Sonication Culture of Antimicrobial Agent-Containing Cement Spacers Removed during Staged Revisions for Arthroplasty Infection

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ABSTRACT Diagnosis of persistent infection at the time of reimplantation for staged revision of infected arthroplasties is challenging. Implant sonication culture for the diagnosis of prosthetic joint infection (PJI) has improved sensitivity compared to standard periprosthetic tissue culture. We report our experience with periprosthetic tissue culture and sonication culture of antimicrobial agent-containing cement spacers (ACSs) collected during second stages of staged revisions for arthroplasty infection. We studied 87 ACSs from 66 patients undergoing two-stage revision arthroplasty for PJI submitted for sonication culture, along with conventional periprosthetic tissue cultures. Two or more positive periprosthetic tissue cultures with the same organism were considered a positive tissue culture. For sonication culture, ≥ 20 CFU of bacteria per 10 ml of sonicate fluid was considered positive. The sensitivity and specificity of periprosthetic tissue and ACS sonication culture in detecting persistent infection, as well as their association with outcome, were assessed. Persistent infection occurred in 26% of cases. Periprosthetic tissue and sonicate fluid culture had specificities of 96.3 and 100% ($P = 0.50$), respectively, and sensitivities of 31.6 and 26.3% ($P = 1.00$), respectively, for the diagnosis of persistent infection. Thirteen subjects deemed not to have persistent infection at time of reimplantation and who had negative periprosthetic tissue and sonicate fluid cultures subsequently developed overt infection. Sonication culture of cement spacers identifies a similar proportion of patients with persistent infection during staged revisions, as detected by periprosthetic tissue cultures; both have low sensitivities to detect persistent infection.

KEYWORDS antibiotic cement, prosthetic joint infection, sonication

Prosthetic joint infection (PJI) is the most common complication of arthroplasty, after aseptic failure. PJI treatment is associated with significant health care cost, with a projected annual cost of \$1.6 billion by 2020 (1). Two-stage arthroplasty revision is the most commonly recommended treatment for chronic PJI. During a two-stage arthroplasty revision, the infected prosthesis is removed, the infected tissue is debrided, and a cement spacer containing one or more antimicrobial agents is placed to maintain the joint space and deliver local antimicrobial therapy. After a course of systemic antimicrobial therapy, another surgery is required to remove the cement spacer and reimplant a new prosthesis. Although two-stage revision arthroplasty for PJI has shown good results, failure rates up to 24% have been reported (2, 3). Recurrent PJI is associated with increased mortality compared to initial PJI (2). If PJI persists after a two-stage revision, the chance of eradication of infection with a subsequent two-stage

Citation Gomez-Urena E, Sierra RJ, Greenwood-Quiantance KE, Karau MJ, Steckelberg JM, Patel R. 2019. Sonication culture of antimicrobial agent-containing cement spacers removed during staged revisions for arthroplasty infection. *J Clin Microbiol* 57:e01483-18. <https://doi.org/10.1128/JCM.01483-18>.

Editor Sandra S. Richter, Cleveland Clinic
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Received 13 September 2018

Returned for modification 8 October 2018

Accepted 1 December 2018

Accepted manuscript posted online 12 December 2018

Published 30 January 2019

revision is decreased (4, 5). Patients with persistent knee arthroplasty infection after two-stage revision may require amputation or knee fusion, and those with persistent hip arthroplasty infection may require a Girdlestone procedure, which are outcomes associated with limited joint function and mobility (6).

Unfortunately, there are limited tools to assess infection clearance at the time of reimplantation. Systemic inflammatory markers and aspiration of the joint for cell count and culture have low sensitivity and specificity to detect persistent infection (7). Intraoperative histopathology has low sensitivity and limited ability to identify subsequent failure (8). In the same manner, periprosthetic tissue cultures have shown poor positive and negative predictive values to detect infection at second-stage surgery (9). In a series of knee arthroplasties, intraoperative cultures of infections caused by oxacillin-resistant staphylococci failed to predict recurrent infection; 11% of patients had recurrent infection with the same organism, and 14% had reinfection with a different organism, despite having negative periprosthetic tissue cultures at the time of reimplantation of the prosthesis (10). Hart and Jones evaluated periprosthetic tissue cultures, histopathology, and inflammatory markers in 48 patients undergoing two-stage revision to assess for infection after the second-stage surgery (9). Eleven patients had positive cultures at time of reimplantation, but only two developed recurrent infections. Thirty-seven had negative cultures at the second stage; four of these patients developed recurrent infection. The authors estimated that the positive and negative predictive value of periprosthetic tissue cultures, frozen section, and inflammatory markers were 18 and 89%, 38 and 88%, and 23 and 91%, respectively. This shows the limitation of current techniques to identify persistent infection and to predict future arthroplasty failure due to recurrent infection.

