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Stefansdottir, Anna; Johansson, Åsa; Lidgren, Lars; Wagner, Philippe; W-Dahl, Annette

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Bacterial colonization and resistance patterns in 133 patients undergoing a primary hip- or knee replacement in Southern Sweden

Anna Stefánsdóttir[1], Åsa Johansson[1], Lars Lidgren[1], Philippe Wagner[2], and Annette W-Dahl[1]

[1]Department of Orthopedics, Clinical Sciences, Lund, Lund University; [2]RC Syd National Register Centre, Skåne University Hospital, Lund, Sweden.
Correspondence author: anna.stefansdottir@med.lu.se
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Background and purpose Prosthetic joint infections can be caused by bacteria derived from the patient's skin. The aim of the study was: (1) to determine which bacteria colonize the nose and groin in patients planned for primary hip or knee arthroplasty, (2) to determine the antimicrobial resistance patterns, and (3) to monitor changes in bacterial colonization and resistance patterns connected to surgery.

Patients and methods 2 weeks before scheduled primary hip or knee arthroplasty, culture samples were taken from the anterior nares and from the groin of 133 consecutive patients. At surgery, cloxacillin was given prophylactically and cement with gentamicin was used. 2 weeks after surgery, another set of samples were taken from 120 of these patients. Bacterial findings and resistance patterns were analyzed.

Results Preoperatively, 95% of the patients had coagulase-negative staphylococci (CNS) in the groin and 77% in the nose. The proportion of patients with a methicillin-resistant CNS in the groin increased from 20% preoperatively to 50% postoperatively ($p < 0.001$), and the proportion of patients with a gentamicin-resistant CNS in the groin increased from 5% to 45% ($p < 0.001$). 28% of the patients had ***Staphylococcus aureus*** in the nose preoperatively, and 7% in the groin. Methicillin-resistant ***Staphylococcus aureus*** (MRSA) was found in the nose of 1 patient.

Interpretation In southern Sweden, beta-lactams were effective against 99% of the Staphylococcus aureus strains and 80% of the CNS strains colonizing the patients undergoing primary hip or knee arthroplasty. Gentamicin protects against most CNS strains in cemented primary joint replacements.

Almost 16,000 hip arthroplasties and 13,000 knee arthroplasties were performed in Sweden (with 9.5 million inhabitants) in 2010 (SHPR 2011, SKAR 2011). Today, 0.8% of the patients who have undergone a primary hip arthroplasty in Sweden are reported to have a reoperation due to infection within 2 years, and infection is the most common reason for early reoperation (SHPR 2011).

Most early infections are acquired during the time of implantation of the prosthesis (Zimmerli et al. 2004). The bacteria may be derived from the patient (endogenous) or from the surrounding personnel and equipment (exogenous) (Tammelin et al. 2001). The most common causative agents in early infections are coagulase-negative staphylococci (CNS) and *Staphylococcus aureus* (Pulido et al. 2008, Stefánsdóttir et al. 2009, Nickinson et al. 2010). In order to reduce the risk of infection, prophylactic antibiotics are used—in Nordic countries, both systemically and in bone cement (Jämsen et al. 2011). In Sweden, the isoxazolylpenicillin derivate cloxacillin has been the most commonly used antibiotic for systemic prophylaxis, followed by clindamycin, which is used in the case of penicillin allergy (SKAR 2011). Almost all the bone cement used in primary cemented hip- and knee replacements contains gentamicin (SHPR 2011, SKAR 2011). In addition, it is standard in Sweden that patients shower at least twice before operation with the disinfectant chlorhexidine gluconate to reduce the amount of bacteria on the skin.

