (1%)   | 13 (4%)  | 0.5 (0.2–1.5)  | 0.2               |
| Esophageal dilation                   | 4 (1%)   | 5 (1%)   | 1.0 (0.2–4.1)  | 1.0               |

<sup>a</sup> p-value calculated by logistic regression.

Table 3. Microbiology of PJI in the 2 study populations<sup>a</sup>

| Microorganism, n (%)                     | Cases with<br>GI endoscopy<br>(n = 70) | Cases without<br>GI endoscopy<br>(n = 269) |
|--|--|--|
| Coagulase-negative <i>Staphylococcus</i> | 24 (34%)                               | 76 (28%)                                   |
| <i>Staphylococcus aureus</i>             | 15 (21%)                               | 80 (30%)                                   |
| Beta-hemolytic streptococci              | 2                                      | 11   |
| <i>Streptococcus viridans</i>            | 2                                      | 9  |
| Enterococci                              | 3                                      | 7  |
| <i>Staphylococcus lugdunensis</i>        | 1                                      | 0  |
| Gram-negative Enterobacteriaceae         | 3                                      | 7  |
| <i>Pseudomonas aeruginosa</i>            | 0                                      | 2  |
| Anaerobic bacteria                       | 4                                      | 8  |
| Others                                   | 4                                      | 15   |
| Polymicrobial                            | 5                                      | 33   |
| Culture negative                         | 7                                      | 21   |
| Total                                    | 70                                     | 269  |

<sup>a</sup> No statistically significant differences in prevalence of individual organisms, or in proportion of GI tract-associated organisms, were found between cases and controls.

score (I/II vs. III/IV), and prothrombin time > 4 h, the OR for infection after EGD with biopsy was 3.8 (95% CI: 1.5–9.7).

It is noteworthy that only 5 cases (1%) and 4 controls (1%) had received antimicrobial prophylaxis at the time of their GI endoscopic procedures. The most common microorganisms obtained from PJI cases included coagulase-negative staphylococci (29%), and *Staphylococcus aureus* (28%). Microorganisms that normally colonize the GI tract, including streptococci, enterococci, Gram-negative bacteria, and anaerobes, accounted for only 17% of the PJIs. There were no statistically significant differences in the pathogens that caused PJI in patients who had undergone a GI endoscopic procedure and in those who had not undergone a GI endoscopic procedure, or in the subgroup of patients who underwent EGD with biopsy (Table 3).

## Discussion

In this hospital-based, prospective, case-control study that included patients admitted to an orthopedic service with prosthetic

hips or knees, an EGD with biopsy within the preceding 2 years was associated with an increased risk of PJI (OR = 4). Biopsy causes disruption of the mucosal lining of the gut and can therefore increase the risk of bacteremia. To our knowledge, this association has not been reported before and it may have implications for the decision as to whether or not peri-procedural antimicrobial prophylaxis should be given to patients with prosthetic hips or knees undergoing EGD with biopsy.

Currently, there is a lack of consensus among orthopedic surgeons, gastroenterologists, and infectious diseases specialists on the proper use of antimicrobial prophylaxis prior to GI endoscopic procedures in patients with joint arthroplasties. Based upon lack of supporting data, the ASGE guidelines published in 2008 do not recommend antimicrobial prophylaxis for endoscopic procedures to prevent PJI (grade 1C+ recommendation, indicating overwhelming evidence from observational studies) (Banerjee et al. 2008). In these recommendations, only 2 published case reports and a survey of

opinions from infectious disease specialists are cited as evidence. Similar recommendations were made by the American Society of Colon and Rectal Surgeons and the British Society of Gastroenterology (Allison et al. 2009). In contrast, the American Academy of Orthopedic Surgeons, in a recently posted information statement, favored the administration of antibiotic prophylaxis prior to GI endoscopic procedures in patients with joint arthroplasties (<http://www.aaos.org/about/papers/advistmt/1033.asp>).

