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Increased Resistance of Skin Flora to Antimicrobial Prophylaxis in Patients Undergoing Hip Revision Arthroplasty

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Abstract. *Background/Aim: Prosthetic joint infection (PJI) remains a major complication after total joint replacement and is the primary indication for revision arthroplasty. Specifically, coagulase-negative Staphylococci (CNS) can cause low-grade infections. Despite the use of cephalosporin-based antimicrobial prophylaxis (AMP) and antiseptic treatment at the surgical site, evidence suggests that a significant number of cases of dermal CNS results in low-grade PJI. Thus, this study examined the bacterial colonization and resistance patterns at the surgical site. We hypothesized that the bacteria developed resistance to antibiotics that are frequently used in primary and revision total hip arthroplasty (THA) procedures. Patients and Methods: Ninety patients, including 63 primary and 27 revision THA patients, were enrolled in this study. For each patient, a single swab of the skin at the surgical site was subjected to clinical microbiology to assess bacterial colonization. Furthermore, resistance to a sentinel panel of antibiotics (benzylpenicillin, erythromycin, tetracycline, oxacillin, fusidic acid, clindamycin, gentamicin, levofloxacin/moxifloxacin, rifampicin, linezolid and vancomycin) was tested. Results: In 96.7% of the patients, at least one bacterial strain was identified at the surgical site, with CNS strains comprising 93.1% of the total. The sentinel panel showed that 30.7% of the CNS strains exhibited maximal resistance to oxacillin, a commonly used cephalosporin. Additionally, oxacillin resistance increased 1.9-fold (p=0.042) between primary and revision THA. Notably, 8.1% of the CNS stains found on patients undergoing primary THA were resistant to gentamicin, an aminoglycoside, and this rate increased 4.7-fold (p=0.001) for patients undergoing revision THA. Conclusion: CNS strains have significant resistance to standard AMP, particularly in individuals undergoing revision THA.*

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Prosthetic joint infection (PJI) remains a major complication after total joint replacement and is the primary indication for revision arthroplasty (1). Data have shown that revisions due to PJI compose approximately 25% of all revision total hip arthroplasty (THA) procedures (2). The challenge in controlling PJI is underscored by projections suggesting a robust increase in THA over the next 15 years (3). The rapid development of PJI shortly after surgery is typically caused by highly virulent bacteria, such as *Staphylococcus aureus*, and associated with acute symptoms, such as pain and fever. In contrast, late manifestations of PJI are often due to a low-grade infection with less virulent bacterial strains of the dermal flora, including coagulase-negative *Staphylococci* (CNS). These low-grade PJI infections frequently result in septic loosening of the prosthetic components over time (4). Although the origin of the microorganisms causing either acute- or low-grade infections cannot be precisely identified in all cases, studies have strongly suggested that intraoperative contamination (nosocomial) either at the surgical site or on the prosthetic components with bacteria from the patient's skin causes PJI (1, 5, 6, 7) despite prophylactic treatment of the skin with antiseptic agents. This is probably because topical antiseptics have limited effectiveness against bacteria in the deeper layers of the stratum corneum (8). Infections at the surgical site occur in approximately 1-1.5% of primary THA cases and there is evidence of a higher rate in patients undergoing revision THA (9-11).

To prevent nosocomial surgical site infections, antimicrobial prophylaxis (AMP) was introduced in the 1980s (12, 13). Current AMP protocols are based on first-generation cephalosporins in the US and second- and third-generation cephalosporins in Europe (14). Despite the use of

AMP, patient data collected in the US between 2001 and 2009 showed an increase in the annual incidence of PJI from 2.05% to 2.18% (15, 16). One potential reason for this observation is that AMP has become increasingly ineffective against strains that commonly cause PJI. This view is supported by the finding that cephalosporin-resistant strains have been detected in patients with PJI after primary joint arthroplasty (17). Previous work on patient cohorts receiving oxacillin-based AMP analysed bacterial susceptibility of nose or groin swabs collected before and after joint revision (2-week period) and showed increases in resistance to isoxazolyl, penicillin, clindamycin, fusidic acid and gentamicin (18). These data support historical observations that nostril swabs obtained from patients two weeks after THA contained an increasing number of bacteria resistant to methicillin, tetracycline, erythromycin, clindamycin and gentamicin than swabs taken one day prior to surgery (19). Based on these findings, we hypothesized that patients undergoing revision THA are colonized with bacteria with an increased resistance to current cephalosporin-based AMP; therefore, we compared resistance to a panel of 12 antibiotics, including the cephalosporin sentinel oxacillin, in patients undergoing primary and revision arthroplasty.