To prevent endogenously acquired infection, the bacteria that colonize the skin of the patient have to be susceptible to the specific antibiotic used. It is known that CNS strains that cause prosthetic knee joint infections in Sweden have become increasingly resistant to methicillin (Stefánsdóttir et al. 2009), and that methicillin-resistant CNS are common in hospitalized patients (Widerström et al. 2012). However, there is limited information on the bacteria that colonize the skin and nose of patients undergoing a primary arthroplasty. This has not been investigated in Sweden since Sanzén and Walder (1988) compared the susceptibility patterns of CNS before and after a total hip arthroplasty, and found that preoperatively 3% of the patients had CNS strains that were resistant to methicillin, as compared to 25% postoperatively.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has become an important pathogen in orthopedic infections in many parts of the world (Stefani and Varaldo 2003, Giannoudis et al. 2005, Patel et al. 2008). The situation in Swedish hospitals is more favorable (Stenhem et al. 2006), but the prevalence of MRSA in the Swedish community is unknown, and there is limited information from other countries (Gorwitz et al. 2008, Donker et al. 2009).

The aim of this study was: (1) to determine which bacteria colonize the nose and groin in patients who are planned for primary hip or knee arthroplasty, (2) to determine the antimicrobial resistance patterns of the bacteria found, and (3) monitor changes in bacterial colonization and resistance patterns linked to surgery.

Material and methods

The study, which was prospective, included 133 consecutive patients scheduled for primary hip- or knee arthroplasty at the arthroplasty unit of the Department of Orthopedics at Skåne University Hospital, Lund, from June to October 2010. There were no exclusion criteria. Mean age was 69 (41–91) years and 62% of the patients were women. Osteoarthritis was the primary diagnosis in 128 patients (96%), rheumatoid arthritis in 2, osteonecrosis of the femoral head in 2, and osteoarthritis secondary to a hip fracture in 1 patient. According to the American Society of Anesthesiologists (ASA) classification, 35 were ASA I (26%), 75 (56%) were ASA II, and 23 (17%) were ASA III. 67 patients (56%) had a hip arthroplasty (39 cemented, 20 uncemented, and 8 hybrids), and 53 patients had a cemented knee arthroplasty (51 tricompartmental knee arthroplasties and 2 unicompartmental knee arthroplasties).

Approximately 2 weeks before the planned surgery, the patients visited the elective unit where the operations were performed. At that time, 2 separate culture samples were obtained with a cotton swab—1 from the anterior nares and 1 from the groin. The reason for not taking the culture immediately prior to the operation was that most patients had had a chlorhexidine shower at home before coming to hospital on the day of operation. The samples were sent to the microbiological laboratory at Skåne University Hospital, Lund for culture and determination of antibiotic resistance patterns. The swabs were applied to 3 different plates (blood agar for aerobic incubation, blood agar for anaerobic incubation, and chocolate agar in 5% CO_2); these were incubated at 35–37ºC for 2 days. A maximum of 4 different bacterial strains was reported from each sample. The CNS species *Staphylococcus lugdunensis* was reported separately from other CNS species, as it is often more virulent and has more favorable resistance patterns than most other CNS strains.

Antimicrobial susceptibility was determined by the use of disk-diffusion antibiotic sensitivity testing on Isosensitest agar plates (Oxoid Ltd, Basingstoke, UK) that were incubated at 35–37ºC for 18–24 h. The interpretation of the inhibition zones as S (sensitive), I (intermediate), and R (resistant) was done according to Swedish standards. Staphylococci with an inhibition zone of gentamicin corresponding to MIC > 1 mg/L were considered resistant. The antibiotics tested included those used as prophylaxis—e.g. isoxazolylpenicillin, clindamycin, and gentamicin—as well as various other antibiotics such as fusidic acid, vancomycin, and rifampicin. Bacteria resistant to isoxazolylpenicillin are termed methicillin-resistant. Detection of the presence of the mecA gene was used to verify detection of MRSA.

At the time of inclusion, the patients answered a simple questionnaire about factors that might predict the finding of resistant bacteria. All patients were living independently, 25% had received antibiotics during the previous 6 months, 24% had been hospitalized during the previous year, and 29% had traveled outside the Nordic countries.

