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Low sensitivity of implant sonication when screening for infection in revision surgery

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Background and purpose — Prosthetic-joint infection (PJI) is the most serious complication of arthroplasty, and accurate identification of a potentially responsible microorganism is essential for successful antibiotic treatment. We therefore determined the diagnostic accuracy of sonication and compared it with tissue culture as a screening tool in detecting prosthetic joint infection in revision arthroplasty.

Patients and methods — 252 consecutive revision arthroplasty cases were enrolled. These cases were determined as being suspected or unsuspected of having infection according to standard criteria. Perioperatively, 6 periprosthetic interface tissue biopsies were obtained from each patient and the implants removed were sonicated. The sensitivity and specificity of periprosthetic tissue culture and sonication fluid cultures were determined.

Results — Preoperatively, 75 revision cases were classified as having PJI (33 early and 42 late) and 177 were unsuspected of having infection. Compared with tissue culture, the sensitivity of the sonication fluid analysis was low: 0.47 (95% CI: 0.35–0.59) for sonication as compared to 0.68 (95% CI: 0.56–0.78) for tissue culture. The specificity of the sonication fluid analysis was higher than that for tissue culture: 0.99 (95% CI: 0.96–1.0) as compared to 0.80 (95% CI: 0.74–0.86).

Interpretation — Sonication is a highly specific test for diagnosis of PJI. However, due to the low sensitivity, a negative sonication result does not rule out the presence of PJI. Thus, sonication is not of value for screening of microorganisms during revision surgery.

dence in primary interventions of 1–2% (Del Pozo and Patel 2009)—and much higher for revision procedures (Trampuz and Zimmerli 2005). In order to determine surgical and antibiotic treatment strategies, it is important to differentiate PJI from other prosthetic complications (Zimmerli et al. 2004).

Synovial fluid and intraoperative periprosthetic tissue cultures are considered to be the standard method for the diagnosis of PJI. However, Trampuz et al. (2007) reported a sensitivity and specificity of 61% (95% CI: 49–72) and 99% (95% CI: 97–100), respectively for these procedures, leading to a potentially high incidence of false-negative results.

In PJI, biofilms are often formed by microorganisms, and are attached to the surface of the prosthesis. A biofilm consists of communities of microorganisms that are enclosed in a glycocalyx matrix (Griffin et al. 2012, Gbejuade et al. 2015). Sample analysis of these implants, and the attached biofilm, might therefore contribute to the diagnosis of PJI and the determination of which microorganisms are involved. One way of analyzing biofilms is to use sonication of the removed implant (Tunney et al. 1998, Donlan 2005). This technique has contributed to improvement in the sensitivity of microbial cultures from implant biofilms, especially when antibiotics have been used shortly before explantation (Trampuz et al. 2007, Piper et al. 2009).

The purpose of the present study was to determine the importance of sonication of the removed implant of revision arthroplasty in diagnosing PJI and to compare it with the most commonly used diagnostic tool, periprosthetic tissue culture, in cases suspected of having infection and in cases not suspected of having infection, based on standard criteria. The hypothesis was that sonication would be a more accurate tool for detection of microorganisms during revision arthroplasty, compared to culture results from periprosthetic tissue samples.

The number of arthroplasties and subsequent revisions will rise substantially in the near future (Kurtz et al. 2007). Prosthetic joint infection (PJI) is a serious complication, with an inci-

Patients and methods

We retrospectively studied 298 patients who underwent revision arthroplasty surgery between March 2011 and November 2012, who were either suspected of having infection or not suspected. Patients were excluded if: fewer than 6 peri-implant tissue specimens were collected for culture; no implant was available for microbiological analysis; obvious contamination of an explanted component had occurred; or the implant did not fit the sample container. After exclusion of these patients, 233 patients were included. Pertinent data on each of the patients were retrieved from the medical records.

None of the patients had received antibiotics less than 10 days prior to surgery. Implants were removed in a sterile environment in the operating room and were transported to the laboratory in a sterilized polypropylene container. Peri-implant tissue samples were obtained before prophylactic antibiotics were administered, in order to optimize the diagnostic accuracy of the cultures. These samples were obtained from prosthesis interfaces and macroscopically suspected areas of inflammation. Each tissue sample was taken with a new and sterilized instrument, placed in a separate sterile tube—either dry or containing 0.9% sodium chloride—and labeled with the specimen site.

