■ ARTHROPLASTY

Implant sonication increases the diagnostic accuracy of infection in patients with delayed, but not early, orthopaedic implant failure

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The purpose of this study was to compare the diagnostic accuracy for the detection of infection between the culture of fluid obtained by sonication (SFC) and the culture of peri-implant tissues (PITC) in patients with early and delayed implant failure, and those with unsuspected and suspected septic failure. It was hypothesised that SFC increases the diagnostic accuracy for infection in delayed, but not early, implant failure, and in unsuspected septic failure. The diagnostic accuracy for infection of all consecutive implants (hardware or prostheses) that were removed for failure was compared between SFC and PITC. This prospective study included 317 patients with a mean age of 62.7 years (9 to 97). The sensitivity for detection of infection using SFC was higher than using PITC in an overall comparison (89.9% *versus* 67%, respectively; p < 0.001), in unsuspected septic failure (100% *versus* 48.5%, respectively; p < 0.001), and in delayed implant failure (88% *versus* 58%, respectively; p < 0.001). PITC sensitivity dropped significantly in unsuspected compared with suspected septic failure (p = 0.007), and in delayed compared with early failure (p = 0.013). There were no differences in specificity.

Sonication is mainly recommended when there is implant failure with no clear signs of infection and in patients with delayed implant failure. In early failure, SFC is not superior to PITC for the diagnosis of infection and, therefore, is not recommended as a routine diagnostic test in these patients.

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The successful management of patients with infected implants or prostheses depends on an early and accurate diagnosis.[1] The ideal diagnostic test must be sensitive and specific enough to detect chronic low-grade infection associated with an implant, pseudoarthrosis or joint replacement that would otherwise be classified as aseptic. Currently no single routinely used clinical or laboratory test achieves optimal diagnostic accuracy, and a combination of clinical data and laboratory, histopathological and microbiological tests is usually used.[2,3] The diagnosis is usually made following microbiological culture of fluid samples and soft tissue from around the implant, although in 7% to 11% of patients with prosthetic joint infection (PJI) cultures are negative.[4] The capacity of the infecting bacteria to form a protective biofilm,[5-7] and their ability to switch to a dormant metabolic form with small-colony variants (SCVs),[8,9] increases the difficulty in making a diagnosis of infection. The biofilm protects bacteria against antibiotics and by changing to the SCV phenotype, bacterial survival is optimised. In addition, previous antibiotic treatment, within 14 days of sampling and processing, reduces the sensitivity of microbiological culture of the tissue around the implant.[10]

The use of ultrasound (sonication) to dislodge biofilms from the surface of implants that have been removed can increase the sensitivity of microbiological studies from 54.4% to 60.8% for peri-prosthetic tissue cultures and from 66.7% to 78.5% for fluid cultures.[10-12] The comparison of the sensitivity and specificity of the diagnosis of infection between sonication and peri-implant tissue culture in relation to the time from insertion to removal of the implant has not been investigated. Also, the diagnostic accuracy of the two methods in patients with unsuspected and suspected septic failure has not been compared. Moreover, the accuracy of these methods in patients with an infected implant rather than in those with a PJI has not been determined.

The main purpose of this study was to compare the diagnostic accuracy for infection between sonication-fluid cultures and peri-implant tissue culture for early and delayed implant failures. We also aimed to compare the sensitivity and specificity of both diagnostic

methods in patients with unsuspected and suspected septic failures, and the type of implant removed. It was hypothesised that sonication would increase the diagnostic accuracy for infection in delayed, but not early, implant failure, and in patients with unsuspected septic failure.

Patients and Methods

At our tertiary referral University Hospital all patients undergoing revision surgery between January 2007 and December 2008 for failure of an implant or a PJI with or without suspected infection were included in this prospective study. Patients were excluded if less than five peri-implant tissue samples were submitted for culture, if obvious contamination of the implant occurred in the operating theatre or if the implant did not fit the container provided for microbiological analysis.

