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Do Culture Negative Periprosthetic Joint Infections Remain Culture Negative?

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Abstract

Background: Diagnosis and treatment of culture negative total knee arthroplasty (TKA) periprosthetic joint infection (PJI) is challenging. There is debate over whether culture negative PJI confers increased risk of failure and which organisms are responsible. It is also unclear as to what factors predict conversion from culture negative to culture positivity. To address these issues, we performed an observational study to detect factors associated with transition from culture negative to culture positive TKA PJI in those patients that failed irrigation and debridement, determine the incidence of this transition, and identify those organisms that were associated with treatment failure.

Methods: A multicenter observational cohort study was performed on patients with TKA PJI as defined by MSIS criteria without cultured organisms and treated with irrigation and debridement (I&D). Primary outcome was failure defined as any subsequent surgical procedure. Secondary outcome included cultured organism within 2 years of initial I&D.

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Results: 216 TKA I&D procedures were performed for PJI, and 36 met inclusion criteria. The observed treatment failure rate for culture negative PJI treated with I&D was 41.67%. Of those culture negative I&Ds that failed, 53.33% became culture positive after failure. Of those that converted to culture positive, 62.5% were Staphylococcus species. The odds ratio associated with becoming culture positive following culture negative treatment failure in the setting of antibiotic administration prior to the initial I&D procedure was 0.69 (95% CI 0.14 to 3.47, p= 0.65).

Conclusions: Many cases of culture negative TKA PJI treated with I&D eventually fail and become culture positive. Staphylococci are common organisms identified after culture negative PJI.

Keywords

Periprosthetic joint infection; Culture negative; Irrigation and debridement; Preoperative antibiotics

Introduction

In total knee arthroplasty (TKA), periprosthetic joint infection (PJI) is the leading cause of failure [1]. Culture negative TKA PJI can be defined as a joint that meets the Musculoskeletal Infection Society criteria for PJI, but has no organisms identified on culture. Treatment can be challenging, as often the causative organism remains unknown. The prevalence of culture negative PJI varies, with a range reported between 0% to 42% [2, 3]. To improve surgical treatment and antibiotic selection, it is important to understand the potential causative organisms and factors that influence failure.

The outcomes of culture negative PJI are not well elucidated. A number of studies demonstrate failure rates of any surgical intervention as similar to those of culture positive infections, while others suggest culture negative infections have increased risk for failure [4–8]. Recent literature has shown that failure rates of irrigation and debridement (I&D) as a treatment option for PJI are generally high, and observed increased rates of failure for culture negative PJI in particular [6]. Few studies have extended follow up for culture negative PJI. Failed treatment may subsequently become a culture positive infection at a later time point. In these cases, studies report a range of organisms cultured between staphylococcal and streptococcal species and more rare organisms such as *Listeria monocytogens*, *Propionibacterium acnes*, and *Coxiella burnetii* [7, 9, 10]. It is unknown if these organisms are related to the initial culture negative infection or represent a new, subsequent infection as this is a high-risk population for PJI [11]. Variation in the prevalence of culture negative infection may be related to administration of preoperative antibiotics, as prior use of antibiotics is an established risk factor for culture negative infection [10, 12, 13]. Literature has classically documented prior antibiotics as a risk factor for subsequent culture negative infection, however there are no reports as to whether prior antibiotic use in culture negative infections affects the rate at which these infections subsequently become culture positive [7, 10, 12, 13].

In order to address the above points, we set out to identify irrigation and debridement outcomes of culture negative TKA PJI. We asked whether (1) culture negative PJIs stay

culture negative after treatment failure, (2) what organisms were associated with failure and (3) what factors predicted a change from culture negative to culture positive.

Materials and Methods

Study Design

A retrospective, multicenter observational cohort study was performed consisting of patients diagnosed with TKA PJI that did not result in any positive culture growth, who subsequently underwent I&D with retention of components between 2005 and 2015. Data was acquired via the electronic medical record, and study patients were from 16 hospitals in a regional health system. Institutional Review Board approval obtained.