Surgical grouping

The cohort was divided into two groups: “clinically suspected of having infection” and “not clinically suspected of having infection”, determined according to guidelines for the definition of PJI, published by the Musculoskeletal Infection Society (MSIS) (Parvizi et al. 2012), and the Infectious Diseases Society of America (IDSA) guidelines for PJI (Osmon et al. 2013). However, tissue cultures were not available from all cases prior to surgery. Thus, in these cases, suspicion of infection was based on clinical features matching the MSIS criteria. The preoperative work-up consisted of defining the presence of clinical signs such as pain, swelling, persistent wound drainage, a sinus tract, or motion deficits of the joint concerned. Also, a C-reactive protein (CRP) blood test was performed and radiological analysis was conducted. Furthermore, a differentiation between early and late revision surgery was made. Patients diagnosed with an early or acute infection underwent thorough surgical debridement and irrigation with exchange of mobile prosthetic components and tissue culture within the first 3 months after primary surgery. Patients diagnosed with a late or chronic infection underwent 2-stage revisions. All other cases, which were not suspected of having an infection, were initially treated with a single-stage revision procedure.

Tissue cultures

Periprosthetic tissue specimens (6 from each surgery case) were collected, put in separate sterile containers, and processed within 6 h. Samples were homogenized manually in

thioglycollate (Oxoid, Haarlem, the Netherlands), and 100 µL of each suspension plated onto sheep blood agar plates (Oxoid), New York City plates (Oxoid), and BBA anaerobic plates (Media Products, Groningen, the Netherlands). In addition, 2 mL was inoculated into thioglycollate and brain-heart infusion broth. The aerobic cultures were incubated for 5 days at 35°C in an atmosphere of 5% CO₂ and anaerobic cultures were incubated in an anaerobic jar with an anaerobic gas mixture consisting of 80% nitrogen, 10% carbon dioxide, and 10% hydrogen (Anoxomat Mart II; Mart Microbiology BV, Drachten, the Netherlands). The plates were examined on a daily basis—except the anaerobic plate, which was examined at 3 and 5 days.

Broths were incubated for 10 days, then subcultured on solid media and examined for a further 4 days for possible growth. Microorganisms were identified using matrix-assisted laser desorption/ionization time-of-flight (MaldiToF) mass spectrometry (Bruker, Bremen, Germany), and broth microdilution antimicrobial susceptibility was performed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST, www.eucast.org). A true positive culture result was defined according to the current standard, i.e. as the growth of the same microorganism in 2 or more tissue samples. The exception was *Staphylococcus aureus*, which was considered significant when isolated from 1 specimen, since this is a highly virulent microorganism (Trampuz and Zimmerli 2005).

Sonication

Sterilized solid polypropylene containers (Lock & Lock, Salo Company BV, Soest, the Netherlands) containing the removed implant were filled with Ringer's solution until > 90 % of the prosthesis was covered (500–800 mL), and then sealed with an airtight lid. After 30 s of vigorous manual shaking, implants were sonicated in a water bath for 5 min at 40 kHz (BactoSonic; Bandelin GmbH, Berlin, Germany) followed by an additional 30 s of manual shaking (Trampuz et al. 2007). After sonication, light microscopy of a Gram stain preparation was performed. 100 µL of fluid was inoculated onto a sheep blood agar plate, a New York City plate, and a BBA anaerobic plate, incubated at 37°C for 5 days, and inspected daily for bacterial growth. Additionally, 2 mL of the remaining sonication fluid was inoculated into 10 mL thioglycollate and brain-heart infusion broth, and incubated at 35°C for 10 days, after which the broth was subcultured on solid media as described above. The latter broth culture was used as a control, and had to grow the same microorganism as the sonication fluid solid medium culture for this to be positive. A positive sonication fluid culture (SFC) was defined as growth of the same microorganism on any plate—of at least 50 colony-forming units (CFU) per mL of sonication fluid (5 CFU/plate) (Trampuz et al. 2007).

