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pVancomycin Powder and Dilute Povidone Iodine Lavage for Infection Prophylaxis in High Risk Total Joint Arthroplasty: A Randomized Prospective Trial

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Principal Investigator:

Ran Schwarzkopf MD MS

1. INTRODUCTION

1.1. BACKGROUND

PJI is a rare but devastating complication associated with TJA that imposes a significant burden on the patient, provider, and healthcare system. It is estimated that the annual burden of this disease on the United States healthcare system will exceed $250 million a year as individual PJI cases can exceed $50,000.[1,2] While the overall incidence has remained stable around 1 to 2.3% of primary TJA, infection rates above 5% have been reported in the literature in certain subgroups of patients with significant co-morbidities and those undergoing revision TJA.[3,4] Specific risk factors that predispose to the development of PJI include the presence of obesity, diabetes mellitus, American Society for Anesthesiologists (ASA) score of three or greater, active smoking status, inflammatory arthritis, and immunocompromised status.

Patients with these risk factors are considered "high-risk" and may benefit from the implementation of additional protocols to reduce the risk of developing PJI. Many interventions to date have been performed to reduce PJI, including reducing OR traffic, positive pressure ventilated ORs with laminar airflow, and use of suit ventilation.[5] Povidone iodine lavage and the administration of vancomycin powder to the local wound have demonstrably reduced the risk of postoperative infection in TJA and spine surgery literature, and may provide similar results in TJA patients.[6–10] We have designed a multi-center prospective study evaluating the effect of povidone iodine lavage and vancomycin powder administered to the local wound after TJA. We seek to investigate the outcomes of combining dilute povidone iodine lavage followed by local wound vancomycin powder (vancomycin povidone iodine protocol, VPIP) for TJA patients at high risk for infection.

Periprosthetic joint infection is perhaps the most challenging complication associated with total joint arthroplasty (TJA) and typically requires revision surgery to treat. The annual incidence of PJI is considerable and reported to be the between .76-1.24% in THA and .88-1.28% in TKA.[11] Thus, given the large number of TJAs performed in the United States each year, PJI places a tremendous burden on the patient, provider, and healthcare system.

PJI is significantly more likely to occur in patients with risk factors that place them at high risk for developing an infection. The orthopaedic literature has demonstrated that comorbidities such as obesity, immunocompromised status, American Society of Anesthesiologists (ASA) scores greater than or equal to 3, active smokers, inflammatory arthritis, and patients with diabetes mellitus are all independent risk factors for PJI.[3]

Although not novel, dilute povidone iodine lavage prior to wound closure has been shown in prior studies to reduce the rate of PJI in orthopaedic and spine surgery.[7,8] Brown et al. demonstrated that dilute povidone iodine lavage was effective in reducing infection rate in TJA from 0.97% to 0.15%.[6] Dilute povidone iodine is inexpensive, readily available, and has broad-spectrum bactericidal activity that includes methicillin-resistant S. aureus (MRSA).[7,9,10] In theory, these antiseptic agents have cytotoxic effects to bacteria in the wound with effectively no risk of resistance. However, these agents come with the inherent risk that they can be cytotoxic to the host tissue, resulting in a possible increase rate of wound-healing complications and infection.

Local wound vancomycin powder has been shown in several large retrospective studies to reduce the rate of infection in spine surgery.[12–17] The largest of these studies showed infection rates that decreased from 2.6% to 0.2%, while a higher-risk population of patients with spine trauma found a decrease in infection rate from 13% to 0% with the use of vancomycin powder.[12–16] Only one study in adult TJA has demonstrated the benefit of vancomycin powder, although it was retrospective in nature and therefore subject to significant bias.[18] However, it is always a concern that local antibiotics could also result in higher rates of antibiotic resistance.

Povidone iodine lavage and local wound vancomycin power may be used alone at varying institutions nationwide, but to our knowledge, no formal investigations have sought to compare these protocols to the current standard of care in this susceptible population undergoing TJA. Moreover, no published studies have investigated the effects of combining povidone iodine and vancomycin powder in high-risk TJA patients. We have designed a multi-center prospective study that seeks to evaluate the effect of a Vancomycin-Povidone Iodine Protocol (VPIP) on PJI incidence in TJA patients at high risk for postoperative PJI.