Participants

The initial cohort was obtained using International Classification of Disease-9 code (ICD-9 code) for periprosthetic joint infection (996.66). TKA PJI was identified as those patients with ICD-9 code and concurrent surgical procedure as indicated by the medical record. PJI was identified using Musculoskeletal Infection Society (MSIS) criteria with modified minor criteria [14]. Inclusion criteria included those patients that underwent irrigation and debridement with retention of components and exchange of the polyethylene liner. Further inclusion criteria included initial onset of symptoms of PJI lasting less than one week before I&D was performed, pan-negative cultures taken within one month of PJI diagnosis, while still meeting MSIS criteria for infection (including purulence surrounding prosthesis, synovial nucleated white blood cell count threshold of 2,500 cells/microL and a synovial polymorphonuclear percentage greater than 65%) [14]. Exclusion criteria included those patients with any previous surgical procedure on their prosthesis after receiving TKA, musculoskeletal oncologic disease, and positive cultures within less than one month of irrigation and debridement procedure. Additionally, patients with cultures taken at outside medical facilities that were reported as positive in the medical record were excluded, even if subsequent culture results were negative. Preoperative, surgical, and postoperative care was directed by and at the discretion of the patient's medical team.

Outcome Measures

Failure of irrigation and debridement procedure was identified as any further surgical procedure on the operative knee excluding manipulation under anesthesia, periprosthetic fracture, and extensor mechanism disruption. Subsequent transition from a culture negative PJI to a culture positive PJI was identified in those subjects with an initial culture negative PJI treated with I&D who subsequently failed, leading to a repeat procedure within two years with positive cultures.

Statistical Analysis

Demographic and clinical characteristics of patients with an initial culture negative PJI were computed to describe the study sample. Central tendency and dispersion were quantified using means and standard deviations for continuous variables with symmetric distributions; medians and IQRs were reported for skewed continuous variables. Counts and percentages were used to summarize categorical variables. Baseline characteristics were formally

compared between patients who remained culture negative and patients who transitioned from culture negative to culture positive. Two-sample t-tests were employed for symmetrical continuous variables, Wilcoxon rank sum tests were used for skewed continuous variables, and Fisher's exact tests were performed for categorical variables.

Next, the effect of preoperative antibiotics on time to failure of I&D was assessed using a Cox proportional hazard model for all 36 patients in the sample. Preoperative antibiotic use was defined dichotomously (any vs. none), and the hazard of treatment failure associated with preoperative antibiotic use was estimated. Time to failure of irrigation and debridement procedure, regardless of initial antibiotic use, was also estimated using a direct-adjusted survival curve with pointwise 95% confidence limits. Lastly, to identify potential predictors of becoming culture positive, univariate logistic regression models were then constructed with conversion to culture positive (yes/no) as the outcome and demographic and clinical characteristics as predictors. The odds ratio associated with each predictor variable was estimated along with 95% confidence intervals, and statistical significance was determined using Wald chi-square tests. All analyses assumed a significance level $\alpha=0.05$, and no adjustments were made for multiplicity.

Results

Demographics

A total of 216 I&D patients had no previous surgery and met modified MSIS criteria. In this group, a total of 36 patients had culture negative PJI. Demographics are included in Table 1. The mean age was 68.2, and mean BMI was 32.5. Twenty-three were female. The median Charlson Comorbidity Index (CCMI) was 3.5 [IQR 3.0, 7.0]. The median length of stay was 5.5 days [IQR 4.6, 8.6]. The proportion of individuals with diabetes mellitus was 32.1%, and the proportion of individuals with rheumatoid arthritis was 32.1%. Sixteen of the 36 patients with culture negative PJI had been treated with antibiotics prior to obtaining cultures.

Transition from Culture Negative to Culture Positive PJI

Of the 36 patients who had culture negative PJI, 15 met criteria for failure, giving a 41.67% failure rate. All 15 patients had symptoms of PJI lasting less than one week before I&D was performed, indicating appropriate timeline for treatment and assuring these were acute-onset PJI as opposed to chronic infections. Average time to failure was 9.93 months. Of the 15 failed culture negative irrigation and debridements, eight of these became culture positive upon failure, giving a 53% rate of change from culture negative to culture positive in failed culture negative irrigation and debridement. Seven out of eight (87.5%) became culture positive within one year of initial culture negative infection. Two of eight patients that transitioned to culture positive were found to be culture positive via sonication of prothesis components upon failure. If we exclude sonicate data, six of 15 failed culture negative infections transitioned to culture positive, giving a 40% rate of change from culture negative to culture positive in failed culture negative irrigation and debridement. Seven culture negative I&Ds failed and never became culture positive.

Organisms Associated with Failure

Table 3 outlines causative organisms associated with the patients who had culture negative PJI. Of the 8 patients that became culture positive, three grew coagulase-negative staphylococci (CoNS), one grew Methicillin-resistant *Staphylococcus aureus* (MRSA), one grew Methicillin Sensitive *Staphylococcus aureus* (MSSA), one grew *Enterococcus faecalis*, one grew *Streptococcus pneumoniae*, and one grew *Pseudomonas aeruginosa*. Overall, five out of eight of those subjects that became culture positive (62.5%), grew a Staphylococcus species on subsequent culture.