Statistics

Descriptive statistics were used to summarize demographic

Table 1. Demographics of patients (n = 233; operations: n = 252)

	Suspected of having infection	Not suspected of having infection
Patients, n (%)	67 (28)	166 (71)
Female, n (%) / male, n (%)	37 (55) / 29 (45)	115 (69) / 51 (31)
Age, years, mean (SD)	64 (11)	67 (10)
Operations, n (%)	75 (28)	177 (72)
Revision, n (%)		
early	33 (44)	15 (8)
late	42 (56)	162 (92)
Joint, n (%)		
hips	23 (31)	54 (31)
knees	48 (64)	100 (56)
other	4 (5)	23 (13)

Table 2. Distribution of sonication fluid culture results and tissue culture results compared to whether there were clinical signs of infection in 252 revision arthroplasty surgery cases

	Clinical signs of infection		
	Positive	Negative	Total
Sonicate (CFU \geq 50/mL)			
Positive	35	2	37
Negative	40	175	215
Total	75	177	252
Tissue cultures (\geq 2)			
Positive (\geq 2)	51	35	86
Negative ($<$ 2)	24	142	166
Total	75	177	252

CFU: colony-forming units.

Table 3. Sonication fluid cultures compared with the presence of clinical signs of infection in revision arthroplasty surgery cases

	Total cohort (n = 252)	Early revision (n = 48)	Late revision (n = 204)
Sensitivity	0.47	0.42	0.50
95% CI	0.35–0.59	0.25–0.61	0.34–0.66
Specificity	0.99	1.0	0.99
95% CI	0.96–1.00	0.78–1.0	0.9–1.00
Positive predictive value	0.95	1.0	0.91
Negative predictive value	0.81	0.44	0.88
Positive likelihood ratio	41	^a	41
Negative likelihood ratio	0.54	0.58	0.51

^a error due to impossibility of calculation with reference to a specificity of 1.00.

Table 4. Periprosthetic tissue cultures compared with the presence of clinical signs of infection in revision arthroplasty surgery cases

	Total cohort (n = 252)	Early revision (n = 48)	Late revision (n = 204)
Sensitivity	0.68	0.73	0.64
95% CI	0.56–0.78	0.54–0.87	0.40–0.78
Specificity	0.80	0.87	0.80
95% CI	0.74–0.86	0.60–0.98	0.73–0.86
Positive predictive value	0.59	0.92	0.45
Negative predictive value	0.86	0.59	0.90
Positive likelihood ratio	3.4	5.5	3.2
Negative likelihood ratio	0.40	0.31	0.45

characteristics, the time between primary surgery and revision surgery, antibiotic treatment, and the microorganism involved. For both tissue culture and implant sonication, calculations of sensitivity, specificity, predictive value, likelihood ratio, and diagnostic accuracy were performed using 2×2 contingency tables (compared to clinical infection). Statistical analysis was performed using SPSS version 21.0.

Ethics

Approval for the study was obtained from the institutional research board (entry no. 562). No competing interests declared.

Results

233 patients with a combined total of 252 operations (148 knee, 77 hip, and 27 other arthroplasties) with implant sonication and a minimum of 6 tissue sample cultures were included (Table 1). 16 patients underwent 2 revision surgeries and 3 patients underwent 3 revision surgeries. In 75 cases, a clinical infection was diagnosed (33 early infections and 42 late infections).

The remaining 177 cases were unsuspected of having infection (Table 2).

Compared with the standard (of clinical infection), the sensitivity of the SFC was lower (0.47, 95% CI: 0.35–0.59) than that of periprosthetic tissue culture (0.68, 95% CI: 0.56–0.78). The specificity of the SFC analysis was high compared to that of tissue culture: 0.99 (95% CI: 0.96–1.00) as opposed to 0.80 (95% CI: 0.74–0.86). When we lowered the KVE/mL threshold to 10 in the sonication analysis, the sensitivity increased to 0.57 (95% CI: 0.45–0.69) and the specificity decreased to 0.86 (95% CI: 0.81–0.91) (Tables 3 and 4). In both periprosthetic tissue culture and SFC, the majority of microorganisms present were coagulase-negative staphylococci (Table 5).

Discussion

We compared the diagnostic accuracy of SFC from removed implants with that of the currently most often used diagnostic tool for PJI, culture from tissue biopsies during the same surgical session, and both were compared with clinical diagnosis.