2 weeks after operation, the patients were planned to visit a specialist nurse at the outpatient clinic in Lund for a postoperative check and removal of the skin staples. At this time, samples were taken for culture in the same manner as preoperatively. In 13 cases, cultures were sampled preoperatively only. 2 patients abstained from surgery, 8 patients had their surgery postponed (1 due to the finding of MRSA and 7 for various other reasons) and so had an extended period of time between the preoperative culture and operation, and 3 patients did not attend the outpatient clinic for removal of the staples. The mean time that elapsed between operation and when the postoperative cultures were taken was 15 (13–23) days.

All the patients had been instructed to take a chlorhexidine shower on the day before operation, both in the morning and in the evening, and all patients also had 1 chlorhexidine shower in hospital on the day of operation. According to local guidelines, prophylactic antibiotic was administrated approximately 30 min before the start of surgery and 2 additional doses were given postoperatively. Cloxacillin (2 g) was used as a systemic prophylactic antibiotic in 107 cases (89%) with 3 doses given over 12 h. Due to a history of allergic reaction, clindamycin (600 mg) was used in 13 cases (11%) with 3 doses given over 16 h. All bone cement used (Optipac Refobacin bone cement R; Biomet) included 0.5 g of gentamicin per 40 g of cement. 8 patients (7%) received additional antibiotics before the postoperative visit (3 had flucloxacillin due to wound drainage, 2 had flucloxacillin "prophylactically" due to skin erosion at a distal site, 1 had flucloxacillin due to clinically diagnosed superficial surgical site infection, 1 had cefuroxime due to suspected sepsis, and 1 had trimethoprim-sulfa due to urinary tract infection). The patients were followed for at least 3 months, and the rate of early deep infection (within 3 months of operation) was noted.

Ethical approval was obtained from the local ethics committee (LU2010/39) and all patients signed an informed consent document.

Table 1. The numbers (%) of patients with different types of bacteria in the nose and the groin before (n = 133) and after (n = 120) a primary hip or knee arthroplasty. Pairwise comparison of pre- and postoperative findings with McNemar's exact test

	Nose			Groin			Nose and groin (either or both)		
	Preop.	Postop.	p-value	Preop.	Postop.	p-value	Preop.	Postop.	p-value
Staphylococcus aureus	37 (28)	27 (23)	0.3	9 (7)	8 (7)	1.0	42 (32)	28 (23)	0.06
Coagulase-negative staphylococci	103 (77)	95 (79)	0.6	126 (95)	101 (84)	0.01	130 (98)	114 (95)	0.4
Staphylococcus lugdunensis	5 (4)	12 (10)	0.1	17 (13)	18 (15)	0.7	21 (16)	27 (23)	0.2
Streptococci	1 (1)	2 (2)	1.0	2 (2)	0 (0)	1.0	3 (2)	2 (2)	1.0
Enterococcus faecalis	0 (0)	1 (1)	1.0	1 (1)	3 (3)	0.3	1 (1)	4 (3)	0.1
Gram-negative bacteria [a]	11 (8)	8 (7)	0.8	7 (5)	21 (18)	0.002	16 (12)	26 (22)	0.02
Other bacteria [b]	3 (2)	1 (1)	1.0	4 (3)	3 (3)	1.0	5 (4)	3 (3)	1.0
No bacteria	10 (8)	11 (9)	1.0	3 (2)	4 (3)	1.0	0 (0)	1 (1)	1.0

[a] *E. coli, Citrobacter diversus, Pseudomonas aeruginosa, Klebsiella oxytoca, Proteus mirabilis, Morganella morganii,* Enterobacteriaceae sp.
[b] *Bacillus cereus, Corynebacterium* sp., *Acinetobacter,* mixed Gram-negative and Gram-positive culture.

Statistics

McNemar's exact test was used to analyze the changes in frequencies of bacteriological findings and antibiotic resistance for paired pre- and postoperative data. In conjunction with this, the odds ratio (OR) with 95% confidence intervals (CIs) for CNS being resistant to a specific antibiotic (comparing pre- and postoperative samples) was calculated. Logistic regression was used to calculate the OR for the finding of a methicillin-resistant CNS depending on several risk factors. Any finding corresponding to a p-value of less than 0.05 was regarded as statistically significant.

