McBroom, Mandy M. <u>Treatment of Infection in High Risk Patients After Total Knee Arthroplasty by Debridement with Prosthesis Retention: Is Oral Suppressive Therapy the Better Option?</u> Master of Public Health, May, 2009, 37 pp., 5 tables, 2 figures, references, 39 titles.

Treatment outcomes of 28 high risk TKA PJI patients treated with either debridement, six weeks I.V. antimicrobial therapy and prosthesis retention, or same treatment with oral chronic suppressive therapy, to ascertain the effectiveness of oral chronic suppressive therapy were retrospectively reviewed in this study. The 2-year cumulative probability of failure for oral suppressive therapy was 7% (95%CI: 0.04 to 27.5) compared to 42% (95%CI: 17.7 to 66.07) for the control group. Oral suppressive therapy was significantly different than control ($P= 0.033$). This study underscores the importance of combining oral suppressive therapy in select patients with débridement and six weeks I.V. antimicrobial therapy.

TREATMENT OF INFECTION IN HIGH RISK PATIENTS AFTER TOTAL KNEE

ARTHROPLASTY BY DEBRIDEMENT AND PROSTHESIS RETENTION: IS

ORAL SUPPRESSION THE BETTER OPTION?

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THESIS

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CHAPTER I

INTRODUCTION

Prosthetic joint infection (PJI) is a rare but serious complication of total knee

arthroplasty (TKA), and is a frequent reason for failure to retain the prosthesis [1].

Annually in the U.S., joint prostheses constitute approximately 600,000 orthopedic

implants; of these about 12,000 (1-2%) are infected, with an estimated average cost of

combined medical and surgical treatments exceeding $30,000 [2]. The costs are even

higher for the patient who undergoes multiple revisions due to hardware loosening and/or

recurrent infections.

Over the past decade, much progress has been made in the treatment and

prevention of PJI [3,4]. New treatment algorithms based on empirical evidence of

treating physicians have led to improved outcomes. Management strategies differ based

upon individual risk factors of the patient (i.e., soundness of prosthesis, type of

microorganism, and immune status) (figure 1). If the patient is infected with an sensitive

microorganism, has a well-seated prosthesis, or has a compromised immune status that

would complicate surgical intervention, treatment outcomes using débridement, long-

term antimicrobial therapy, and prosthesis retention have proved to be efficacious in most

patients (between 82-100 percent); otherwise the patient should undergo one or two stage

reimplantation [2].

Over the past decade, several investigators have reported success rates of >80%

with débridement and retention of prosthesis between 2 to 5-year follow-up periods [5-9].

The outcomes for treatment failure differ due to variations in study design (i.e. patient

selection, microbiological findings, type and duration of antimicrobial therapy and follow up) and discrepant definitions of infection. Lack of consensus on definitions of PJI and risk factors between centers makes evaluation of true risk factors and outcomes difficult. Though improved success rates have been reported for the conservative approach of débridement, intravenous (IV) antimicrobial therapy and prosthesis retention, little data exists on combining the use of oral suppressive therapy with this treatment option.

Success rates that have addressed the use of oral suppressive therapy vary between 63 to >80 percent [10, 11]. However, due to variable patient selection for the various studies, it is difficult to ascertain the actual effectiveness of oral suppressive therapy. I retrospectively reviewed the treatment outcomes of 28 high risk PJI after TKA patients who had been treated with débridement, six weeks IV antimicrobial therapy and prosthesis retention, or the same treatment with oral chronic suppressive therapy, and who had a relatively long duration of follow-up to ascertain the effectiveness of oral chronic suppressive therapy in our patient population.

Are all three of the following criteria present?
Duration of clinical manifestations of infection ≤10 days
Mechanically stable prosthesis
Infecting pathogen susceptible to oral antibiotics

Yes

No

May attempt to salvage the prosthesis:
Perform aggressive surgical débridement and provide a prolonged course of systemic antibiotics (total duration, 3 to 6 mo) selected on the basis of the susceptibility profile (a quinolone plus rifampin given intravenously for at least the first 2 wk; other options include a β-lactam plus rifampin, and trimethoprim–sulfamethoxazole)

Proceed with a replacement of the prosthesis:
Stage 1: remove infected implant, insert antimicrobial-impregnated spacer, and administer systemic antibiotics for 6 wk
Stage 2: implant a new joint prosthesis if no clinical or microbiologic evidence of infection exists

Is there recurrent staphylococcal infection or reinfection by a new organism?
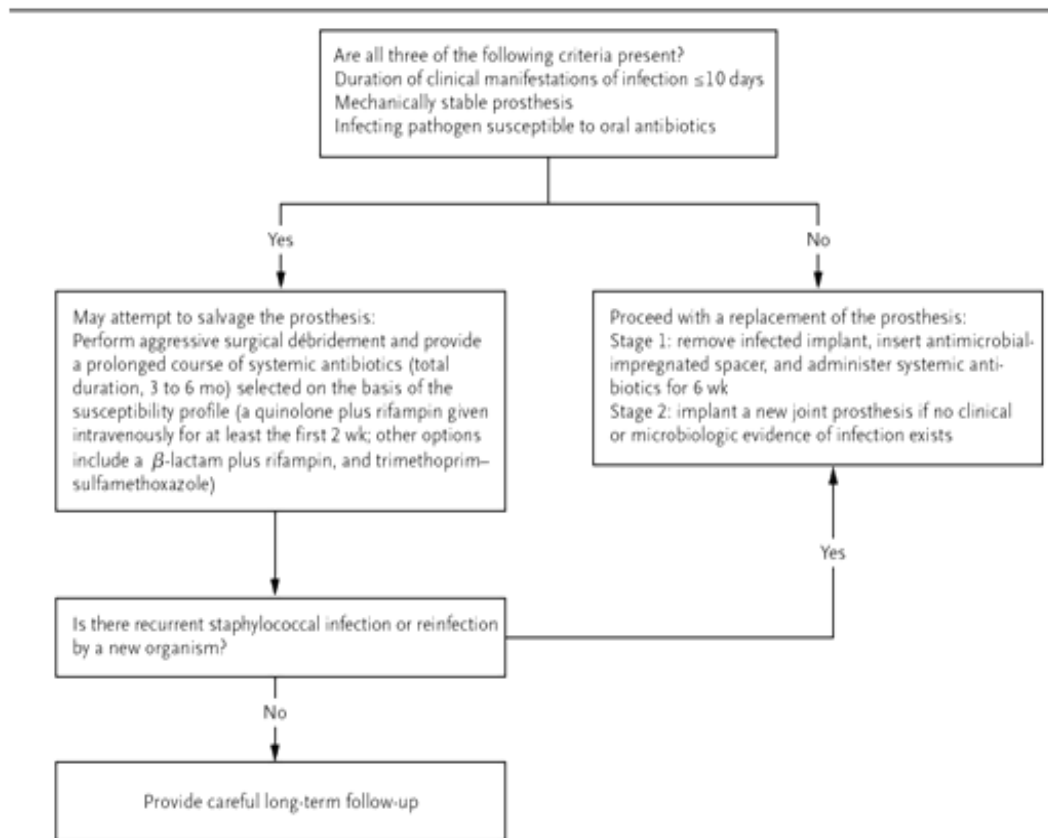
Yes

No

Provide careful long-term follow-up

Figure 1. Medical managment for treating S. aureus or coagulase-negative prosthetic joint infection [2].