Infection following TJA remains a major cause of patient morbidity with a prevalence of 0.5% to 3% in patients with baseline risk.[3,19] Several studies have demonstrated that infection rates can be significantly higher in patients with certain risk factors that predispose to infection.[3] The orthopaedic literature has demonstrated that comorbidities such as obesity, immunocompromised status, ASA scores greater than or equal to 3, active smokers, and patients with diabetes mellitus are all independent risk factors for PJI. Obesity is a particularly problematic risk factor for infection and has been demonstrated to correlate directly with increasing BMI.[3,20,21] In fact, TJA recipients with a BMI greater than 50 kg/m2 are estimated to have an 18 fold increased risk for PJI

compared to those below 50 kg/m2.[3] In addition, morbidly high BMI patients often present with other risk factors, namely diabetes mellitus and poor nutritional status. Diabetes mellitus can prevent proper wound healing, thus increasing a surgical candidate's risk for infection and wound dehiscence.[22,23] Moreover, other patient risk factors including immunosuppression, smoking status, and MRSA colonization have been shown to also adversely affect outcomes while increasing the risk for PJI following TJA.[24]

Early results from a pilot study at NYU Langone Health demonstrate promising results with the implementation of the Vancomycin-Povidone Iodine Protocol (VPIP). From March 2014 to March 2015, 260 subjects met our institution's criteria for high-risk total joint arthroplasty and received VPIP. High-risk TJA candidates included patients with a BMI over 40, active smoker, ASA score greater than or equal to 3, diagnosis with diabetes mellitus, established colonization with S. Aureus, patient undergoing revision TJA, or immunosuppressed patients. The PJI rate in the non-VPIP group was 1.8%, and the VPIP group was 1.3%. This was a 27.8% risk reduction when compared to the control group of high-risk subjects not treated with VPIP (5,585 subjects). Noninfectious complications were limited to 2 cases (0.5%) of sterile hematoma/seroma formation requiring return to the operating room (OR). There were no medical complications secondary to the VPIP, and no cases of either ototoxicity or acute renal impairment secondary to application of local vancomycin. Although promising, our results did not meet statistical significance because this pilot study was underpowered. Based on our initial power analysis, we would need approximately 3,100 patients in each arm of the study to determine a 50% reduction from our baseline 1.5% "high-risk" cohort PJI rate. By expanding to other institutions and establishing a multi-center study, it would be possible to reach adequate power and statistical significance.

Our study seeks to define the potential benefits that an additional prophylactic protocol involving the use of povidone iodine and vancomycin powder on the incidence of PJI in high risk TJA patients. To our knowledge, no previous study has sought to investigate this question in a prospective manner. The potential benefits of these interventions are significant both from the perspective of reducing morbidity and mortality for the patient, and from a cost-effectiveness and value-based perspective. To this end, our study seeks to assess the direct and indirect costs associated with the treatment and control groups. We anticipate that the administration of a VPIP protocol will both reduce the incidence of PJI in high risk groups relative to the control arm and will demonstrate added value from a cost-effectiveness perspective.

This study looks to examine off-label use of Vancomycin Powder and Povidone Iodine 10% solution. Both products are lawfully marketed in the United States. This study is not intended to be reported to the FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling or advertising of either drug. Current FDA-approved indications with dosing and route of administration for Vancomycin Powder and Povidone Iodine 10% solution are the following:

- Vancomycin Powder
    - Use: Should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria
    - Dosage and Administration: The usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. Each dose should be administered at no more than 10 mg/min or over a period of at least 60 minutes, whichever is longer.
- Povidone-Iodine Solution
    - Use: First aid antiseptic to help prevent the risk of infection in minor cuts, scrapes and burns
    - Dosage and Administration: apply small amount of product to affected area 1-3 times daily

This study does not involve a route of administration, dose, patient population, or other factor that significantly increased the risk (or decreases the acceptability of the risk) associated with the use of the drug product. The routes and dosages being tested in this protocol are part of standard clinical care in most total joint arthroplasty surgeries. There are multiple research articles published that the safety profile for this administration is similar to the package insert and does not increase the risk in multiple specialties.[7,8,12-14,18]

1.2. RATIONALE

The scientific rationale for antibiotic prophylaxis is to inhibit or eliminate contaminating microorganisms that gain access to the surgical site during the procedure. Periprosthetic joint infection (PJI) is a devastating complication associated with total joint arthroplasty (TJA) that is disproportionately experienced by patients who possess predisposing risk factors. These high-risk patients may benefit from the implementation of additional prophylactic protocols to reduce the risk of PJI. Dilute povidone iodine lavage and administration of

vancomycin powder to the local wound has been shown retrospectively to reduce postoperative infection in high risk patients undergoing TJA and spine surgery. However, to date, there have been no randomized control trials to demonstrate if these prophylactic measures improve outcomes free from bias. This prospective trial seeks to determine whether these two agents reduce the risk of PJI in high-risk patients undergoing TJA.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. OVEREACHING STUDY OBJECTIVE

PJI after TJA represents a catastrophic complication. Controversy still exists regarding the utility of dilute povidone iodine lavage and administration of vancomycin powder. Level I data with regard to these prophylactic measures in elective TJA is limited. The purpose of this study is to assess the incidence of PJI within three months following the index arthroplasty in each of the treatment arms (povidone iodine and vancomycin combined and alone) and the control arm.