Recently, antimicrobial agent-containing cement spacer (ACS) culture has been studied in the diagnosis of persistent or subclinical infection in patients undergoing two-stage revision for PJI (11, 12). Moreover, an association of positive sonicate fluid cultures of the removed ACS and subsequent arthroplasty infection has been reported (13). These studies have included a limited number of patients using qualitative, semiquantitative, and quantitative ACS sonicate fluid culture, which makes the generalization of results difficult. New data from other authors raise questions regarding the utility of ACS sonicate fluid culture in the management of PJI (14, 15). Further studies are needed to define the utility of ACS sonicate fluid culture in patients undergoing two-stage arthroplasty revision for PJI; hence, we report our experience with sonication of ACSs for the diagnosis of persistent infection.

MATERIALS AND METHODS

Between November 2007 and October 2014, 97 ACSs from 76 patients undergoing staged arthroplasty revision by a single orthopedic surgeon for PJI were submitted for sonication culture, alongside conventional periprosthetic tissue cultures (Fig. 1). ACSs were submitted for sonication at the discretion of the surgeon. Patients meeting the IDSA definition for PJI were included in the study (16); all had undergone arthroplasty resection with removal of the prosthesis and cement (if present), debridement of the infected periprosthetic soft tissue and placement of an ACS. The choice of antimicrobial agents within the spacer was based on antecedent culture results (e.g., from arthrocentesis) when available. All subjects had received a 6-week course of culture-guided intravenous antimicrobial therapy. After treatment and prior to reimplantation, the joint was clinically assessed for findings of infection (i.e., pain, edema, erythema, warmth, and surgical wound drainage). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were measured. At reimplantation, tissue specimens for culture and histopathology were collected. The ACS was removed and submitted for sonication culture. If there was evidence of persistent infection based on histopathology or gross inspection, further debridement of periprosthetic tissue was performed with exchange of the ACS, followed by another course of intravenous antimicrobial therapy.

Persistent infection was defined by the presence of at least one of the following: (i) purulence in the synovial fluid or periprosthetic tissues, (ii) sinus tract communicating with the prosthesis, (iii) histopathology showing acute inflammation in periprosthetic tissues, or (iv) clinical symptoms or signs of infection (pain, edema, warmth, erythema, or draining surgical wound) plus elevated CRP (>10 mg/dl) and/or ESR (>30 mm/h).

Tissues were processed for culture and cultures performed as previously described (17). A tissue culture was considered positive when the same organism was isolated from ≥ 2 tissue samples. The explanted ACSs were collected aseptically in the operating room into autoclaved 1-liter polypropylene

FIG 1 Study flow chart. PJI, prosthetic joint infection; ACS, antimicrobial agent-containing cement spacer. *, Some subjects had several spacer revisions performed. **, Three subjects had 2 PJIs.

wide-mouthed containers (Nalgene, Lima, OH). Sonication cultures were performed as previously described (17). Growth of ≥ 20 CFU/10 ml was considered significant.

After the final surgical procedure, subjects were followed to assess outcome. Treatment failure was defined by one of the following: (i) two or more positive intraoperative cultures at the final surgical intervention (reimplantation, arthrodesis) showing the same organism, with further antimicrobial therapy administered; (ii) PJI due to a new organism (new infection) after the surgical procedure; (iii) PJI due to same organism as found in the previous PJI (relapsed infection) after the surgical procedure; (iv) persistent infection (as defined above) requiring chronic antimicrobial therapy; or (v) permanent resection arthroplasty due to persistent infection.