CHAPTER II

Background

Pathology

Prosthetic knee infections occur when bacteria (i.e. coagulase-negative staphylococcus or streptococcus) colonize the surgical site postoperatively, and synthesize a "slime" layer called a biofilm [12]. Once established, this layer serves as a physical barrier to the diffusion of antimicrobials and host phagocytes, hence, biofilm microorganisms are far more resistant to antimicrobial therapy than planktonic bacteria (non-biofilm bacteria within the body). It has been suggested that the reduced rate of growth (or stationary phase of growth) that ensues after establishment of a biofilm is a consequence of the biofilm's lack of permeability to metabolic substrates (i.e. glucose or oxygen), though studies that have been performed in humans have yielded inconclusive results [12].

The presence of the prosthesis creates an environment for the development of biofilms and can impair host response to the infectious agent. The polymethylmethacrylate bone cement that is used in TKA procedures may inhibit the activity to leukocytes and complement function [13]. Additionally, the heat released in the polymerization process of the polymethylmethacrylate has been shown to destroy adjacent cortical bone, resulting in devascularization of the surrounding tissue. Therefore, bacteria have a very favorable medium for growth while being protected from the host's circulating defenses [14].

The release of oxygen and lysosomal enzymes from biofilm bacteria could result in damaging surrounding host tissue and combined with local vascular insufficiency, create conditions that promote development of osteomyelitis, a serious and difficult-to-treat bone infection. If osteomyelitis develops, the only therapeutic option is removal of the implant [15, 16].

Another serious complication of PJI is septic arthritis. In nonimmunocompromised patients the rate of this infection is only about one to two percent, however, in immunocompromised patients (i.e. rheumatoid arthritis and diabetes mellitus) the incidence rate increases to four percent. When PJI develops less than three months after surgery, nosocomial infection is the most probable cause. The predominant isolate in this case is *Staphylococcus epidermidis*. In late-onset infection *S. aureus* is the most common isolate followed by Streptococcus spp., gram-negative bacilli, and anaerobes [17].

Several factors have been shown to increase the risk for PJI. The most reliable source of risk factors for PJI are found in a large, retrospective case-control study of 486 total hip arthroplasty (THA) and TKA patients, which determined the following are usually associated with treatment failure: (1) a history of superficial wound infection (OR 35.9), (2) a diagnosis of malignant disease (OR 3.1), (3) prior surgery on the replaced joint (OR 2) and, (4) a National Nosocomial Infections Surveillance (NNIS)[1] system patient risk index score of 1 (OR 1.7) [18]. Also, two independent risk factors for superficial wound infection are post-operative drainage greater than five days duration

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[1] NNIS is a composite score in which prolonged operation time (over 3 hours), wound status, and an ASA score of >2 equal one point [12].

and presence of a hematoma [12]. TKA's are more susceptible to infection because they remain close to the surface and have poor soft tissue coverage or are subject to prolonged surgery [13].

<center>*Symptoms*</center>

PJI is classified into early, late chronic, and acute hematogenous as the clinical setting for which infectious disease specialists and orthopedic surgeons use to base treatment decisions. Early infections are diagnosed within the first month after arthroplasty, late chronic infections have an insidious clinical course and are diagnosed later than one month postoperatively, and acute hematogenous infections are characterized by an acute onset of symptoms, more than one month after the operation, in a patient in whom the prosthesis previously had been functioning well [19, 20].

Early onset ($<$ 3 months after surgery) prosthetic infections resemble acute septic arthritis and presents as joint swelling, pain, leukocytosis, and a febrile response [13]. Conversely, patients with late-onset infections, while exhibiting an elevated erythrocyte sedimentation rate (ESR), are often afebrile (50%), lack leukocytosis, and have less pronounced clinical features and progressive joint pain [13]. Acute hematogenous infections can present with all of the above symptoms, depending upon the infectious agent, and is often the result of hematogenous seeding from another infection site [12].

<center>*Diagnosis*</center>

PJI is currently defined as "$\geq$ 2 cultures of joint aspirates or intraoperative specimens yielding the infectious agent or by one such positive culture in addition to (1) purulence surrounding the prosthesis at the time of surgery, (2) acute inflammation

<center>6</center>

consistent with infection on histopathological examination, or (3) a sinus tract communicating with the prosthesis [19]."

There are several discrepancies regarding the best method of diagnosis, so few 'gold standard' tests exist for the detection of PJI. However, when there is evidence of purulence and drainage in the wound, spreading cellulitis, and persistent erythema, infection should be suspected [12]. This should hold true for any prosthesis that fails early or presents with signs of inflammation [12].

The current tests used to detect PJI are: laboratory, histological samples, microbiological cultures, imaging studies, and molecular studies. Before making a diagnosis in early infections, exploration should be performed before planning antimicrobial therapy, as long as the overall health and condition of affected soft tissue permits it. If there is drainage from a sinus tract, then diagnosis of infection is certain [12].

Laboratory studies: The ESR, C-reactive protein (CRP), and white blood cell count (WBC) are usually elevated in early infection, whereas in late infections these parameters may be normal [12]. The blood leukocyte count and the percentage of band forms are not reliable predictors for the presence or absence of infection. CRP, a biomarker for inflammation, is usually elevated post surgery; therefore, serial postoperative measurements are better indicators of an infectious process. In a recent study, a synovial-fluid leukocyte count of more than 1700 cubic millimeters or a finding of more than 65 percent neutrophils demonstrated sensitivities for infection of 94 and 97

percent, respectively, and specificities of 88 and 98 percent, respectively, in patients who did not have underlying inflammatory diseases [21, 22].

Histopathological studies: The definition of acute inflammation in the periprosthetic tissue varies in studies from 1 to 10 or more neutrophils per high-power field at a magnification of 400 [22]. In the absence of inflammation, the presence of neutrophils indicates infection, especially in frozen sections during surgery. Often, the histological changes are focal, with some specimens being negative and others showing evidence of acute inflammation [12]. This is likely due to a low number of microorganisms in an uneven distribution throughout inflamed tissue [12]. Specificity of this test is high, which allows the surgeon to decide between one- and two-stage revisions [12].