Results

CNS were the bacteria most commonly cultured. Preoperatively, 95% of the patients had at least 1 strain of CNS in the groin, and 77% had at least 1 strain of CNS in the nose (Table 1). *S. aureus* was found preoperatively in the noses of 28% patients, but was less common in the groin (7%). Gram-negative bacteria were found preoperatively in the noses of 8% of the patients and in the groin of 5%. Apart from *S. lugdunensis* in the groin (13%), other bacteria were uncommon (Table 1).

Preoperatively, only 1 patient (1%) was found to have MRSA in the nose, whereas no MRSA was found in the groin. 12 patients (9%) had a methicillin-resistant CNS in the nose, and 26 patients (20%) had a methicillin-resistant CNS in the groin (Table 2). None of the *S. lugdunensis* strains were methicillin-resistant. 3 patients (2%) had a gentamicin-resistant CNS strain in the nose, and 6 patients (5%) had one in the groin. There were no gentamicin-resistant S. aureus or *S. lugdunensis* strains. No bacteria were found to be resistant to vancomycin or rifampicin.

There was no statistically significant difference in the proportion of patients with different types of bacteria in the nose postoperatively compared to preoperatively. The proportion of patients with a CNS strain in the groin was lower postoperatively than preoperatively (OR = 0.25, CI: 0.06–0.77; p = 0.01), whereas the proportion of patients with a Gram-negative bacterium in the groin increased (OR = 6.0, CI: 1.8–32; p = 0.002) (Table 1).

Apart from higher proportion of CNS being resistant to clindamycin and fusidic acid postoperatively, we did not find any statistically significant difference in the antimicrobial resistance patterns of the CNS found in the nose postoperatively and preoperatively. In the groin, a significantly higher proportion of patients were found to have CNS strains resistant to methicillin, clindamycin, and gentamicin postoperatively than preoperatively (Table 2). We found no statistically significant difference in postoperative resistance patterns compared to those preoperatively between those who had undergone a hip arthroplasty and those who had undergone a knee arthroplasty. There was no statistically significant difference in gentamicin resistance of CNS strains between those patients receiving a cemented implant and those receiving an uncemented implant (p = 0.2).

There was no correlation between age, sex, ASA classification, prior antibiotics, hospitalization, and traveling, and the finding of methicillin-resistant CNS preoperatively.

1 patient had an early deep infection. An 80-year-old woman with OA had a polymicrobial knee prosthesis infection with *Enterobacter cloacae,* Enterococcus faecalis, and E. coli. None of these bacteria were found in the nose or groin, either preoperatively or postoperatively.

Discussion

The major limitation of our study was that the culture techniques used did not allow detection of slow-growing anaerobic bacteria, for example *Proprionibacterium acnes.* Another limitation was that the bacterial colonization of the personnel in the operation room and the ward was not studied, so no information about potential exogenous bacterial contamination of the joint during surgery was available.

Table 2. The number (%) of patients with a CNS strain resistant do different antibiotics [a] in the nose and the groin before (n = 133) and after (n = 120) a primary hip or knee arthroplasty. Pair-wise comparison of pre- and postoperative findings with McNemar´s test.

	Isoxazolyl-penicillin	Clindamycin	Fusidic acid	Gentamicin	Rifampicin
Nose					
Preoperatively	12 (9)	8 (6)	20 (15)	3 (2)	0 (0.0)
Postoperatively	22 (18)	15 (13)	34 (28)	6 (5)	2 (1.7)
p-value	0.06	0.006	0.005	0.5	0.5
OR (95% CI)	2.4 (0.96–6.9)	11 (1.6–474)	3.3 (1.4–9.1)	2 (0.4–13)	–
Groin					
Preoperatively	26 (20)	9 (7)	54 (41)	6 (5)	0 (0.0)
Postoperatively	60 (50)	47 (39)	61 (51)	54 (45)	4 (3.3)
p-value	< 0.001	< 0.001	0.06	< 0.001	0.1
OR (95% CI)	4.3 (2.2–9.1)	9 (3.6–29)	1.8 (0.98–3.5)	26 (6.7–216)	–
Nose or groin					
Preoperatively	33 (25)	15 (11)	60 (45)	7 (5)	0 (0.0)
Postoperatively	69 (58)	54 (45)	76 (63)	56 (47)	4 (3.3)
p-value	< 0.001	< 0.001	0.002	< 0.001	0.1
OR (95% CI)	4.8 (2.4–11)	12 (4.3–45)	2.6 (1.4–5.3)	26 (6.8–220)	–