A total of 363 patients underwent surgery during this time, 38 of whom were excluded because the implants removed were cement spacers used in a two-stage revision arthroplasty, which were analysed in a separate study.[13] Of the remaining 325 patients, eight were excluded as a result of improper transportation of the sample to the laboratory (n = 3), contamination of the ultrasonic bath by *Ralstonia pickettii* (n = 3), and accidental opening (n = 2), leaving 317 patients available for analysis. There were 132 males and 185 females with a mean age of 62.7 years (9 to 97). The mean time from the introduction to the removal of the implant was 3.6 years (0.17 to 19). The indications for surgery were suspicion of PJI in 80 patients, aseptic failure in 120, elective removal in 88, pseudoarthrosis in 23, dislocation of the prosthesis in three, and fracture of the implant in three. Elective removal refers to those patients with local symptoms and normal laboratory tests, those with prominent implants and those with limitation of movement attributed to the implants. As subclinical infection could not be ruled out in these patients, these implants were included in this study. Fixation devices accounted for all cases of pseudoarthrosis and elective removal.

The diagnostic accuracy, as reflected by the sensitivity and specificity of the cultures of fluid from the sonication of the implants and cultures of peri-implant tissue was compared in each patient. This comparison was performed for the following conditions: all patients with suspected or unsuspected septic failure, depending on the time between introduction and removal of the implant (early or delayed failure), and depending on the type of implant that was removed. A suspected infection was defined by the presence of fever, pain, redness, swelling and increased local temperature or increased white cell count, ESR and C-reactive protein in the blood. Patients were considered to have an unsuspected infection when these indicators were absent. Zimmerli, Trampuz and Ochsner[14] classified PJI as early if it developed < three months after surgery, delayed between three and 24 months after surgery, and late > 24 months after surgery. For this study, delayed and late infections were grouped together, so the time from introduction to removal was early if < three months or delayed if > three months after surgery. The term 'failure' instead of 'infection' was used because not all failures were finally diagnosed as being as a result of infection. As a secondary analysis of diagnostic accuracy, positive and negative predictive values were calculated. In order to control for the potential risk of contamination, one sterile surgical saw blade was sent to the laboratory for each group of 50 implants that were removed. These sterile control samples underwent the same protocol as all implants undergoing sonication, and personnel from the laboratory were blinded to the type of implant (potentially infected or control).

Both diagnostic tests were compared with a gold standard. Patients were classified as having definite (gold standard) implant infection if at least one of the following was present: 1) visible purulence in the synovial fluid or surrounding the implant; 2) a sinus tract communicating with the implant; 3) acute inflammation consistent with infection during histological examination of tissue sections; or 4) positive culture (either from sonication or tissue culture) with the development of corresponding post-operative clinical signs. Acute inflammation consistent with infection was considered if there was infiltration by neutrophil polymorphonuclear leukocytes. It has been found that the presence of at least five neutrophils per high-power field strongly correlates with bacteriological growth.[15] Definite aseptic failure was defined as failure of an implant in the absence of any of these criteria. Data on antibiotic therapy before surgery were also collected and included the type and duration of treatment, the time between withdrawal of the antibiotic and removal of the implant, and the results of antibiotic susceptibility testing.

Implants were aseptically removed in the operating theatre and transported to the microbiology laboratory in a two litre wide-mouthed polypropylene receiver previously sterilised for 24 hours in ethylene oxide. Sonication of the implant and incubation of the resultant fluid were performed as previously described.[13] A positive sonication-fluid culture was defined as growth of at least five colony-forming units (CFU) of the same micro-organism from any plate.[10,16]

Tissue specimens with the most obvious inflammatory or infective changes, and tissue found between the bone and the implant were removed at operation. For each patient, five tissue samples were collected and sent for microbiological analysis.[15] Sample processing and incubation was performed as previously described.[13] A positive culture was defined as growth of the same micro-organism in two or more tissue samples. All tissue samples and implants were processed within six hours of harvesting.

Statistical analysis. Descriptive statistics were used to summarise demographic characteristics, history of orthopaedic infection, time between the introduction and removal of the implant, clinical signs of infection, previous antibiotic therapy, type of micro-organisms obtained and type of implant removed. The sensitivity and specificity of

Table I. Diagnostic accuracy for infection between sonication-fluid culture and culture of peri-implant tissue in relation to the type of failure

	Sensitivity*			Specificity*		
Type of failure	**SFC**	**PITC**	**p-value†**	**SFC**	**PITC**	**p-value†**
Suspected septic failure (n = 79)	85.5	75	0.057	100	100	1
Unsuspected septic failure (n = 238)	100	48.5	< 0.001	99	99.5	1
p-value†	0.032	0.007		0.864	1	
Early (< 3 mths) (n = 43‡)	92.6	85.2	0.625	93.8	100	1
Delayed (> 3 mths) (n = 240‡)	88	58	< 0.001	99.4	100	1
p-value†	0.723	0.013		0.169	1	