Patients and Methods

A total of 90 consecutive patients (48 men and 42 women) undergoing either primary arthroplasty or aseptic revision arthroplasty at the Department of Orthopaedic Surgery, Klinikum rechts der Isar, Technische Universität München, München, Germany, were included in this prospective study. The age of the patients ranged between 22 and 85 years with a mean patient age of 65±14.7 years. Osteoarthritis was the primary diagnosis for all patients undergoing primary THA, with aseptic loosening being the primary diagnosis for the revision surgery. None of the patients received antibiotics within three months prior to surgery and no local antiseptic treatment, such as chlorhexidine decolonization, was provided. Patients received a single 1.5 g dose of the second-generation cephalosporin cefuroxime as their AMP. Primary and revision THA was performed on 63 and 27 patients, respectively. For primary THA, a direct anterior approach (n=37) or an antero-lateral approach (n=26) was used, whereas all revision THA procedures exclusively used the antero-lateral technique.

Samples were collected the morning before surgery based on established procedures (18). In brief, a single culture sample was obtained with a sterile cotton swab of the skin at the planned surgical site. Standard clinical microbiology was performed at the Department of Microbiology at our Hospital. The swabs were then applied to aerobic agar plates (Columbia sheep blood agar, chocolate agar, MacConkey agar) (Becton Dickinson Gmbh, Heidelberg, Germany) and incubated in an aerobic atmosphere at 37°C for 48 h, after which the bacterial strains were identified using a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometer (Bruker Daltonik, Bremen, Germany). Antimicrobial susceptibility to the antibiotics benzylpenicillin, erythromycin, tetracycline, oxacillin, fusidic acid, clindamycin, gentamicin, levofloxacin/moxifloxacin, rifampicin, linezolid and vancomycin was determined using a VITEK 2 XL (bioMerieux, Nürtingen, Germany). Resistance patterns of the dermal bacteria from patients undergoing primary arthroplasty were compared to those of patients undergoing revision arthroplasty using SPSS software (SPSS Inc., Chicago, IL, USA) and Pearson's Chi-square test. Furthermore, the absolute and relative frequencies, as well as the confidence intervals (CIs) were calculated.

Table I. *Resistance rates.*

Sentinel antibiotics	Class of anitbiotic	Resistance rate (%)	95%-CI
Benzylpenicillin	Penicillin	77.3	70.6-84
Erythromycin	Macrolide	58	50.1-65.9
Tetracycline	Tetracycline	42	34-49.9
Oxacillin	Cephalosporin	34.7	27.1-42.3
Fusidic acid	Steroid antibiotics	32	24.5-39.5
Clindamycin	Lincosamide	28.7	21.4-35.9
Gentamicin	Aminoglycoside	15.3	9.6-21.1
Levofloxacin	Fluocinolone	14	8.4-19.6
Moxifloxacin	Fluocinolone	14	8.4-19.6
Rifampicin	Ansamycin	2	0-4.2
Linezolid	Oxazolidinone	0.7	0.001-2
Vancomycin	Glycopeptide	0	n.p.

CI, Confidence interval; n.p., not possible.

Results

Among the 90 patients analysed, 96.7% had at least one strain on the skin at the surgical site. The detected bacteria comprised 144 strains; CNS strains were the most frequent strains at a rate of 93.1%. To determine the antibiotic susceptibility of the CNS strains, we used a panel of 12 antibiotics according to the standard microbiological diagnostics at our Institution. The highest resistance rate was observed for benzylpenicillin (77.3%, Table I), which was an expected result (20). More importantly, we observed substantial resistance to several of the antibiotics frequently employed in the management of orthopaedic patients. For example, 34.7%, 28.7% and 15.3% of the CNS strains displayed resistance to oxacillin, clindamycin and gentamicin, respectively (Table I); notably, no vancomycin-resistant strains were identified. A comparison between patients undergoing primary *versus* revision THA revealed a significant increase in the resistance to four of the 12 tested antibiotics (Table II). Oxacillin and gentamicin demonstrated 1.9-fold and 4.7-fold increases in resistance, respectively, which corresponded to 46.2% and 38.5% of patients undergoing revision THA. As oxacillin is a commonly used cephalosporin, these data suggest the limited efficacy of standard cephalosporin-based AMP currently employed in the US and Europe.