[a] No vancomycin resistance was found in any of the strains isolated.

The prevalence of MRSA was low (1%), which indicates that a beta-lactam antibiotic is still the first choice of antibiotic for prevention of infections caused by *S. aureus.* In Sweden, isoxazolylpenicillin derivates have been used in favor of cephalosporins, which are often used in many other countries (Engesaeter et al. 2003, Meehan et al. 2009, Swierstra et al. 2011), but which might affect the development of resistance in Gram-negative bacteria (ESBL) (Zahar et al. 2009). In 5 cases (4%), *S. aureus* was found in the groin but not in the nose, and would have been missed in nasal screening (Bode et al. 2010).

The prevalence of methicillin-resistant CNS in nasal cultures taken preoperatively (9%) was higher than the 4% reported by Sanzén and Walder in 1988. A higher incidence of methicillin-resistant CNS was found in the groin (20%), which indicates that nasal screening is not sufficient for detection of methicillin-resistant CNS. The general use of a glycopeptide, such as vancomycin, as a prophylactic antibiotic to control these CNS strains is not feasible, as vancomycin is more toxic and more difficult to administer (Meehan et al. 2009). It is, however, important to be aware of the fact that the systemic prophylaxis is not effective against all CNS strains. Other measures, such as the use of gentamicin in bone cement (Parvizi et al. 2008), reduction of the number of CNS on the skin by the use of chlorhexidine (Hedin and Hambraeus 1993), clean air in the operating theater (Evans 2011), and short preoperative hospital stay (Ridgeway et al. 2005) are of importance. In addition, alternative prophylactic measures may become available for uncemented prostheses (Neut et al. 2011).

We found a reduced proportion of patients with CNS in the groin postoperatively, and an increased proportion of patients with Gram-negative bacteria. It is likely that the use of chlorhexidine reduced the amount of CNS, but it is not clear what caused the increase in Gram-negative bacteria. To reduce the risk of secondary infection of the wound by Gram-negative bacteria during the postoperative period, it is important to have good standards of hygiene in both patients and healthcare personnel.

We have no explanation for the change in the resistance pattern of CNS found in the groin postoperatively compared to preoperatively. It may have been an effect of the antibiotics given in conjunction with the operation. This, however, only partly explains the increasing resistance to clindamycin, which was used in 11% of cases. An alternative, and perhaps more likely explanation is that during their hospital stay, the patients become exposed to more resistant CNS strains found in the hospital environment. It is notable that in the previous study by Sanzén and Walder (1988), 25% of the patients had a methicillin-resistant CNS strain postoperatively compared to 18% of patients in the present study. In the earlier study, the prophylactic antibiotics were given for a longer period of time—and at that time, patients spent longer in hospital after the operation. We found no differences in the increase in gentamicin-resistant CNS strains depending on whether or not bone cement was used. Due to the low number of patients studied, it is, however, not possible to reject the hypothesis that gentamicin in bone cement increases the risk of having gentamicin-resistant CNS infection postoperatively.

The clinical implications of the study were that beta-lactam antibiotics were effective against 99% of the *S. aureus* strains and 80% of the CNS strains that were found in patients planned for primary hip or knee arthroplasty in southern Sweden. Gentamicin provides additional protection in primary cemented joint replacements.

AS, LL, and AW-D designed the study. ÅJ, AS, and AW-D collected the data and analyzed them together with PW. AS wrote the manuscript, which was edited by all authors.

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