Microbiological studies: Presence of infectious agents in PJI cultures usually occur in the following pattern: coagulase-negative staphylococcus (30-40%), *Staphylococcus aureus* (12-23%), mixed flora (10-11%), streptococci (9-10%), gram-negative bacilli (3-6%), enterococci (3-7%, and anaerobes (2-4%) [23]. Negative cultures constitute about 11 percent of all cultures. The growth of a virulent microorganism generally indicates infection, while growth of low-virulence organisms are more likely due to skin or laboratory contamination; often the location of the prosthesis leads to interpretation of the significance of an isolated microorganism [23].

Multiple (at least three), deep cultures around the implant should be obtained during débridement to maximize diagnostic yield [12]. Cultures of a superficial wound or sinus tract are often positive as a result of contamination from the surrounding skin and

should be avoided [24]. The sample should be processed in a laminar air flow cabinet to avoid contamination of the specimen in the laboratory. Gram's staining of synovial fluid and perioprosthetic tissue has a high specificity (>97 percent) but sensitivity is rather low (<26 percent) [24].

Interpretation of cultures should be approached with caution. Swab cultures have low sensitivity and should not be used [25]. The presence of microbes in a culture from a superficial wound likely indicate normal flora (i.e. *S. epidermidis*) and should be avoided [24]. Also, in aspirated synovial fluid, the infectious agent can be detected in 45 to 100 percent of cases, resulting in a sensitivity of 65 to 94 percent [24]. Infections that are early or acute late infections usually have a high microbial load, thus making sensitivity higher in these cases [12]. It is also good practice to discontinue antimicrobial therapy at least two weeks before collecting tissue samples to ensure detection of low-grade infection [24].

Imaging studies: Plain radiographs can aid in detecting infection when they are studied serially over time after implantation [26]. The presence of new sub-periosteal bone growth and transcortical sinus tracts indicate infection; however, slight movement of the implant with periprosthetic osteolysis can occur without infection. The prosthesis (especially if it is uncemented) can be loose without accompanying radiologic abnormalities, which is often the case for late infections [12]. Arthography is useful for detecting implant loosening, pseudobursae, and abscesses, that are not apparent on plain radiograph [25]. Even if loosening is not detected, the prosthesis is considered to be loose if pain is alleviated by the administration of local anesthetic [12]. Nuclear scintigraphy

detects inflammation in periprosthetic tissue. Bone scintigraphy with technetium-99m-labeled methylene diphosphate is very sensitive; however, it lacks specificity for infection because the scan can remain positive for more than a year post-implantation because of increased periprosthetic bone remodeling [27]. Computed tomography (CT) and magnetic resonance imaging (MRI) studies are not useful for viewing prosthetic components due to metal artifact and safety issues, but can be helpful in evaluating periprosthetic soft tissue [12].

Molecular studies: Polymerase chain reaction (PCR) and other methods to detect bacterial DNA are gaining popularity in diagnosing infection due to their speed and high sensitivity; however, it has not been validated as a practical (expensive) diagnostic test. Not only do molecular methods need to provide evidence for infection, but specific identification and antibiotic sensitivities, which require more refinement of the test, potentially leading to greater expense [12].

Treatment

The goal of treating infection associated with a prosthetic joint is a pain-free, functional joint which is best achieved by elimination of the infection. Treatment is usually directed toward the type of infection present. Available treatment options include surgical removal of all infected tissue by débridement with implant retention and long-term antibiotic therapy that is active against biofilm microorganisms or, if the infection is severe, and implant loosening occurs, one and two-stage reimplantation [14].

Early infections should be treated as emergencies because infection can lead to bacteremia or soft tissue loss (or both). In many cases, early débridement of the wound combined with appropriate antibiotic therapy yields good, long-term outcomes [12]. The best approach before management decisions are made concerning both early and acute late infections is exploration, débridement of infected and devitalized tissue, and inspection of the prosthesis. Salvage may be possible if the implant is well-seated, but if the implant is loose it should be removed.

Once specimens have been collected, broad-spectrum IV antibiotics that are active against methicillin-resistant staphylococci and aerobic Gram-negative rods should be administered (i.e. rifampin and vancomycin); subsequent antibiotic therapy can be rationalized after culture results [12]. In most cases, the disease progresses to a state in which the prosthesis must be removed to eliminate bone infection. It is recommended that arthrodesis should be attempted before repeated attempts at re-implantation [13]. If the patient elects against or is a poor candidate for re-implantation, oral suppressive antimicrobial therapy is a good alternative.

It has been recommended by several authors that prosthesis retention should not be attempted in the late chronic patient. Part of the rationale for this is that recurrence rates for late chronic patients with rheumatoid arthritis (a large portion of PJI patients) have been found to approach 60%, and the prosthesis eventually had to be removed [13]. In both types of infection, factors that appear to be associated with good, long-term outcomes are: a thorough, early débridement (< 3 weeks onset of symptoms); infection

with a sensitive organism; the absence of a draining sinus, and a well-seated prosthesis [12].

Antimicrobial therapy: There is a growing body of evidence that optimum duration of IV antibiotics should be six weeks. Outpatient parenteral antimicrobial therapy (OPAT) has become a popular method of treatment to encourage adherence to treatment, and reduces costs. This involves insertion of a central venous catheter (Hickman, Broviac or as a peripherally inserted line or PICC). Also, administering ceftriaxone (methicillin-sensitive organism) or teicoplanin (methicillin-resistant Gram-positives) once daily aids to ensure compliance. Portable infusion or elastomeric devices can also be installed to administer more frequent dosing or continuous infusion [12].

Rifampin had been found to be effective in treating staphylococcal infections, but only in combination with fluoroquinolones or other culture-directed antibiotics (i.e. vancomycin or daptomycin). Rifampin should never be administered alone, due to the propensity for staphylococci to develop antimicrobial resistance [28]. Fluoroquinolones are effective as combination agents because of their bioavailability, and tolerability [29]. One randomized, controlled trial of ciprofloxacin and rifampin compared to ciprofloxacin alone indicated infection was eradicated in 12 subjects (different orthopedic devices implanted) treated with the combination therapy compared to five of 12 failing in the placebo group. Newer quinolones (i.e. levofloxacin, modifloxacin, and gatifloxacin) are more active against gram-positive microorganisms than ciprofloxacin (resistance is growing), but there is a paucity of data on toxicity and efficacy with long-term use.

Other combinations that do not use quinolones are fusidic acid and rifampicin (achieved a success rate of 55% in one clinical trial), trimethoprim-sulfamethoxazole, minocycline, linezolid and rifampin (no data on these combinations have been reported) [30]. Table 1 summarizes the most common infectious agents and drug therapies used to treat PJI.