Null Hypothesis

The implementation of a VPIP protocol in high-risk patients undergoing TJA will demonstrate similar rates to the development of PJI when compared to the non-VPIP cohorts

To examine the Null Hypothesis, this proposal uses a prospective, multi-center, randomized controlled clinical study design.

2.2. SUB-HYPOTHESIS & SPECIFIC AIMS

The implementation of a VPIP protocol in high-risk patients undergoing TJA will demonstrate similar rates to the development of persistent wound drainage, fistula formation, excessive joint pain following the index arthroplasty, and death when compared to the non-VPIP cohorts

To evaluate the development of persistent wound drainage, fistula formation, and excessive joint pain following the index arthroplasty in each of the treatment arms and the control arm.

There will be no differences in the safety profile relating the implementation of a VPIP protocol when compared with the control arm in high-risk for PJI patients undergoing THA.

As this will be a large multi-center study, there is an opportunity to better define the safety profile of these interventions

3. STUDY DESIGN/METHODOLOGY

3.1. STUDY DESIGN

This is a prospective, randomized, controlled, open label, parallel four-arm design, multi-center, pragmatic study to compare different intraoperative interventions in the prevention of acute PJI development

Participating sites include Columbia University Medical Center, University of Pittsburgh Medical Center, Ortho Carolina Hip and Knee Center, London Health Sciences Centre, Rush University Medical Center, Eisenhower Health, Penn Medicine, Cleveland Clinic, Rothman Institute, Brigham Women's Hospital, Massachusetts General Hospital, University of Florida, University of Minnesota, Hospital for Special Surgery, Orthopedic Institute of NJ, Morristown Medical Center, New England Baptist Hospital, Colorado Joint Replacement, Boston University, Hackensack Meridian Health, University of Kentucky, Emory University, Penn Medical Center, University of Iowa and St. Francis Hospital.

All patients eligible for enrollment will be asked to sign a consent form prior to beginning the study by a study team member (sub-investigator, research coordinator, etc.). Subjects will be recruited by prescreening participating surgeons' clinic and surgical schedules. Prior to initiation of the study, research personnel will evaluate all patients

to determine if their participation in the study protocol would have any possible negative interactions with their current medicinal treatments or co-morbidities. Participants will continue the use of all medications deemed necessary by their medical doctor during the study period.

Once TJA candidates are successfully screened, patients meeting eligibility criteria will be placed into one of four treatment cohorts: povidone iodine and vancomycin powder, povidone iodine alone, vancomycin powder alone, and conventional (neither povidone iodine, vancomycin powder, nor polymyxin/bacitracin irrigation). Medical records will be reviewed for preoperative patient data and laboratory values (Table 1).

Table 1. Collected Baseline Patient Characteristics

Baseline Patient Characteristics
Age
Gender
Body mass index (BMI)
Zip code
American Society of Anesthesiologist (ASA) Score
Insurance type
Preoperative complete blood count (CBC), basic metabolic panel (BMP), and hemoglobin A1c (HbA1c)
Presence of diabetes mellitus
Cigarette smoking status
E-Cigarette smoking status
Immunocompromised status
Charlson Comorbidity Index (CCI)