We evaluated the sensitivity and specificity of ACS sonicate fluid culture for the diagnosis of persistent infection and association with subsequent infection. Continuous variables were expressed as medians and interquartile ranges (IQRs). Sensitivities and specificities of each of the microbiology tests were compared to the definition of persistent infection, using McNemar's test for related proportions. The binomial exact method was used to calculate 95% confidence intervals (CI). Medians for continuous variables were compared using the Mann-Whitney test. *P* values of <0.05 were considered statistically significant. Statistical analyses were performed using MedCalc (version 12.1.4.0).

RESULTS

Ten patients with 11 ACS sonicate fluid cultures were excluded from the study, since the criteria for PJI were not met (Fig. 1). Sixty-six subjects who met the IDSA definition of PJI were included (Table 1). Prior to arthroplasty resection, 43 patients (65.2%) had a history of one or more surgical treatments (debridement and implant retention and/or two-stage resection) of the involved joint because of infection. Twenty patients (30.3%) were referred to our institution after having had arthroplasty resection.

Second-stage surgery. Eighty-seven ACSs from 66 patients were submitted for sonication during the second-stage surgery. One ACS sonicate fluid culture from an infected knee arthroplasty due to vancomycin-resistant *Enterococcus* species was excluded from the analysis; this ACS was removed 6 days after placement to replace the originally placed vancomycin/tobramycin spacer with one containing daptomycin. Eighty-six ACSs were included in the assessment of persistent infection (Fig. 2).

Clinical symptoms and/or signs of infection were present in 17.4% (15/86) of cases prior to the second-stage surgery. ESR and CRP were elevated in 34.9 and 48.8% of

TABLE 1 Patient characteristics

Characteristic ^a	Result (n = 66)
Median age in yr (IQR)	60.5 (51–71)
No. (%) of male patients	63.6
Arthroplasty (%)	
Knee	69.7
Hips	30.3
Comorbid conditions (%)	
Diabetes	18.2
Rheumatoid arthritis	7.6
Immunosuppressed	10.6
Type of PJI (%)	
Early onset (<3 mo)	33.3
Delayed onset (3 to 12 mo)	24.2
Late onset (>12 mo)	42.4
Microbiology of index PJI (%)	
<i>Staphylococcus aureus</i>	28.8
Coagulase-negative staphylococci	22.7
Gram-negative bacilli	12.1
Polymicrobial	12.1
Culture negative	13.6
Enterococci	6.1
Streptococci	3.0
<i>Candida</i> species	1.5
Median age (days) of the spacer (IQR)	89 (71–103)
Persistent infection (no. of patients)	19
Acute inflammation	8
Intraoperative purulence	10
Sinus tract	1
Clinical signs ^b	12

^aIQR, interquartile range; PJI, prosthetic joint infection.^bClinical signs of infection plus elevated inflammatory markers.

cases, respectively. The median days off antibiotics prior to ACS removal was 43.5 days (IQR, 26 to 55 days). Vancomycin and aminoglycosides were present in 79% (68/86) and 82.6% (71/86) of spacers, respectively.

Tissue samples were not sent for histopathologic examination in 15.1% (13/86) at the time of the second surgery; therefore, these patients were excluded due to insufficient data to fulfill the definition of persistent infection. In the remaining 73 patients with histopathology reports, persistent infection was present in 19 (26%). A second debridement with exchange of the ACS was performed in 24 cases, 15 of which met criteria for persistent infection.

A median of 3 (IQR, 2 to 4) tissue cultures were taken at time of spacer removal. Periprosthetic tissue culture was positive in 9 (10.5%) of 86 cases. *S. aureus* was isolated in 8 cases and a coagulase-negative *Staphylococcus* species (SCN) in 1 case. ACS sonicate fluid cultures were positive in 5 cases (5.8%), all which yielded *S. aureus*. Nonsignificant growth was noted in 19 cases. In all cases with positive ACS sonicate fluid cultures, periprosthetic tissue cultures were also positive.

Periprosthetic tissue and ACS sonicate fluid cultures had a sensitivity of 31.6% (6/19) and 26.3% (5/19), respectively ($P = 1.00$) to detect persistent infection. Periprosthetic tissue cultures and ACS sonicate fluid cultures had a specificity of 96.3% (52/54) and 100% (54/54), respectively ($P = 0.50$) to detect persistent infection.