Table II. *Comparison of antibiotic susceptibility of CNS strains between primary and revision THA.*

	Primary THA			Revision THA		Comparison	
Sentinel	Rate	95%-CI	Sentinel	Rate	95%-CI	*p*-Value	Chi-square
Oxacillin	24.2	13.5-34.9	Oxacillin	46.2	27-65.3	p<0.05	4.154
Benzylpenicillin	72.6	61.5-83.7	Benzylpenicillin	84.6	70.7-98.5	*p*>0.05	1.46
Gentamicin	8.1	1.3-14.8	Gentamicin	38.5	19.8-57.2	*p*<0.01	11.97
Levofloxacin	8.1	1.3-14.8	Levofloxacin	26.9	9.9-44	*p*<0.05	5.532
Moxifloxacin	8.1	1.3-14.8	Moxifloxacin	26.9	9.9-44	*p*<0.05	5.532
Erythromycin	56.5	44.1-68.8	Erythromycin	61.5	42.8-80.2	*p*>0.05	0.195
Clindamycin	29	17.7-40.3	Clindamycin	34.6	16.3-52.9	*p*>0.05	0.268
Vancomycin	0	n.p.	Vancomycin	0	n.p.	n.p.	n.p.
Tetracycline	25.8	14.9-36.7	Tetracycline	34.6	16.3-52.9	*p*>0.05	0.699
Linezolid	1.6	0.0-4.7	Linezolid	0	n.p.	*p*>0.05	0.424
Rifampicin	1.6	0.0-4.7	Rifampicin	7.7	0.0-17.9	*p*>0.05	2.056
Fusidic acid	32.3	20.06-43.09	Fusidic acid	38.5	19.8-57.2	*p*>0.05	0.314

CNS, Coagulase-negative *Staphylococci*; THA, total hip arthroplasty; CI, confidence interval; n.p., not possible.

Discussion

Our study led to three central findings. First, and perhaps most importantly, we demonstrated that approximately 50% of all patients undergoing revision THA are likely not to benefit from standard cephalosporin-based AMP due to resistance to cephalosporins. Second, we observed that approximately 40% and 30% of patients are resistant to gentamicin and clindamycin, respectively; these two antibiotics are frequently used in cemented THA to protect against infection (21, 22), an observation that has been reported in previous studies (18, 23). Finally, we noted a relatively low prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) (0.4%), indicating that cephalosporin-based AMP is effective to prevent surgical side infections caused by *S. aureus*.

The considerably high rate of resistance to oxacillin was partially due to an increase in resistance between primary and revision THA. The underlying cause for this increase is currently unclear; however, two potential contributing factors should be discussed. First, bacterial colonization during the hospital stay may result in a higher probability of CNS strains on the skin of patients undergoing revision surgery. Several studies suggest a correlation between days of hospitalization and the presence of resistant CNS strains on the skin (23, 24). Indeed, the ward staff rather than the theatre staff or surgeons have been identified as a common source of oxacillin-resistant CNS strains (23). Therefore, patient exposure to the ward staff during their hospital stay is a risk for acquiring oxacillin-resistant CNS strains. Second, there is the possibility of the initial AMP selecting for oxacillin-resistant strains. To this end, it appears to be critical that hospitals strictly adhere to the guidelines for the proper use of AMP (25).

An important consideration is how to improve current AMP regimens and achieve lower infection rates in patients undergoing THA, especially those requiring a revision. Notably, our data suggest a role for vancomycin as we found no vancomycin-resistant strains during either primary or revision THA. However, some reports have raised concerns regarding the toxicity of glycopeptides due to the slow tissue distribution of vancomycin (21, 26, 27). This notwithstanding, in our experience (Mühlhofer, unpublished data), administration of vancomycin (10-15 mg/kg) one to two hours prior to surgery yields adequate tissue concentrations with less than 1% nephrotoxicity after a single dose. Furthermore, due to its longer half-life, a second dose of vancomycin is typically unnecessary (28, 29). The use of AMP regimens for patients undergoing revision arthroplasty should account for CNS strains with potentially significant oxacillin resistance and short-term decolonization of the skin may provide additional value prior to revision arthroplasty.

Ethics and Consent to Participate

The present study was approved by the local ethics committee (4092/11) and written consent was obtained from each subject prior to inclusion.

Conflicts of Interest

All Authors declare that they have no competing interests.

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