Table 5. Microbiological findings in 67 PJI cases according to the type of diagnostic specimen

	Positive periprosthetic tissue cultures (≥ 2) (n = 67)	Positive sonicate fluid cultures (n = 37)
Coagulase-negative staphylococci	30	17
Anaerobes	14	2
<i>Staph. aureus</i>	7	5
Gram-positive cocci	6	5
Gram-negative rods	6	5
Streptococci	4	3

sis of PJI. Our results showed that sonication of implants did not lead to identification of more PJIs than did culture from 6 tissue biopsies. This was not in line with our hypothesis, and also contrasted with the results of other studies (Trampuz et al. 2007, Puig-Verdié et al. 2013, Portillo et al. 2014, Janz et al. 2015, Shen et al. 2015). In agreement with these other studies, we found that the specificity of SFC was higher than that of tissue cultures in all our groups. This means that a positive SFC is highly associated with PJI in all types of revision cases, whether suspected or unsuspected of having infection.

In PJI, classic symptoms of infection such as erythema, fever, and swelling are often lacking, while other signs such as elevated serum CRP or elevated white blood cell count are rather unspecific (Fink et al. 2008, Müller et al. 2008). Culture from periprosthetic tissue samples is widely used for diagnosis of PJI, but it has the disadvantage of generating false-negative results in up to 30% of cases (Spangehl et al. 1999, Tsukayama et al. 2003, Berbari et al. 2007, Müller et al. 2008).

In the absence of a gold standard for diagnosing PJI, we compared the preoperative clinical diagnosis—as the reference standard—with the results of tissue cultures and SFC. In our opinion, this provided a better comparison of the results of tissue and sonication cultures, instead of using the full set of MSIS criteria and thereby already incorporating the results of tissue cultures in the diagnosis of PJI.

In their landmark paper, Trampuz et al. (2007) reported the sensitivity of SFC to be a promising 79%, as opposed to 61% for periprosthetic tissue cultures, with a cutoff point of 5 CFU per plate. However, as pointed out before by Diekema (2007), in 13 out of 14 cases where infection was detected in SFC but not in tissue cultures, the same microorganism was detected in joint-fluid cultures or earlier tissue cultures (see Supplementary Appendix, Trampuz et al. 2007). Thus, the added value of this sensitivity—and therefore of SFC—is unclear. Also, a higher sensitivity was found for SFC in cases where antibiotics were given prior to revision surgery.

Numerous other studies have also reported encouraging results, although not all the methods in these publications were comparable. Puig-Verdié et al. (2013) found the overall sensitivity of SFC and peri-implant tissue cultures to be 90%

and 67%, respectively. Portillo et al. (2014) found SFC and tissue culture sensitivities of 81% and 61%, respectively, with a cutoff of ≥ 50 CFU/mL. However, sonication cultures with < 50 CFU/mL were also included in the results and accounted for 12 of 56 sonication-positive cases, exclusion of which would bring the sensitivity down to 64%.

In their prospective study, Janz et al. (2015) found a sensitivity of 74% for sonication, although the cutoff CFU value was not given. And in the study by Shen et al. (2015) where SFC results were compared with the results of synovial fluid cultures, sensitivities of 88% and 64%, respectively, were found—but no CFU cutoff was given.

In a meta-analysis performed by Zhai et al. (2014), an overall sensitivity of 0.82 (95% CI: 0.76–0.87) was reported for the pooled data from 8 studies regarding arthroplasties. Sub-group analysis showed that the sensitivity with a CFU cutoff of ≥ 50/mL was 0.69 (95% CI: 0.63–0.76). Also, in the recent review article by Liu et al. (2017), 16 studies evaluating SFC for the diagnosis of PJI were assessed, and a pooled sensitivity of 0.79 (95% CI: 0.76–0.81) and a specificity of 0.95 (95% CI: 0.94–0.96) were found. However, the difference in CFU cutoff used between the studies included was high and varied widely, without the unit (CFU per plate or CFU per mL) being specified.

The cutoff we used in all of our subjects was ≥ 50 CFU/mL, which is consistent with ≥ 5 CFU per plate—as advised by Trampuz et al. (2007). This chosen value for CFU cutoff has a direct influence on specificity and sensitivity, and is therefore an important criterion in the study design. Lowering the threshold for a positive SFC, as was, for example, the case in the study by Portillo (2014), did not result in acceptable sensitivity and specificity in our study.