Factors Predicting Conversion to Culture Positive

We investigated the association between preoperative antibiotic administration and culture negative PJI. Of the 15 subjects that with culture negative PJI that failed treatment with I&D, five had been treated with antibiotics before initial I&D was performed, specifically Cefepime, Vancomycin (two patients), Amoxicillin/Clavulanic acid, and Moxifloxacin. Of these five culture negative I&Ds that had been treated with antibiotics prior to culture, three subsequently became culture positive; one grew MRSA (pre-treated with Vancomycin), one grew CoNS (pre-treated with Amoxicillin/Clavulanic acid), and one grew MSSA (pre-treated with Vancomycin) (Table 3). Univariate logistic regression modeling revealed that the odds of becoming culture positive if preoperative antibiotics were administered before initial I&D was estimated to be 0.69 (95% CI 0.14, 3.47; p = 0.65). Though not statistically significant, the effect size is clinically notable. Additionally, for every one year increase in age, the odds of becoming culture positive decreased, with an OR of 0.95 (95% CI 0.89–1.02, p=0.144; Table 4). It is worth noting that, due to our small sample size of 36, univariate logistic regression models did not converge to a solution when diabetes mellitus and ASA score were treated as predictors. Univariate Cox proportional hazard modeling revealed an estimated hazard ratio of 0.82 with 95% confidence interval (0.28, 2.43) for culture negative patients who had taken preoperative antibiotics compared to those who did not. Alternatively stated, the hazard of failure for those culture negative patients on preoperative antibiotics was estimated to be 17.8% less than the hazard for those not on preoperative antibiotics, however this was not statistically significant (p=0.72).

Discussion

Irrigation and debridement as a treatment for culture positive PJI has a high rate of failure [6, 7]. Our study observed a high rate of failure for culture negative PJI, and that upon failure of I&D, half of these infections transitioned to culture positive PJI. Furthermore, the organism subsequently cultured was often more pathogenic than might be expected. Our study did note a trend between preoperative antibiotic administration and subsequent conversion from culture negative to culture positive infection, but these results were not statistically significant.

There are two possibilities to explain transitions from culture negative to culture positive PJI. First, the organism cultured after failure was unable to be initially cultured, either due to imperfect culture techniques, low disease burden upon presentation or prior exposure to antimicrobial therapy. The second possibility is that treatment failure was not associated

with recurrence of the initial uncultured organism, but a new infection with a different organism. In positive culture two-stage exchange, failure can be associated with a new organism that was not initially cultured during the initial treatment. This suggests that the initial infection was either polymicrobial where the new organism was not initially cultured or that the treatment failure was associated with a new organism [15]. Given that there was no initial cultured organism, transitions to culture positive were associated with bacteria that form biofilm, and that organisms in a biofilm are challenging to culture because of being metabolically dormant [16–18], our study suggests that these transitions were more likely the same organism, but both hypotheses are probably correct. Although delay of treatment in culture negative infections could be considered as a potential cause for failure due to unclear etiology of symptoms, all subjects who transitioned from culture negative to culture positive had symptoms for less than 1 week. This indicates treatment delay was unlikely a factor in transition from culture negative to culture positive, however more research will need to be done to determine if treatment delay is related to initial failure of culture negative PJI.

Other diagnostic tests are needed to identify organisms in PJI. A paucity of literature exists on the conversion rates of culture negative to culture positive infections. Our study found that upon failure, culture negative PJI transitioned to culture positive PJI 53% of the time after irrigation and debridement. Sonication of implants has been shown to improve culture yield and help identify the organism in PJI [17, 19, 20]. If we exclude sonicate data from our analysis, our results were unchanged; the use of sonication did not alter the incidence of conversion from initially culture negative PJI to a culture positive PJI upon failure. This provides additional evidence to the dormant metabolic state of biofilm [16–18]. Furthermore, recent proposed changes to the definition of PJI incorporate results of diagnostic biomarkers and molecular tests, which may increase the sensitivity of PJI diagnosis from 79.3 % to 97.7% [21]. Additional work to assess cost-benefit analysis and DNA contamination will need to be done to assess practicality of these additions [21].