* SFC, sonication-fluid culture; PITC, peri-implant tissue culture
† McNemar's test
‡ 34 cases were excluded from this analysis because they were operated on in other hospitals and no exact date of implant placement could be provided

Table II. Distribution of micro-organisms depending on the type of failure (early *versus* delayed)

Micro-organism*	Early failure (n, %)	Delayed failure (n, %)	p-value†
Staphylococcus aureus	13 (*30.2*)	8 (*3.3*)	< 0.001
GNR	7 (*16.3*)	7 (*2.9*)	0.002
CNS	6 (*14*)	36 (*15*)	0.86
Streptococci	3 (*7*)	5 (*2.1*)	0.11
GPR	2 (*4.7*)	12 (*5*)	1
Anaerobes	3 (*7*)	11 (*4.6*)	0.45

* GNR, Gram-negative rods; CNS, coagulase-negative staphylococci; GPR, Gram-positive rods
† chi-squared test

both diagnostic methods were calculated with 2 × 2 contingency tables. Statistically significant differences in the diagnostic accuracy were assessed with the McNemar's test for the following comparisons: 1) sensitivity and specificity between the two diagnostic methods in all patients; 2) sensitivity and specificity within each diagnostic method between those with suspected and unsuspected septic failure; 3) sensitivity and specificity of both diagnostic methods depending on the time between introduction and removal of the implant (early *versus* delayed failure), according to Zimmerli et al[14]; and 4) sensitivity and specificity of both diagnostic methods depending on the type of implant. Statistically significant differences in the distribution of micro-organisms depending on the type of failure (early *versus* delayed) were calculated using the chi-squared test. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with SPSS v.17.0 (SPSS Inc., Chicago, Illinois).

Results

Of all 317 patients, 109 (34.4%) were finally diagnosed with infection. Of these, 12 were polymicrobial and 97 had a single bacterial species. None of the control samples was positive for infection. A total of 292 patients (92.1%) had no past history of orthopaedic infection, and 245 (77.3%) had no clinical signs of infection.

The sensitivity for the diagnosis of infection in the 317 patients for sonication-fluid culture was significantly higher compared with culture of peri-implant tissue culture (89.9% *versus* 67%, respectively; $p < 0.001$). However, there were no significant differences for specificity, positive predictive value, and negative predictive value for the diagnosis of infection when comparing the two diagnostic methods (specificity 99% and 99.5% respectively, positive predictive value 98% and 98.6% respectively, and negative predictive value 94.9% and 85.2% respectively).

Table I summarises the sensitivity and specificity of both diagnostic methods in four subgroups depending on the type of failure: suspected septic failure, unsuspected septic failure, early failure, and delayed failure. The positive predictive values for the sonication-fluid culture in suspected septic failure, unsuspected septic failure, early failure and delayed failure were 100%, 94.3%, 96.2% and 98.5%, respectively. The same positive predictive values for the culture of peri-implant tissue were 100%, 94.1%, 100% and 100%, respectively. The negative predictive values for the sonication-fluid culture in suspected septic failure, unsuspected septic failure, early failure and delayed failure were 21.4%, 100%, 88.2% and 94.8%, respectively. The same negative predictive values for peri-implant tissue culture were 13.6%, 92.3%, 80% and 84.2%, respectively. Table II compares the distribution of different micro-organisms in early and delayed failure.

Table III. Diagnostic accuracy for infection between sonication-fluid culture and peri-implant tissue culture depending on the type of implant

	Sensitivity†			Specificity†		
Type of implant*	**SFC**	**PITC**	**p-value‡**	**SFC**	**PITC**	**p-value‡**
Knee prostheses (n = 98)	90.6	56.2	0.003	100	100	1
Hip prostheses (n = 54)	87	60.9	0.031	100	100	1
Tibial inserts (n = 13)	80	80	1	100	100	1
Acetabular components (n = 22)	100	100	1	100	100	1
Fixation devices (n = 101)	93.3	76.7	0.063	97.2	100	0.5
Spinal devices (n = 20)	100	50	1	100	100	1

* nine patients had other implants (see Results)
† SFC, sonication-fluid culture; PITC, peri-implant tissue culture
‡ McNemar's test