Patients with prosthetic joints (particularly in new or loose prostheses) are at an increased risk of developing transient bacteremia. Therefore, careful consideration should be given when planning procedures that are known to cause bacteremia, especially when the patient has an active infection elsewhere (i.e. dental infection). In these cases, it is judicious to use prophylaxis, but the routine use of prophylaxis is not recommended because of the propensity for microorganisms to develop antibiotic resistance [12].

Problem/Hypothesis

Little is known about the effectiveness and the optimum duration of treatment of oral suppressive agents when combined with débridement and six weeks of IV antimicrobial therapy. To my knowledge, no previous studies evaluated PJI after TKA being symptom free after six weeks of intravenous antimicrobial therapy and débridement to be able to assess the true effectiveness these drugs in preventing a relapse or failure of the prosthesis. Here I hypothesized that failure of treatment in those high risk patients with PJI after TKA who completed débridement, six weeks IV antimicrobial therapy and oral suppressive therapy and those patients who only complete a six week course of IV antimicrobial therapy with débridement will be statistically different.

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Specific Aims

The specific aims of the retrospective study are to:

Primary Specific Aim:

Evaluate the effectiveness of six weeks I.V. antimicrobial therapy and

débridement alone vs. six weeks I.V. antimicrobial therapy,

débridement, and oral suppressive therapy combined in the high risk

TKA PJI patient.

Secondary Specific Aim:

To determine the risk factors for treatment failure in this patient

population.

Significance

The role of oral suppressive therapy in high risk PJI patients has not been

adequately elucidated in the literature. Differences in patient selection and definitions of

infection and treatment failure have not adequately described the benefit of using this

alternative therapy. By eliminating potential confounders that are known to suppress the

immune system (i.e. steroids and chemotherapy for malignancies) and evaluate only

patients that have achieved a cure based on preset criteria, I believe that the role of oral

suppressive therapy can be better elucidated for patients who have well-seated prostheses

or in whom excision arthroplasty or delayed reimplantation is contraindicated.

Effectively managing high risk PJI patients with safe, nontoxic oral suppressive antimicrobials is an attractive alternative to revision or replacement surgery.

Using strict case definitions of PJI and treatment failure, this retrospective study was designed to calculate the probability of treatment failure for patients with PJI after TKA treated with débridement, six weeks of I.V. antimicrobial therapy, and prosthesis retention compared to patients with PJI after TKA treated with debridement, six weeks of I.V. antimicrobial therapy, prosthesis retention and oral suppressive therapy.

Table 1. Treatment of Infection Associated with a PJI caused by Common Microorganisms

Microorganism	Antimicrobial Agent	Dose	Route
Staphylococcus aureus or staphylococci	Nafcillin or floxacillin plus	2 gm every 6 hr	IV
	Rifampin for 2 wk, *followed by*	450 mg every 12 hr	PO or IV
	Rifampin *plus*	750 mg every 12 hr	PO
	Ciprofloxacin *or*	750 mg every 12 hr to	PO
	Levofloxacin	500 mg every 12 hr	
Methicillin-resistant	Vancomycin *plus*	1 gm every 12 hr	IV
	Rifampin for 2 wk, *followed by*	450 mg every 12 hr	PO or IV
	Rifampin *plus*	450 mg every 12 hr	PO
	Ciprofloxacin *or*	750 mg every 12 hr	PO
	Levofloxacin *or*	750 mg every 24 hr to	PO
		500 mg every 12 hr	
	Teichoplanin *or*	400 mg every 24	IV or IM
	Fusidic acid *or*	500 mg every 8 hr	PO
	Trimethoprim-sulfamethoxazole *or*	1 DS tablet every 8 hr	PO
	Minocycline	100 mg every 12 hr	PO
Streptococcus species (except *Streptococcus agalactiae*)	Penicillin G *or*	5 million U every 6 hr	IV
	Ceftriaxone for 4 wk, *followed by*	2 g every 24 hr	IV
	Amoxicillin	750-1000 mg every 8 hr	PO
Enterococcus species (penicillin-susceptible) and *Streptococcus agalactiae*	Penicillin G or	5 million U every 6 hr	IV
	Ampicillin or amoxicillin *plus*	2 g every 4-6 hr	IV
	Aminoglycoside for 2-4 wk, followed by		IV
	Amoxicillin	750-1000 mg every 8 hr	PO
Enterobacteriaceae (quinolone-susceptible)	Ciprofloxacin	750 mg every 12 hr	PO
Nonfermenters (e.g., *Pseudomonas aeruginosa*)	Ceftazidime or cefepime plus Aminoglycoside for 2 wk, *followed by*	2 g every 8 hr	IV
	Ciprofloxacin	750 mg every 12 hr	PO
Anaerobes	Clindamycin for 2-4 wk, followed by	600 mg every 6-8 hr	IV
	Clindamycin	300 mg every 6 hr	PO
Mixed Infections (without methicillin-resistant staphylococci)	Amoxicillin-clavullanic acid or	2.2 g every 8 hr	IV
	Ampicillin-sulbactam or	3 g every 6 hr	IV
	Carbapenem fo 2-4 wk, followed by individual regimens according to antimicrobial susceptibility	According to compound	IV

[14]

Methods

Study Design

In this retrospective cohort study, the medical and surgical therapies were not standardized. Management decisions were made by the treating physicians. All patients were followed from the date of the initial débridement until death, evident treatment failure, reinfection, or prosthesis removal or until they were lost to follow-up.

Study Population

The study population consisted of patients with PJI TKA who underwent débridement and prosthesis retention as their initial surgical treatment and had completed six weeks of I.V. antimicrobial therapy at the Tarrant County Infectious Disease Associates clinic in Fort Worth, Texas, between January 1, 2000 and December 31, 2008. Cases and controls were identified with use of ICD-9[2] codes for treatment of prosthetic joint infection of the knee or débridement as a result of prosthetic joint infection, using a standardized data collection tool for demographic information and data related to potential host and postoperative risk factors for prosthetic joint infection. Follow-up data for all patients were obtained through patient medical records, as one record was maintained for an individual patient over time.   Identifiable reasons for patients in this

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[2] a. 996.62 (Bacteremia; for infection and inflammatory reaction due to internal vascular device, implant, and graft-p.1112)
b. 998.3 (Surgical site infection- p1106)
c. 711.0/996.66 (Septic arthritis for prosthetic joint infections- p824)
(International Classification of Diseases. 9th Revision. Clinical Modification. 6th ed. Hospital Ed. Vol 1, 2 & 3. Practice Management Information Corp. Los Angeles, Ca)

cohort to elect this treatment modality are: patient's age, refusal to undergo a more expensive procedure, poor bone stock, and a well-seated prosthesis.