Outcomes. One patient (patient 38) died prior to reimplantation knee arthroplasty. Three patients (patients 13, 17, and 21 in the Table 2) had subsequent infections involving the same arthroplasty, resulting in 68 distinct PJIs in 65 patients. At the time

FIG 2 Periprosthetic tissue and ACS culture results at the time of the antimicrobial cement removal. ACS, antimicrobial-containing cement spacer.

of final surgery, 58 arthroplasties were reimplanted in 56 patients (2 patients had two distinct PJIs). Seven patients underwent arthrodesis; one was initially reimplanted but, due to subsequent infection, an arthrodesis was ultimately performed. Three patients had permanent resection arthroplasty due to persistent infection.

Cure was obtained in 45 of 68 of cases. The median follow-up of the cured cases was 854 days (IQR, 464 to 1,569 days). Twenty-eight patients had >2 years, 12 patients had 1 to 2 years, and 5 patients had less than 6 months of follow-up. Treatment failure occurred in 19 cases. In four patients, recurrent or new PJI was suspected but not confirmed (one refused further evaluation, three were lost to follow-up); these cases were considered clinical failures.

Thirteen patients developed infections after the final surgical treatment, 11 after prosthesis reimplantation and 2 after arthrodesis. The median follow-up to infection was 602 days (IQR, 199 to 1,036). None of these patients had signs or symptoms of infection, evidence of persistent infection intraoperatively, or positive periprosthetic or ACS cultures during the previous surgery. Only one patient with PJI had an elevated CRP at the time of reimplantation (but with a decreasing trend). ESR was normal in all patients. Six infections were considered relapses due to *S. aureus* ($n = 2$), coagulase-negative staphylococci (CNS; $n = 2$), and *Streptococcus* species ($n = 2$). Seven patients had new infections due to *Streptococcus* species ($n = 3$), *S. aureus* ($n = 2$), CNS ($n = 1$), and *Corynebacterium striatum* ($n = 1$).

Treatment failure was not increased in subjects with positive compared to those with negative sonicate fluid cultures (odds ratio [OR] = 10.58, 95% CI = 0.49 to 230.0, $P = 0.13$). Likewise, treatment failure was not increased in subjects with positive compared to those with negative periprosthetic tissue culture (OR = 15.53, 95% CI = 0.77 to 314.81, $P = 0.07$). Subjects with one or more surgical treatments on the involved joint were more likely to develop treatment failure (OR = 3.5, 95% CI = 1.03 to 12.30, $P = 0.04$).

DISCUSSION

In the management of PJI by two-stage revision, the use of ACSs has become the standard of care as it not only provides local antimicrobial delivery to the joint but it also preserves the anatomy of the joint space, facilitating later reimplantation (18).

Detecting persistent infection at the time of the reimplantation of the arthroplasty after surgical and medical therapy is highly desirable to prevent the placement of a new prosthesis in an infected joint. Several studies have evaluated culture of removed ACSs

TABLE 2 Characteristics of patients with treatment failure and persistent infection^a