The sensitivity and specificity of both diagnostic methods depending on the type of implant is shown in Table III. In addition to these implants, five shoulder replacements, three elbow replacements and one ankle replacement were removed, only two of which (one shoulder and one elbow) were infected. The positive predictive value for infection of knee prostheses, hip prostheses, tibial inserts, acetabular components, fixation devices and spinal devices was 100%, 100%, 100%, 100%, 93.3% and 100% in the sonication-fluid culture, respectively, and 100% in all types of implants for the peri-implant tissue culture. The negative predictive value for infection in knee prostheses, hip prostheses, tibial inserts, acetabular components, fixation devices and spinal devices was 95.7%, 90.9%, 60%, 100%, 97.2% and 100% in the sonication-fluid culture, respectively, and 82.5%, 76.9%, 60%, 100%, 91% and 75% in the peri-implant tissue culture, respectively.

A total of 298 patients (94%) did not receive antibiotics before microbiological analysis. In these patients, the sensitivity of sonication-fluid culture was significantly higher than the peri-implant tissue culture (91.2% *versus* 69.2%, $p < 0.001$). The specificity was 99% *versus* 99.5%, respectively ($p = 1.0$). In contrast, in the 19 patients (6%) who received antibiotics before removal of the implant, the sensitivity and specificity of sonication-fluid culture for infection was 83.3% and 100%, respectively, and 55.6% and 100% for the peri-implant tissue culture, respectively ($p = 0.125$). Patients stopped antimicrobial therapy at a mean of 9.4 days (1 to 22) before surgery.

Discussion

The diagnosis of infection associated with orthopaedic implants is still challenging. The culture of microorganisms after sonication of removed implants was recently found to be more sensitive for the diagnosis of infection than culture of peri-implant tissue.[10] While most studies agree that sonication increases the diagnostic accuracy of infection by microbiological culture in orthopaedic surgery,[10-12] there is no information on the usefulness of this technique in different types of failure. The principal finding of our study was the significantly higher sensitivity of implant sonication compared with peri-implant tissue culture for the diagnosis of infection in delayed, but not early, failures. Also, sonication was mainly useful in cases of unsuspected septic failure. Overall, sonication was more sensitive to infections compared with culture of peri-implant tissue but a significant difference was only found for total knee and hip replacement, with a marginal difference for infections of fixation devices.

This study has some limitations. First, the gold standard for the definition of an infection remains contentious. Infections have many causes and a wide range of clinical presentations, and the diagnosis of orthopaedic infection is difficult as a result of the many investigations that may be used and their differing accuracy. Therefore, as in this study, the final diagnosis should be based on a combination of clinical and laboratory methods. Also, the fourth gold standard criterion was a positive culture with the development of postoperative clinical signs of infection. This does not exclude the possibility of a new bacterium contaminating the implant during its removal. However, it should be noted that the general rate of infection during elective orthopaedic operations is very low (1% to 2%).[14] Secondly, there is an inherent risk of the contamination of samples collected in the operating theatre and during transportation and manipulation to the laboratory. However, control samples were used in this study to reduce the risk of false positive results. Thirdly, there was a limited number of certain implants (tibial inserts, acetabular components and spinal devices), which increased the risk of a type-II error in the statistical analysis. Fourthly, the diagnostic criteria for infection in sonication were described for hip and knee prostheses, but not for other implants. Although it was found that the diagnostic accuracy for infection in sonication of other implants (acetabular components, fixation devices and spinal devices) was very high, further studies are needed to define the diagnostic criteria for infection better in the sonication of implants other than hip and knee prostheses.

The most interesting finding of this study is that sonication had a higher sensitivity compared with the culture of peri-implant tissue for the diagnosis of infection in delayed, but not early, implant failure. This finding seems to be

explained by the dramatic drop in sensitivity of the culture of peri-implant tissue in delayed compared with early failures. Early failure may be caused by acute infections, which are usually caused by rapidly-growing micro-organisms that may not have had enough time to produce a biofilm. The absence of this biofilm may explain the high sensitivity of culture of peri-implant tissue. This speculation is in part supported by the fact that there were more high-virulence micro-organisms such as *Staphylococcus aureus* and gram-negative rods in early compared with delayed failures. In contrast, delayed failure may be caused by chronic infection originated by slow-growing, biofilm-producing micro-organisms that would isolate bacteria from peri-implant tissue. Unfortunately, the proportion of coagulase-negative *staphylococci*, Gram-positive rods and anaerobic bacteria was not higher in patients with delayed, compared with early, failure. The clinical implication of these findings is that sonication may be mainly indicated in patients with delayed failure. In contrast, in early failure sonication may not be superior to peri-implant tissue culture for the diagnosis of infection and should therefore not be recommended routinely as a diagnostic test in these patients.