Organisms that were found to be associated with conversion from culture negative to positive PJI included a high incidence of pathogenic organisms. There is an expectation that indolent organisms would be associated with conversion to culture positive PJI. Smaller studies have demonstrated that culture negative PJI that eventually did culture out microorganisms included species such as rare fungi, mycobacterium, and other uncommon bacteria including *Listeria monocytogens*, *Propionibacterium acnes*, and *Coxiella burnetii* [7, 9, 10]. Our study found culture negative PJI that converted to culture positive PJI grew organisms including Staphylococcus and Pseudomona*s*. Over 50% of those patients that converted from culture negative to culture positive grew Staphylococcus species. No *P. acnes*, mycobacterial, or fungal infections were associated with culture negative conversion. Past research indicates that culture negative PJI treated with first-generation cephalosporins had similar outcomes to patients treated with broad-spectrum antimicrobial agents [7, 22]. Additionally, other studies have demonstrated that culture negative PJI outcomes are comparable to those associated with PJI of known bacterial pathogens. This research hypothesized that culture negative PJI were due to biofilm producing pathogens, and were treated with antibiotics that covered Staphylococcus and Streptococcus species [7]. Biofilm has a high tolerance to antibiotics and can be associated with culture negative infections [23, 24]. Our findings support the hypothesis that many culture negative infections are possibly

more virulent organisms associated with biofilm formation. Providing first generation cephalosporins in culture negative infections appears to be appropriate, as they cover these *Staphylococcus* and *Streptococcus* species. In the early post-operative period, prior to infectious disease consultation, an empiric regimen consisting of a first-generation cephalosporin and vancomycin (if risk factors) would be appropriate. We highly recommend consultation with a fellowship trained infectious disease physician to determine appropriate antibiotic regimens for these patients to ensure appropriate broad spectrum coverage based on different scenarios, management of long term antibiotic delivery, and monitoring for potential side effects and drug interactions of the antibiotics.

It is not an unusual scenario for preoperative antibiotics to be administered before evaluation by an orthopaedic surgeon. Initial evaluation by primary care, the emergency department, or a hospitalist service will often administer antibiotics out of concern for infection, without appreciating that this administration may decreases intraoperative culture yield. It remains unclear if preoperative antibiotics are associated with an increased rate of culture negative conversion to culture positive PJI [13]. Our study did find a decreased hazard of culture negative failure in the setting of preoperative antibiotics; however this result was not statistically significant potentially due to our small sample size. Additionally, we found a decreased odds of becoming culture positive if preoperative antibiotics were given; this result was also not statistically significant ($p=0.65$). Overall, our data shows a trend that preoperative antibiotics are related to culture negative infection. Other studies have demonstrated that antibiotics administered as surgical prophylaxis prevent secondary wound infections[25]. Combined, when the patient is medically stable, our results support the recommendation to hold antibiotics until surgery and administer proper surgical prophylaxis.

Our findings should be interpreted in the context of limitations expected with any observational data set. The retrospective study design gives potential for selection bias. Information gathered is completely dependent on the medical record which varied between centers, as the study included a variety of practice types. Although we had access to inpatient medical records, we did not have access to all outpatient notes that would likely include more complete documentation. An additional limitation is the implementation of the MSIS criteria as a screening tool to rule in infection as opposed to clinical judgement of infection. Subjects were excluded from the cohort if they did not meet specific MSIS criteria for infection, however recent research has shown there are limitations to these criteria and that it may be influenced by the type of pathogen and less accurate for culture negative infections [26]. It may be that there were more potential culture negative infections within our multicenter population that were treated clinically yet excluded from our analysis. There is a possibility that patients met MSIS criteria for PJI but were not infected with bacterial organisms. A possibility exists that rare but alternative causes of elevated WBC and inflammatory markers was present, including crystalline arthropathy or Lyme disease. However, there has been only one case report of Lyme disease in TKA and crystalline arthropathy is rare [27, 28]. MSIS criteria has a high specificity to rule out false positives at 99.5% and additionally has sensitivity of 79.3% [29].

Culture negative PJI remains a challenging clinical dilemma. Our results suggest that clinical outcomes after irrigation and debridement in culture negative PJI are similar to culture

positive PJI. Ultimately more than half of the cases that fail treatment will have an organism identified. This provides additional evidence for the role of metabolically dormant biofilm in PJI. First generation cephalosporins and coverage for MRSA when appropriate, provide acceptable initial antibiotic coverage. There was an association between preoperative antibiotic administration and culture negative infection providing additional evidence that antibiotics should be held until the time of surgery when prophylactic antibiotics can be administered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Patient Demographic Characteristics