Patient	Age (yrs)/sex	Joint	Type of surgery	Clinical symptoms	ESR (mm/h)/CRP (mg/dl)	Sinus tract	Joint purulence	Acute inflammation by histopathology	Tissue culture	ACS sonicate fluid culture	Previous pathogen	Follow-up (days)	Outcome
Infection detected at first surgery													
3	48/M	H	Reimplantation	No	22/3.4	No	No	No	(-)	(-)	<i>Enterococcus</i> species	663	New infection due VGS
10	71/F	K	Reimplantation	No	43/40.9	No	No	No	(-)	(-)	<i>Staphylococcus</i> species and yeast	1,674	New infection due to MSSA
13	51/F	K	Reimplantation	No	2/3.5	No	No	No	(-)	(-)	VRE	212	New infection due to GGS
13	51/F	K	Arthrodesis	No	1/9.3	No	No	No	(-)	(-)	GGS	283	Relapsed infection due to GGS
17	80/M	K	Reimplantation	No	7/7	No	No	No	(-)	(-)	VGS	685	New infection due to <i>Finnegalia magna</i> , VGS, <i>Serratia marcescens</i>
21	43/M	H	Reimplantation	No	11/<3.0	No	No	No	(-)	(-)	MSSA	25	Relapsed infection due to MSSA
23	77/M	K	Arthrodesis	No	6/<3.0	No	No	No	(-)	(-)	CNS	1,414	Relapsed infection due to CNS; sinus tract
26	30/M	H	Reimplantation	No	5/5.9	No	No	No	(-)	(-)	MSSA	1,009	Relapsed infection due to MSSA
37	43/F	H	Reimplantation	No	19/20.4	No	No	No	(-)	(-)	MSSA	1,118	New infection due to <i>Staphylococcus epidermidis</i> ; sinus tract
40	73/M	K	Reimplantation	No	15/<3.0	No	No	No	(-)	(-)	CNS	587	New infection due to <i>Corynebacterium striatum</i>
41	66/F	K	Reimplantation	No	65/23	No	No	No	(-)	(-)	MSSA	43	New infection due to GBS
61	60/M	H	Reimplantation	No	20/4.6	No	No	No	(-)	(-)	GBS/ <i>Pseudomonas aeruginosa</i>	602	Relapsed infection due to GBS; sinus tract
66	63/M	K	Reimplantation	No	14/13.9	No	No	No	(-)	(-)	<i>S. epidermidis</i>	161	Relapsed infection due to <i>S. epidermidis</i>
Persistent infection at the second surgery													
11	75/M	H	Permanent arthroplasty resection	Yes	50/15.3	No	Yes	Yes	MRSA	MRSA	MRSA	NA	Reimplantation aborted due to persistent infection
15	56/M	K	Permanent arthroplasty resection	Yes	127/64.7	No	Yes	No	MRSA	MRSA	MRSA	NA	Patient had two debridements and ACS exchange
45	70/M	K	Permanent arthroplasty resection	No	33/42.7	No	Yes	Not done	(-)	(-)	VRE	NA	Intraoperative purulence noted at last surgery; ACS sonicate fluid culture showed <20 CFU/ml of VRE
53	64/M	K	Reimplantation	Yes	55/6.6	No	No	Yes	(-)	(-)	(-)	NA	Pain, elevated ESR and acute inflammation on histopathology during reimplantation; prescribed chronic antimicrobial suppression
64	69/M	K	Reimplantation	No	44/3.3	No	No	Yes	(-)	(-)	MRSA and <i>Porphyromonas brennisonis</i>	NA	Elevated ESR, acute inflammation on histopathology at reimplantation; ACS sonicate fluid culture showed <20 CFU/ml of <i>Ralstonia mannitolilytica</i> ; given chronic antimicrobial suppression
65	50/M	K	Reimplantation	No	0/5	No	No	Not done	MRSA	(-)	(-)	NA	This patient did not meet criteria for persistent infection but had positive intraoperative cultures. New infection; chronic antimicrobial suppression

^aM, male; F, female; H, hip; K, knee; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ACS, antimicrobial agent containing cement spacer; (-), negative result; VGS, viridans group streptococci; MSSA, methicillin-susceptible *Staphylococcus aureus*; GGS, group G streptococcus; MRSA, methicillin-resistant *Staphylococcus aureus*; CNS, coagulase-negative *Staphylococcus* species; GBS, group B streptococcus; NA, not applicable.

for the diagnosis of persistent infection, subsequent episodes of PJI, and poor outcome (11–13). Esteban et al. evaluated 50 ACSs from 46 subjects and showed that sonicate fluid culture showed a slightly higher sensitivity (56 versus 50%) than periprosthetic tissue cultures for the diagnosis of persistent infection (19). However, other groups have reported different experiences with the ACS sonication. Some studies have shown that ACS sonicate fluid culture has low diagnostic yield and does not seem to add information beyond that provided by periprosthetic tissue cultures (14, 20). Recently, Olsen et al. reported no benefit of ACS sonicate fluid culture for the diagnosis of persistent infection or to predict outcomes of 41 subjects undergoing two-stage revision for PJI (15). Similar to our study, these authors reported a low rate of ACS sonicate fluid culture positivity, with only two positive ACS cultures, neither of which were associated with subsequent infections. Four subjects had recurrent infections, all of whom had negative ACS and periprosthetic tissue cultures. Comparable to these more recently published studies, we found that culture of ACSs does not seem to add value to tissue cultures, as all cases with positive sonicate fluid cultures also had positive periprosthetic tissue cultures.