Inclusion Criteria

Stability of the implant, the type of microorganism, and the interval between the onset of symptoms and treatment with débridement and antimicrobial therapy are vital predictors of success. Patients who were included in the study met the following criteria:

- Patients that were candidates for retention of the infected prosthetic knee joint.

- Patients that were 18 years of age or older.

- Patients in whom surgical replacement (one or two stage) was contraindicated.

- Patients who had experienced recurrent infections at the prosthetic site.

- Patients in whom infection was eradicated after six weeks of treatment with I.V. antimicrobial therapy and débridement.

Those patients who will be excluded from the study are:

- Patients who were receiving chemotherapy for malignancies

- Patients diagnosed with HIV

- Patients who received steroid therapy for any reason.

- Patients who were malnourished at the time of treatment.

- Patients who had evidence of infection after six weeks I.V. antimicrobial therapy and débridement.

Definitions and risk factors

The following factors were used to define assessment of the primary endpoint:

Infection

Infections will be classified with the use of the criteria of Brandt et al [19]. According to that system, early postoperative infections are diagnosed within the first month after the arthroplasty; late chronic infections have an insidious clinical course and are diagnosed later than one month postoperatively; and acute hematogenous infections are characterized by an acute onset of symptoms, more than one month after the operation, in a patient in whom the prosthesis previously had been functioning well [20].

Treatment failure

The occurrence of PJI due to the original infection strain of infectious agent (isolated at the time of the original débridement) or culture-negative PJI will be considered evidence of a treatment failure. Differences in susceptibility to various antimicrobial therapies, as reported by the clinical microbiology laboratory, were used to distinguish between relapse or re-infection caused by a differing strain of the original infecting organism [19].

Culture-Negative PJI

Culture-negative PJI is defined by negative cultures of a joint aspirate or intraoperative specimen, in conjunction with (1) purulence surrounding the prosthesis at the time of surgery, (2) acute inflammation consistent with infection on histopathologic

examination at the time of surgery, or (3) a sinus tract communicating with the prosthesis [19].

Reinfection

Definition of reinfection includes infection with the same organism, infection with a different strain of the same organism, or infection with another organism. It is often difficult to know if a subsequent infection with a different organism occurs because of the emergence of antimicrobial resistance during treatment, the development of a secondary acquired infection during treatment, or an inability to initially identify all organisms. Since the goal of treatment is salvage of the prosthesis, reinfection with any organism generally necessitates removal of the prosthesis to eradicate the infection and thereby represents failure of treatment [19].

Culture-Positive Failure

Culture-positive failure was defined as culture conformation of original infectious agent or evidence of antimicrobial resistant strain (after negative cultures were obtained at baseline) during follow-up period.

Culture-Positive Relapse

Culture-positive relapse was defined as culture conformation of original infecting agent or resistant strain (after negative cultures were obtained at baseline) during follow-up period [19].

Clinical Relapse

Clinical relapse was defined as clinical conformation of PJI after evidence of eradication (achievement of normal ESR, WBC, or CRP values described above in diagnosis, and/or negative cultures at baseline) [19].

Clinical Failure

Clinical failure was defined as clinical and/or radiological conformation of original infectious agent (see above) or radiolucence on MRI, CT, or plain radiograph during follow-up period [19].

Complications

Perioperative medical complications included recurrent dislocation of the knee, deep venous thrombosis, periprosthetic femoral fracture, and death due to sepsis and adult respiratory distress syndrome (ARDS). Complications that were directly attributable to the antibiotic therapy were recorded and are expected to be mild maculopapular rashes, pseudomembraneous colitis and ototoxicity [14].

Statistical Analysis

The cumulative probability of treatment failure was estimated by the Kaplan Meier method [31]. A total curve comparison was obtained by using the Mantel-Cox logrank method. Fisher's exact test and the Wilcoxon rank sum test were used for univariate analysis [32, 33].

Variables used for obtaining the survival curves and univariate analysis were the following: age (<70, ≥70), gender, revision arthroplasty (yes/no), prosthesis age (in days; <30 or ≥ 30, rheumatoid arthritis (yes/no), diabetes mellitus (yes/no), steroid use (yes/no), symptom duration (in days; ≤2, >2), infectious agent group (Table 2), prosthetic loosening (yes/no), intraoperative purulence (yes/no), sinus tract (yes/no), number of surgical débridements (<2, ≥2), antimicrobial therapy (six weeks (no therapy), oral suppressive), presence of radiolucent lines at time of presentation (yes/no).

Definition of postoperative factors

Radiographic evidence of prosthetic loosening was defined as the presence of any prosthetic radiolucencies detected on radiographs obtained before débridement. Prosthesis age was defined as time between implantation and initial débridement. Sinus tract was defined as presence of a sinus tract communicating with prosthesis [14].

Risk Factors for Univariate Analysis

Host risk factors used in this study were rheumatoid arthritis, which was defined by the American Rheumatism Association [34], and diabetes mellitus, was diagnosed by the treating physician.

Laboratory values used to determine cure at baseline were: ESR < 30mm/h or a CRP concentration of <20 mg/L, and a white blood cell count (WBC) <10,000/mm^3 [35].

Results

Study population

Approximately 70 episodes of PJI after TKA were treated at TCIDA during the study period; of these 28 patients met the inclusion criteria for the study. Cohort description and demographics are presented in Table 2.

The average duration of follow-up was 12.75 months for controls (range: 3 weeks to forty eight months) and 14 months for the oral suppressive group (range 1 to 68 months). Failure occurred in an average of 14.87 months (range: 1 month and 24 months). The average age of subjects at the time of failure was 63.5 (range: 39 and 81). Median age of prosthesis was 90 days (range: 7 to 3285 days). All patients had multiple revisions with a median of one débridement.

Four patient's symptoms were early onset, seven were late chronic, and 11 were acute onset (table 4). Four out of eight patients with early onset infections were failures that required prosthesis removal, while one acute hematogenous treatment failure out of

13 required prosthesis removal. There was one failure due to reinfection as defined in this study.

Surgical and Medical Treatment

Twenty-five patients underwent only one surgical débridement during treatment, three had two débridements. Intraoperative purulence was noted in 66% of cases and 61% of controls. Seven percent (1/13) of patients in the control group had prosthesis loosening, while 13 percent (2/15) had prosthesis loosening. Only patient no. 22 had a sinus tract communicating with the prosthesis, and patient no. 26 had radiolucent lines visible on radiograph. Suction-irrigation devices were not used in the treatment of any of the patients.