Another interesting finding is that sonication significantly increases sensitivity for infection in patients with unsuspected septic failure. The reason for this difference is two-fold. First, and foremost, the sensitivity of peri-implant tissue cultures drops significantly in unsuspected, compared with suspected, septic failure. Secondly, the sensitivity of sonication significantly increases in unsuspected, compared with suspected, septic failure. We speculate that most cases of unsuspected septic failure may be caused by slow-growing, less-virulent, biofilm-producing micro-organisms involved in chronic infections where pathogens are more isolated from the peri-implant tissue, thus resulting in a decreased sensitivity of tissue culture for the diagnosis of infection. The clinical implication of this finding is the recommendation to use sonication to look for infection whenever an implant fails with no clear signs of sepsis.

The diagnostic accuracy obtained in the present study for hip and knee prosthesis may be compared with that reported by others, as Trampuz et al[10] found similar values of sensitivity and specificity in the diagnosis of hip and knee prosthetic infection for sonication-fluid and peri-implant tissue cultures. As reported in the present study (Table III), Trampuz et al[10] reported a significantly higher sensitivity, but not specificity, for infection in sonication compared with peri-implant tissue culture in both hip and knee replacement. A novel aspect of this study was the investigation of diagnostic accuracy for several implants other than hip and knee prostheses. Of note, there was a trend towards significant differences in sensitivity between the two diagnostic methods for fixation devices ($p = 0.06$). It is possible that increasing the number of infected implants that were removed from our total of 31 of 101 would have elicited a significantly higher sensitivity for implant sonication, compared with tissue culture for the diagnosis of infection. In contrast, there were no significant differences in diagnostic accuracy between sonication and tissue culture for other implants (tibial inserts, acetabular components and spinal devices). The differing results between the later implants and hip and knee prostheses may be explained by the low number of these implants rather than the fact that bacterial adherence may be affected by the kind of biomaterials, as all implants, except for the tibial inserts, in this study were made of either stainless steel, titanium or chrome-cobalt alloy. Also, given that a significant difference was found for larger (hip and knee) prostheses, it might be argued that the larger the implant, the greater the surface where the biofilm can be formed and, thus, the greater the difference between the two diagnostic methods in detecting bacteria. The influence of the size of the implant on the accuracy of the diagnosis of infection using sonication needs further research.

Treatment with antibiotics before removal of the implant may decrease the diagnostic accuracy of different methods of culture.[10,14,17,18] It was found in this study that in patients who had not previously taken antibiotics, sonication was more sensitive than peri-implant tissue culture whereas there were no differences if antibiotics had been previously used. In contrast, Trampuz et al[10] found a higher sensitivity for infection in hip and knee prostheses in patients receiving antibiotics within 14 days before surgery using sonication compared with peri-implant tissue culture. They speculated that this may be related to the fact that bacteria in biofilms may be less sensitive to antibiotic treatment.[2,8,10,19] It might be argued that the absence of significant differences in the diagnostic accuracy in the present study between the two methods when previous antibiotic therapy was used is because of the small sample size, as only 19 patients had taken antibiotics before removal of the implant. While stopping antibiotics before the collection of samples is recommended,[20] the optimal antibiotic-free period required before surgery to prevent the decrease in diagnostic accuracy has not been identified.[10] In general, the influence of antibiotic treatment before surgery on the diagnostic accuracy of orthopaedic infections needs further research.

In conclusion, the culture of the fluid from the sonication of removed implants significantly increases the sensitivity for the diagnosis of infection compared with the culture of peri-implant tissue in patients with delayed, but not early, implant failure. Also, implant sonication was mainly useful in patients with unsuspected septic failure. Essentially, the clinical implications of these findings are two-fold. First, we recommend that sonication is used in the diagnosis of orthopaedic infection whenever there is implant failure without clear signs of sepsis and secondly, while the sonication of removed implants is useful in patients with delayed implant failure it is not recommended in cases of early failure.

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