The role, if any, of antimicrobial prophylaxis for GI endoscopic procedures in prosthetic joint patients has never been addressed in prospective, comparative trials. In a prospective, observational study, Ainscow and Denham (1984) followed 1,000 patients for 6 years who had previously undergone total joint arthroplasty, and evaluated the risk of hematogenous seeding in PJI following certain procedures, including GI endoscopy. Only 14 of these 1,000 patients underwent a GI endoscopic procedure and none developed PJI. This study, however, was not adequately powered to detect an increased risk of PJI after a GI endoscopic procedure. It was also not adequately powered to detect a difference in organisms causing PJI between cases with and without a preceding endoscopy.

Despite the paucity of case reports of PJI following GI endoscopic procedures, it is possible that there is a causal link, particularly with upper endoscopic procedures. Infection of a prosthetic joint can occur by contamination of the prosthesis or joint space during surgery, by local extension of a deep surgical wound infection, or by hematogenous seeding. While bacteremia occurs in up to 5% of patients undergoing EGD, rates as high as 31% and 45% occur during variceal sclerotherapy and esophageal dilation, respectively (Botoman and Surawicz 1986, Deacon et al. 1996). Due to the possibility of low-grade, delayed infection, clinical presentation of PJI caused by transient bacteremia associated with GI endoscopy could be delayed after the procedure. We attempted to account for this possibility by assessing GI endoscopic procedures that had been performed up to 2 years before study entry. On the other hand, in 3 of the 4 previous case reports in the literature, PJI occurred 2 months to 2 years after the arthroplasty; the time to PJI was not reported in the fourth case.

The present study had several possible limitations. First, not all GI endoscopic procedures were included in our evaluation. None of the cases or controls had undergone an ERCP or an EUS. While bacteremia may commonly occur after ERCP, the ASGE guidelines recommend antimicrobial prophylaxis in patients not already on antibiotic therapy for biliary cholangitis (Banerjee et al. 2008). Bacteremia has been shown to occur in 2–4% of patients undergoing EUS of the upper GI tract (Janssen et al. 2004) and up to 6% of patients undergoing EUS of the lower GI tract (Levy et al. 2007). Likewise, flexible sigmoidoscopy, particularly with biopsy, and esophageal dilation were underrepresented in our dataset, and the study may not have been powered to detect any associations with

PJI with these procedures. Secondly, the sample size was initially chosen for power to detect an association between dental procedure (without antibiotic prophylactic use) and prosthetic joint infection. The prevalence of EGD with biopsy was lower in the patient cohort than was occurrence of a dental procedure, therefore power for assessment of EGD was lower in this study. Given the observed EGD with a biopsy rate of 2.4% in the control (non-PJI) patients, this study had 80% power (2-sided test at an alpha-level of 0.05) to detect a rate of at least 7.1% (i.e. odds ratio  $\geq 3.1$ ) in the case (PJI) patients. Thirdly, patients with prosthetic joints at sites other than the hip and knee were not included; therefore, any findings from our study may not be applicable to patients with shoulder arthroplasties, for example. Next, due to the low number of patients who received antimicrobial prophylaxis at the time of GI endoscopy, we were not able to assess the efficacy of prophylaxis in preventing PJI. The indications for the endoscopic procedures performed were not available. Finally, our study was performed at a single, tertiary referral center, and the findings may have been affected by local/ regional patient characteristics and referral bias, potentially limiting the generalizability of the study. It should also be noted that this study was not designed to necessarily prove causality.

In conclusion, we found that EGD with biopsy was associated with an increased risk of PJI in patients with total hip or knee arthroplasties. This association was not present with other gastrointestinal procedures. This positive association should be confirmed in other epidemiological studies. Whether prophylaxis is needed and whether current guidelines need to be amended will most likely require adequately powered prospective clinical trials in future. Currently, antibiotic prophylaxis cannot be routinely recommended at the time of endoscopic procedures in patients with prosthetic joints.

NCP: analysis and interpretation of the data, and writing of the article. ASO and THB: critical revision of the manuscript for important intellectual content, and final approval. DRO, ADH, WRW, JMS and LMB: conception and design, critical revision of the manuscript for important intellectual content, and final approval. WSH and JM: analysis and interpretation of the data, and final approval. EFB: conception and design, and final approval.

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