All patients received six weeks of I.V. antimicrobial therapy. Oral antibiotic suppression ranged from one month to five years and eight months (mean, 30.0 months). Patients were taken off suppressive therapy at the patient's request and the discretion of the treating physician. Patient no. 8 in the control group that failed treatment had a history of deep vein thrombosis, and had difficulties managing coagulopathy, which ultimately resulted in removal of the prosthesis. Patient nos. 21 and 24 failed treatment in the control group due to prosthesis failure, though there were no signs of infection upon culture. Patient no. 17 failed treatment in the control group due to development of osteomyelitis that required prosthesis removal, but there was no evidence of reinfection upon culture. Patient no. 10 in the oral suppressive group was a complicated case, in which there was another infected wound (sternal wound post-coronary artery bypass

Table 2. Data on the Twenty-eight Patients who Underwent No Treatment and Oral Suppressive Therapy

Case	Gender, Age at Deb.	Diagnosis	Type of Therapy	No. of Debridements	Immune Status	Type of Infection	Outcome
1	F, 64	Inf. Lt Knee	No Tx	1	0	Late	Success
2	M, 34	Inf. Rt. Knee	No Tx	1	1	Acute	Success
3	M, 56	Inf. Rt. Knee	Chronic	1	1	Late	Success
4	F, 50	Inf. Rt. Knee	Chronic	1	1	Acute	Success
5	M, 63	Inf. Lt Knee	Chronic	1	0	Acute	Success
6	M, 62	Inf. Lt Knee	No Tx	1	1	Acute	Success
7	M, 51	Inf. Rt. Knee	No Tx	1	1	Early	Success
8	F, 54	Inf. Lt Knee	No Tx	1	0	Early	Failure
9	M, 87	Inf. Lt Knee	Chronic	1	0	Late	Success
10	M, 66	Inf. Lt Knee	Chronic	2	1	Early	Failure
11	M, 65	Inf. Rt. Knee	Chronic	1	0	Late	Success
12	M, 64	Inf. Rt. Knee	Chronic	1	1	Early	Success
13	M, 71	Inf. Lt Knee	Chronic	1	1	Early	Success
14	F, 66	Inf. Lt Knee	Chronic	1	1	Late	Success
15	M, 78	Inf. Rt. Knee	Chronic	1	1	Acute	Success
16	F, 58	Inf. Lt Knee	No Tx	1	1	Late	Success
17	F, 81	Inf. Lt Knee	No Tx	1	0	Acute	Failure
18	F, 55	Inf. Lt Knee	Chronic	1	1	Late	Success
19	M, 65	Inf. Lt Knee	Chronic	1	1	Acute	Success
20	F, 72	Inf. Lt Knee	No Tx	1	1	Acute	Success
21	M, 78	Inf. Rt. Knee	No Tx	1	1	Early	Failure
22	F, 62	Inf. Lt Knee	No Tx	1	1	Early	Success
23	F, 82	Inf. Rt. Knee	No Tx	1	1	Acute	Success
24	F, 39	Inf. Rt. Knee	No Tx	2	1	Early	Failure
25	F, 74	Inf. Lt Knee	Chronic	1	1	Acute	Success
26	M, 72	Inf. Lt Knee	No Tx	2	1	Acute	Success
27	F, 67	Inf. Lt Knee	No Tx	1	1	Acute	Success
28	M, 73	Inf. Lt Knee	Chronic	1	1	Acute	Success

0= Nonimmunocompromised

1= Immunocompromised (i.e., arthritis or diabetes mellitus or both)

graft) that seeded to the prosthesis site; this is the only patient in the oral suppressive group to have culture-positive failure (MRSA).

Infectious Agents

Results for the distribution of infectious agents can be seen in Table 3. Of the infectious agents, four patients presented with culture-negative PJI (14.3%), six were positive for *Staphylococcus aureus* infection (21.4%), three for *Staphylococcus epidermidis* (10.7%), seven presented with Methicillin-resistent *Staphylococcus aureus* (25%), two presented with Enterococcal spp. (7.1%), one with Corynebacterium (3.6%), two presented with Streptococcal spp. (7.1%), and three presented with mixed flora (10.7%).

Of the eight early postoperative infections, four were treated successfully of which three were on suppressive therapy (table 4). Five of the seven late chronic postoperative infections were placed on suppressive therapy, with no failures, and only one of the acute hematogenous infections failed, with six out of 13 being placed on suppressive therapy.

Table 3. Number of Isolates Recovered According to
Clinical Setting

| | Group | | |
Pathogen	Early Postop Infection	Late Chronic Infection	Acute Hem. Infection
None Cultured (n=4)	1	0	3
Gram-positive			
Staphylococcus aureus (n=3)	2	1	0
MSSA (n=3)	1	0	2
MRSA (n=7)	2	2	3
Staphylococcus epidermidis (n=3)	2	0	1
Streptococcus species			
Group B (n=2)	0	0	2
Corynebacterium species (n=1)	0	1	0
Gram-negative			
Enterococcus species (n=2)	0	1	1
Mixed Flora† (n=3)	0	2	1

† *Serratia marcescens, Bacterioides fragilis, Enterococcus fecalis*

Treatment Outcome

Figure 2 shows the cumulative probability of treatment failure (2 *S. aureus*, 2 MRSA, and 1 MSSA) between control and oral suppressive group. The times to failure for the control group and the oral suppressive group were significantly different (*P*= 0.033) at the 0.05 level.

The 2- year cumulative probability of treatment failure for the control group was 42% (95% CI: 17.7 to 66.04), and that for the oral suppressive group was 7% (95% CI: 0.04 to 27.5).
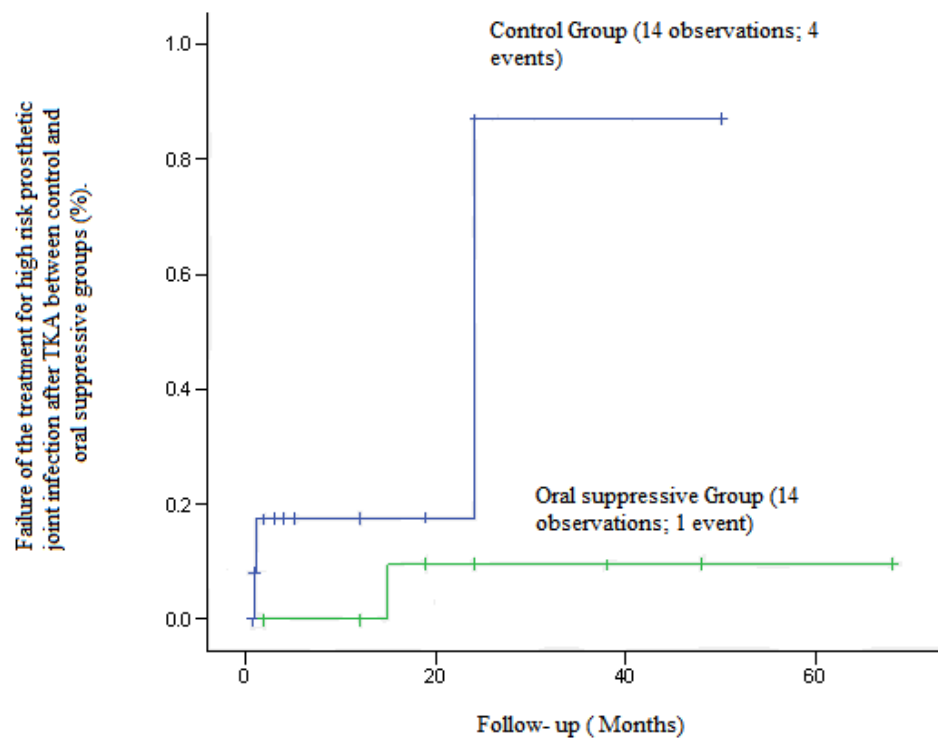
Figure 2. Cumulative probability of failure of treatment for high risk PJI after TKA after early debridement, six weeks intravenous antimicrobials, and prosthesis retention based on control or treatment arm. Short vertical marks indicate censored events.