	Neg → Pos (N=8)	CNeg (N=28)	Total (N=36)	p-value
Age	61.7 (17.1)	70.1 (11.4)	68.2 (13.1)	0.1096
BMI	29.2 (5.9)	33.5 (8.0)	32.5 (7.7)	0.1673
CCMI	3 [2.5, 3.5]	4 [3, 7]	3.5 [3, 7]	0.0045
LOS	4.5 [3.9, 8.3]	5.9 [4.9, 8.8]	5.5 [4.6, 8.6]	0.3347
Female	3 (37.5%)	20 (71.4%)	23 (82.1%)	0.1072
DM	0 (0%)	9 (32.1%)	9 (32.1%)	0.1596
RA	1 (12.5%)	2 (7.1%)	9 (32.1%)	0.5412
Preop Abx	3 (37.5%)	13 (46.4%)	16 (44.4%)	0.7086
ASA Score				0.4352
1	0 (0%)	1 (3.6%)	1 (2.8%)	
2	4 (50.0%)	7 (25.0%)	11 (30.6%)	
3	4 (50.0%)	14 (50.0%)	18 (50.0%)	
4	0 (0%)	6 (21.4%)	6 (16.7%)	
Days Symptomatic				0.9999
<1 wk	6 (75.0%)	17 (60.7%)	23 (63.9%)	
2–4 wk	1 (12.5%)	6 (21.4%)	7 (18.9%)	
>4 wk	1 (12.5%)	4 (14.3%)	5 (13.9%)	
Host Score				0.9999
A	2 (25.0%)	5 (17.9%)	7 (19.4%)	
B	5 (62.5%)	18 (64.3%)	23 (63.9%)	
C	1 (12.5%)	5 (17.9%)	6 (16.7%)	

LOS, length of stay; SD, standard deviation; RA, rheumatoid arthritis; ASA, American Society of Anesthesiologists

Table 2:

Organisms Cultured Post-Culture Positive Transition

Subject	Max ESR (mm/hr)	Max CRP (mg/L)	Max Synovial Count	Max neutrophils	Sinus Tract	Purulence	Time from CN to CP (months)	Organism
1	76	63	66600	93	No	No	18	MRSA
2	122	9.9	34442	94	No	Yes	11	Coag Negative Staph
3	57	40.2	1610	73	No	No	4	MSSA
4	112	28.1	116700	99	No	Yes	23	Coag Negative Staph
5	120	2.3	25000	86	No	No	9	*E. faecalis*
6	68	16.2	40200	91	No	Yes	10	Alpha Hemolytic Strep
7	74	122	-	-	Yes	No	1	Coag Negative Staph
8	112	21.1	143800	98	No	No	2	*P. aeruginosa*

Table 3:

Antibiotic Use in Subjects Becoming Culture Positive

Subject	Time from CN to CP (months)	Organism	Abx Prior to Initial I&D	Duration of Abx Prior to initial I&D	Abx After Initial I&D	Duration of Abx After initial I&D
1	18	MRSA	Vancomycin	10 days	Vancomycin	6 weeks
2	11	Coag Negative Staph	Amoxicillin-Clavulanic Acid	>1 year	Cefepime/ Daptomycin	6 weeks
3	4	MSSA	Vancomycin	1-time bolus 4 days prior to I&D	Keflex	4 weeks
4	23	Coag Negative Staph	None		Vancomycin/ rifampin; Bactrim	6 weeks; ~4 months
5	9	*E. faecalis*	None		Vancomycin/ Ceftriaxone	6 weeks
6	10	Alpha Hemolytic Strep	None		Daptomycin; Bactrim	6 weeks; ~4 months
7	1	Coag Negative Staph	None		Bactrim/ Ciprofloxacin	3 weeks
8	2	*P. aeruginosa*	None		Ciprofloxacin	4 days

Note: Subject two on suppressive antibiotic regimen for previous hip MRSA PJI.

Table 4:

Odds of Becoming Culture Positive

Variable	Odds Ratio	95% Confidence Interval	P-value
Preop Abx			
Yes	0.692	(0.138, 3.472)	0.6549
No	- reference level-		
Age	0.953	(0.893, 1.017)	0.1443
BMI	0.913	(0.794, 1.050)	0.2010
Gender			
Female	0.253	(0.048, 1.319)	0.1027
Male	- reference level -		
CCMI	0.686	(0.433, 1.087)	0.1089
DM: Did not converge			
RA			
Yes	1.786	(0.140, 22.700)	0.6549
No	- reference level -		
ASA Score: Did not converge			
Days Symptomatic			0.8029
2–4 wk	0.472	(0.047, 4.770)	
>4 wk	0.708	(0.066, 7.659)	
<1 wk	- reference level -		
Host Score			0.8795
B	0.735	(0.108, 5.011)	
C	0.500	(0.034, 7.452)	
A	- reference level -		