In addition to diagnosis of persistent infection, bacterial detection on ACSs has been associated with subsequent infections and poor outcomes. Several studies have reported an increased risk of reinfection in patients with positive ACS cultures even when the organism isolated from the ACS was different from that isolated during the first stage or during the following infection (13, 19, 21). The lack of agreement between ACS cultures and first-stage cultures suggests a new infection of the ACS. It is possible that the ACS acts as foreign body that not only allows persistence of preexisting infection but also facilitates adherence of new organisms, putting the joint at risk for a new infection. In our study, a positive ACS culture was not associated with subsequent arthroplasty infection, whether new or relapsed infection. Of the cases considered relapsed, based on isolation of the same pathogen as the index infection, periprosthetic and ACS cultures were all negative during the second-stage surgery. However, since we did not perform genotypic analysis on bacterial strains, it is possible that these cases considered relapses might actually be new infections not detected during the second surgery or that occurred after implantation. Recent studies have shown that septic failure after two-stage revisions is mainly due to new infection and not persistent infection (22). This could explain why other tests, such as histopathology and inflammatory markers, lack sensitivity to detect subsequent infections during the second-stage surgery (22, 23). These reinfections might be not due to persistent infection harbored on the spacer but to a host predisposition to infection, which could be the reason we observed an association between previous surgical procedures involving the same joint and subsequent septic failure. Further studies looking at host factors and/or genetic predisposition as causes of repeated PJI are needed.

There is variation among studies regarding the duration of the antimicrobial release from the cement, but elution of antibiotics above the MIC of the infecting organism can be observed for several months (24). Some studies have reported the theoretical possibility that sonication of the spacer would leach antimicrobials out of the cement and result in inhibition of bacterial growth in culture (14, 25). In some of our patients, the ACS was broken and processed in several pieces, which could potentially result in elution of sequestered antibiotic from the ACS, leading to negative-culture results (26). Mariaux et al. measured antimicrobial concentrations in ACS sonicate fluid showing levels at or above the MIC of common PJI pathogens (14). All ACS sonicate fluid cultures were negative, which was partially attributed to the presence of high antibiotic levels on the sonicate fluid. However, the amount of fluid used for sonication of the ACSs was not measured, and patients were also receiving systemic antibiotics at the time of explantation of the ACS, factors that could additionally or alternatively affect culture results. On the other hand, a study performed by our group showed that antimicrobial-loaded cement used for the fixation of the prosthesis did not negatively impact sonicate fluid culture of the explanted prostheses (27). It is possible that even if sonication increases the release of antimicrobials from ACSs, the lactated Ringer's used

in our study for the sonication of ACS could have diluted the antimicrobial agents and that the concentration step used may have facilitated microbial growth in sonicate fluid cultures; however, in our study, sonicate fluid was not specifically assayed for antimicrobial concentrations.

This study has several other limitations. Patients were enrolled in a nonconsecutive manner by a single orthopedic surgeon. Initially, ACSs were evaluated in high-risk patients only and subsequently in every patient undergoing two-stage arthroplasty revision for infection. Although this selection bias could affect the results, we believe this likely had little impact; had we assessed subjects with a higher suspicion for persistent infection, we would have expected a higher rate of positive ACS cultures. Several patients had less than 1 year of follow-up which may not be sufficient to detect relapse of infection, especially with low-virulence organisms. Nevertheless, with the majority of subjects having negative ACS cultures, we do not think that the short-term follow-up poses a significant limitation, as subjects with positive cultures during the second surgical procedure would, theoretically, be at higher risk for persistent infection and poor outcomes compared to subjects with negative cultures. Lastly, the definition of persistent infection and outcomes of PJs used in these studies was based on our clinical practice and is not universally standardized. The lack of a gold standard definition for persistent infection and outcomes of PJI makes it difficult to compare our results to those previously published.

Based on the results of this study, routine sonication and culture of removed ACSs in patients undergoing two-stage arthroplasty revision for PJI yields results similar to those obtained by tissue culture for the detection of PJI; the results do not predict outcome. Therefore, we do not recommend routine sonication of ACSs for assessment of persistent infection during two-stage arthroplasty revision for PJI or to assess subsequent infection risk in patients after treatment of PJI.

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