Table 4. Treatment results of Twenty-eight high risk PJI patients

Type of Infection	Successful Treatment	Failed Treatment	Suppression
Early	4	4	3
Late Chronic	7	0	5
Acute Hematogenous	12	1	6

Administration of vancomycin with levofloxacin, doxycycline, or rifampin constituted 50% of the total IV antimicrobial therapies given to patients before baseline for failures and 39% of successes. Doxycycline (21%) was the most commonly used oral suppressive antimicrobial, followed by clindamycin and Bactrim (14%) (table 5). Rifampin was not prescribed for oral suppressive therapy. No significant side effects (hypersensitivity, hepatotoxicity, nephrotoxicity, ototoxicity, or *Clostridium difficile* colitis) due to oral suppressive therapy were reported.

Risk factors

Given the small number of failures, it was not possible to perform multivariate analysis to ascertain risk factors for failure occurring within 2 years after débridement. Patient's age or sex, evidence of prosthesis loosening, rheumatoid arthritis, diabetes mellitus or presence of sinus tract communicating with prosthesis were not found to be statistically significant risk factors on univariate analysis. The only independent predictor for treatment failure in this study population was receiving <2 débridements during treatment ($P= 0.012$).

Table 5. Oral suppressive agents, infectious agent before cure, duration of therapy, and outcome for treatment group

Patient no.	Suppressive antibiotic(s) (dosage)	Infectious Agent	Duration (mo) of therapy	Outcome
3	Bactrim (300 mg po b.i.d)	MRSA	48	Success
4	Ciprofloxacin (500 mg po q.d.)	MSSA	24	Success
5	Ceftin (500 mg po b.i.d)	*Enterococcus coli*	24	Success
9	Levofloxacin (500 mg po q.d)	*Enterococcus* spp.	12	Success
10	Cleocin (300 mg po t.i.d)	MRSA	14	Failure
11	Clindamycin (300 mg po t.i.d.	*Staphylococcus aureus*	36	Success
12	Clindamycin (300 mg po b.i.d.	*Staphylococcus epidermidis*	68	Success
13	Bactrim (300 mg po b.i.d)	MRSA	24	Success
14	Trimethoprim/Sulfamethoxazole (100 mg po b.i.d)	MRSA	24	Success
15	Keflex (500 mg po b.i.d)	MSSA	12	Success
19	Bactrim (300 mg po b.i.d)	MRSA	12	Success
25	Doxycycline (100 mg po q.d)	MRSA	3	Success
27	Doxycycline (100 mg po q.d)	Culture-negative PJI	1	Success
28	Doxycycline (100 mg po q.d)	Group B *Streptococcus*	2	Success

MRSA = Methicillin-resistant *Staphylococcus aureus*; MSSA = Methicillin-sensitive *Staphylococcus aureus*

Discussion

The aim of this study was to evaluate the effectiveness of early débridement, six weeks IV antimicrobial therapy, and oral suppression in a high risk (defined as having multiple revisions, recurrent infections at the prosthesis site, and presence of risk factors that could possibly lead to interference with success of antimicrobial therapy) PJI after TKA.

These data agree with other studies in terms of predominant isolates (i.e. *Staphylococcus aureus* and coagulase-negative staphylococcal aureus species) and lack of association between treatment failure and patient's age or sex, evidence of prosthesis loosening, intraoperative purulence, or history of rheumatoid arthritis or diabetes [19, 36, 37].

It has been suggested by several studies with similar sample sizes that patients in which symptoms of infection have been present for more than three weeks should not undergo debridement with retention of the components [36-38]. However, in this study the average time of duration of symptoms before initial debridement for the cohort was four weeks. Those patients with early postoperative infections who failed treatment had an average of two weeks elapse between the start of symptoms and initial debridement. More importantly, this criteria did not seem to apply to late chronic infections (defined as having symptoms greater than 30 days postoperatively); none of the late chronic postoperative infections failed treatment in either the control or oral suppressive group.

With exclusion of potential confounding factors such as steroid therapy or chemotherapy for malignancies (which suppress the immune system), these data suggest

that even when the patient is not treated promptly with early debridement the outcome is more favorable for those patients who receive oral suppressive therapy. Treating high risk patients with only six weeks of I.V. antimicrobial therapy and debridement, especially in early postoperative infections, could lead to relapse or failure sooner than when treating patients with oral suppressive therapy. Even patients who elected to discontinue oral suppressive therapy did not return with signs of infection over two years of follow-up. This could reflect the effectiveness of using rifampin and vancomycin combinations on susceptible organisms during the six weeks treatment preceding the baseline of this study [5,8, 39]. However, due to the small sample size of our study, these results should be interpreted cautiously.

Though using these combinations have shown to decrease treatment failure in other studies, three of the early postoperative infections that were treated with these combinations failed treatment; including the only failure in the oral suppressive group. In this retrospective view, reasons for why these treatment combinations failed could not be accounted for. My results were similar to that of Marculescu et al. [11] that even without use of rifampin, the risk of treatment failure among patients with PJI due to coagulase-negative staphylococci was low. This author and colleagues recommended the routine use of three-six months of rifampin therapy, for appropriate cases of PJI due to *S. aureus* that is treated with débridement and retention of the prosthesis, followed by long term suppressive antimicrobial therapy with an oral regimen free of rifampin. These data suggest that increased use of such a regimen at TCIDA could possibly account for the low failure rates at two years' post débridement [11].