In contrast to other literature, our sonication results turned out to show a rather disappointing sensitivity. A variety of possible explanations can be given. First of all, there are numerous reasons for false-negative results from periprosthetic tissue cultures, including technical errors (inappropriate culture medium or inadequate incubation time of cultures), an inadequate number of samples, previous treatment with antibiotics, and a prolonged time between tissue sampling and processing in the laboratory. All of these issues also apply to the technique of sonication, since it is also dependent on culturing. Furthermore, we only included subjects with 6 or more peri-implant tissue cultures, unlike the authors of previously mentioned studies who included from only 2 to 5 peri-implant tissue samples (Trampuz et al. 2007, Puig-Verdié et al. 2013, Portillo et al. 2014). Also, these studies described a higher sensitivity, especially in cases with antibiotic treatment before culture from the explanted material. In our study, none of the subjects received antibiotics before revision surgery. No influence on the tissue cultures would therefore be expected, since it has been speculated that bacteria present in tissue are more susceptible to anti-infective agents than biofilm bacteria (Trampuz et al. 2007), thus leading to a lower sensitivity of SFC.

We found a low sensitivity regarding sonication in the early infection group. This could possibly be explained by the composition of this group. The majority were patients 10–14 days postoperatively, a few up to 3 months postoperatively. In all cases, thorough surgical debridement and irrigation with exchange of mobile prosthetic components and tissue culturing was performed. It could be that in the majority of these cases, the clinical parameters on which the decision for debridement was based (according to MSIS and IDSA criteria (Parvizi et al. 2012, Osmon et al. 2013)) were elevated due to superficial wound defects and not infection, so that there was no microbial growth in any of the cultures. This misclassification bias might have led to an underestimated diagnostic accuracy.

Furthermore, as pointed out by Puig-Verdié et al. (2013), the sensitivity of sonication in early infections is not higher than that of tissue cultures. The most likely explanation for this finding is that in acute infection, there is not enough time for the microorganisms to establish sufficient biofilm (Donlan 2001). In these early cases, however, bacteria are still present in high numbers in the interface tissue, which makes identification by culturing from tissue rather easy. In late infections, on the other hand, the number of bacteria present in the interface tissue is limited, whereas the biofilm has become firmly established—containing most of the microorganisms.

Our study had some limitations. Firstly, there is no gold standard for diagnosing PJI. The MSIS criteria, as laid out by Parvizi et al. (2012), combine some of the traditional diagnostics. The authors stated that PJI could be diagnosed by the presence of a sinus tract or a combination of other criteria. PJI is also considered to be present if a pathogen is isolated by culture from at least 2 separate tissue or fluid samples obtained from the affected prosthetic joint. Since these positive cultures from periprosthetic tissue samples are still widely regarded and accepted as the leading method for establishment of the diagnosis of PJI, we used this diagnostic test as a tool for comparison. Use of the MSIS criteria to diagnose infection before the results of the tissue cultures have been obtained could lead to false negatives, since an infection could be present without any clinical signs, but with positive tissue cultures. As stated, we chose to use the preoperative clinical diagnosis as the reference standard to which the results of tissue cultures and SFC were compared, but this method could give rise to misclassification bias.

Moreover, since our study had many patients who had late revisions due to mechanical problems and did not have signs of clinical infection, the proportion of clinical infections was relatively small. Also, an unexpected positive SFC could mean that these mechanical problems were due to a low-grade infection. Nevertheless, an additional study on this specific cause of revision should be undertaken to define the role of SFC in diagnosing a low-grade infection.

In summary, we found that sonication of arthroplasty components is highly specific for the diagnosis of PJI, which

means that sonication could lead to a low level of false-positive test results. On the other hand, we cannot confirm the results of previous publications that reported a higher sensitivity (for infection) with sonication than with peri-implant tissue cultures, especially in cases with antibiotic treatment before surgery. With a sensitivity of 0.47 in the overall group, we cannot recommend the use of sonication as a screening tool for PJI, since a negative sonication result did not rule out the possibility of an infection. A multiplex approach is still warranted before and during a revision procedure, in order to rule out an infection.

FvD: collection, analysis, and interpretation of data; writing of manuscript. CA and MvH: collection and interpretation of data; writing of manuscript. JM: coordination of tissue cultures and sonication fluid culture; writing and reviewing of manuscript. JG: conception of study; interpretation of data; writing and reviewing of manuscript.

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