Limitations

Our study has several limitations. First, the sample size is small, which limits the external validity of the results. Second, it is a single-center retrospective study, with potential for uncontrolled selection biases (i.e. though physician's decision to place a patient on oral suppressive therapy could be considered a random factor). Also, the orthopedic surgeons referred patients to TCIDA only when their treatment was most likely to fail, possibly introducing potential bias towards alternative findings. Third, it is possible that the treating physician may have unintentionally misclassified prosthetic joint infection, despite the use of common diagnostic guidelines, as a surgical site infection. Also, there is the possibility of misclassification bias in determining a cure at baseline because even if the criteria are met, the specificity of cultures could result in misclassifying a patient as cured when the infection is merely suppressed.

In summary, the optimal duration of I.V. antimicrobial therapy when attempting to salvage a prosthetic knee joint is uncertain, however, this study agrees with other studies that at least six weeks of I.V. therapy and débridement, followed by oral suppressive therapy is an attractive alternative to excision arthroplasty and delayed reimplantation in patients that have well-seated prostheses and in whom more extensive surgical procedures is contraindicated. Since this study excluded those patients that must take steroid therapy (i.e. COPD or asthma sufferers), or chemotherapy for malignancies, these results cannot be generalized to a larger portion of patients electing to undergo the more conservative treatment option. Lack of consensus in clinical studies regarding definitions of PJI, diagnostic criteria, and treatment options underscore the need for

prospective, randomized, placebo-controlled clinical trials, but due to the rare nature of

the disease, the data from these trials are long forthcoming. Until these data are

evaluated, it is recommended that decisions of care reside upon the individual patients

and treating physician with regard to the patient's overall health and risk factors.

APPENDIX A

STANDARDIZED DATA COLLECTION TOOL

Patient's Name: **DOB:**
Period of Consultation:

1. What was the patient's consulting diagnosis?

2. What type of therapy was used (i.e., which medications were used during the course of tx)?

3. Were there any debridement's, and if so, how many?

4. Was patient on chemotherapy for any malignancies?

5. Was patient diagnosed with HIV?

6. What was the duration of symptoms before coming to TCIDA?

7. Were chronic infections experienced in the prosthetic site?

8. Describe the infection: was it early (within the first month post-op), late chronic infection, or an acute hematogenous infection?

9. Did the strain occurring during original infection change at any point during treatment or follow-up period?

10. Was there evidence of culture-negative PJI (defined by negative cultures of a joint aspirate or intraoperative specimen, in conjunction with (1) purulence, surrounding the prosthesis at the time of surgery, (2) acute inflammation consistent with infection on histopathologic examination at the time of surgery (debridement), or (3) a sinus tract communicating with the prosthesis?

11. Was there evidence of a superinfection (i.e., a nosocomial surgical site infection due to an organism other than the original strain of infecting organism (recovered after the

initial debridement) which occurred while the patient was still receiving IV antimicrobial therapy)?

12. **Did any reinfection occur with the same organism after patient's isolates were negative?**

13. **Did the prosthesis loosen?**

14. **Did patient have any revision arthroplasties while on treatment at TCIDA?**

15. **What was the age of prosthesis?**

16. **Did patient have arthritis, DM, or use steroids for the purpose of arthritis pain control?**

17. **What was the infecting agent?**

18. **Upon aspiration, was any purulence observed post-op?**

19. **Were there any radiolucent lines on X-ray?**

20. **Did patient complete the one year follow-up period? If not, when did he/she drop out?**

Do any of the following apply? Please circle

Culture-positive failure: culture conformation of original infectious agent or evidence of antimicrobial resistant strain after six weeks therapy.

Clinical failure: clinical and/or radiological conformation of original infectious agent or radiolucence on MRI, CT, or plain radiograph after six weeks of treatment.

Culture-positive relapse: culture conformation of original infecting agent or resistant strain after completing PJI therapy.

Clinical relapse: clinical conformation of PJI after completing therapy.

APPENDIX B

INTERNAL REVIEW BOARD DOCUMENTS

BOARD ACTION

IRB PROJECT #: 2008-098   DATE SUBMITTED: March 6, 2009

PRINCIPAL INVESTIGATOR: Sumihiro Suzuki, PhD (with student Mandy McBroom)

PROJECT TITLE: A Comparison of Treatment Outcomes for Infected Prosthetic Knee Joints Treated with Debridement, Antimicrobial Therapy, and Prosthesis Retention

PROTOCOL #:

DEPARTMENT: Biostatistics-SPH   TELEPHONE EXTENSION:

In accordance with UNT Health Science Center policy on the protection of human subjects, the following action has been taken on the above referenced project:

Approval, when given, is **only** for the project as submitted. **No changes** may be implemented without first receiving IRB review and approval.

_____ Project has received approval through_____.

_____ Informed Consent approved as submitted on _____.
You **MUST** use this version (attached) rather than previously approved versions. In addition, only consent documents which bear the official UNTHSC IRB approval stamp can be used with subjects.

_____ Study Protocol dated _____approved as submitted.

__✓__ Protocol Synopsis approved as submitted on March 17, 2009_____.

__✓__ Amendment March 17, 2009_____to the protocol approved as submitted.

_____ Based upon the recently completed Continuing Review (IRB Form 4), project has received continued approval through_____.

_____ Project has been reviewed. In order to receive approval, you must incorporate the attached modifications. You must submit one "highlighted" copy and one "clean" copy of the revised protocol synopsis, informed consent and advertisements to the IRB for review. YOU MAY NOT BEGIN YOUR PROJECT UNTIL NOTIFIED BY THE IRB.

_____ Consideration of the project has been tabled pending resolution of the issue(s) outlined below.

_____ Project is disapproved for the reason(s) outlined below.

_____ Completion of project is acknowledged and all required paperwork has been received.

__✓__ Special Findings:

The PI requested the following changes to the protocol synopsis:
1) Extend the dates for inclusion in the study from eight years (January 1, 2000 to December 31, 2007) to nine years (January 1, 2000 to December 31, 2008).
2) Modify the inclusion criteria to include patients that have experienced chronic infections at the prosthetic site. (continued on next page)

_____   March 17, 2009
Chairman, Institutional Review Board   Date

IRB Form 2 revised 12-03   MA 04-1487

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March 17 2009

IRB Project #2008-098

3) Modify the exclusion criteria. Patients with symptoms of infection exceeding three weeks will no longer be excluded from the study. Patients who received steroid therapy for any reason will be excluded from the study.

4) Change one of the two subject groups from "Inflammatory disease" to "Immunocompromised" to be more inclusive. The immunocompromised group will be defined as those with arthritic disease or diabetes mellitus.

5) Change the follow up period after surgery from two years to one year. The PI noted that a two year follow up is not necessary due to the high frequency of chronic suppression with antimicrobial therapy.

Following federal guidelines, modifications are approved under the provisions of 45 CFR 46.110 (b) Category (5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

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