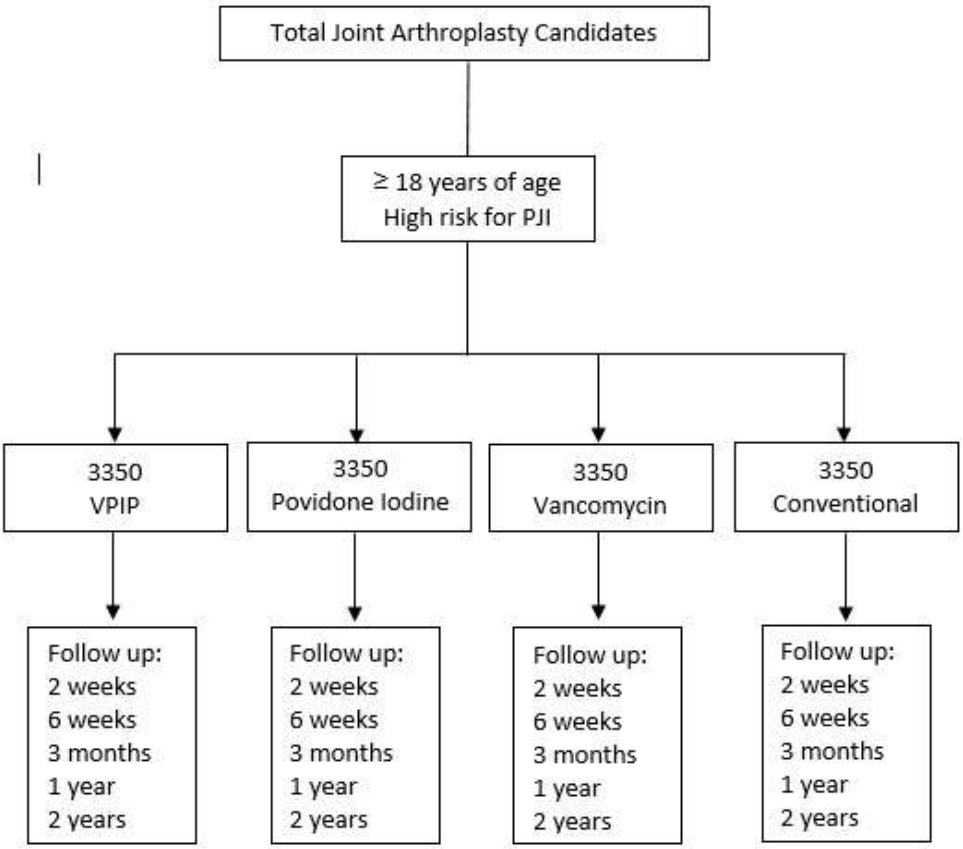
During the hospitalization, only basic data will be collected from the surgical procedure. This will allow for minimal interruption of clinical activities and ease burden on participating sites. The coordinating site will provide a template for surgical dictation to streamline data collection and further reduce burden on participating surgeons. Variables are listed in Table 2

After total hip or knee replacement surgery, the surgical site infection occurrence will be assessed at 90-days postop. This simplifies the site adherence and facilities enrollment. SSI rates can be assessed during clinic visits, or via patient follow-up calls. Again, this should significantly reduce the burden on participating sites.

Numeric Results for Non-Inferiority Tests for the Difference Between Two Proportions
Test Statistics: Z-Test with Unpooled Variance

3.2. STUDY DESIGN – SCHEMATIC CONSORT FLOW DIAGRAM

Figure 1. Study flow chart



3.3. STUDY INTERVENTIONS & RANDOMIZATION

3.3.1. STUDY INTERVENTIONS

3.3.1.1. STUDY GROUP #1

Patients in Group #1 will receive a dilute povidone iodine lavage and administration of vancomycin powder as the VPIP arm of the study. For the dilute povidone iodine lavage, the povidone iodine will be obtained from a sterile, single-dose 17.5mL packet. The povidone iodine solution will be sourced as standard practice at each institution. To create the dilute solution, a staff member will draw up 17.5 mL of 10% povidone iodine with a syringe and mix it with 500 mL of normal saline, resulting in a dilution of 0.35% povidone iodine solution for use before wound closure. After implantation of components, the wound will be soaked with 500 mL of the dilute povidone iodine solution for three minutes, followed by pulsatile lavage of 1 L of isotonic sodium chloride solution without antibiotics. After the final lavage, a total of 2 grams of vancomycin powder will be applied to the wound and will be distributed so that approximately 1 gram is administered deep to the fascia and 1 gram superficial to the fascia. The vancomycin will be sourced as standard practice at each institution. The wound will then be closed in standard layered closure according to the surgeons' standard protocol. The use of subfascial and subcutaneous drains will be left to the discretion of the operating surgeon

3.3.1.2. STUDY GROUP #2

Patients in Group #2 will receive dilute povidone iodine lavage alone. For the dilute povidone iodine lavage, the povidone iodine will be obtained from a sterile, single-dose 17.5mL packet. The povidone iodine solution will be sourced as standard practice at each institution. To create the dilute solution, a staff member will draw up 17.5 mL of 10% povidone iodine with a syringe and mix it with 500 mL of normal saline, resulting in a dilution of 0.35% povidone iodine solution for use before wound closure. After implantation of components, the wound will be soaked with 500 mL of the dilute povidone iodine solution for three minutes, followed by pulsatile

lavage of 1 L of isotonic sodium chloride solution without antibiotics. No vancomycin powder will be utilized in this cohort.

3.3.1.3. STUDY GROUP #3

Patients in Group #3 will obtain vancomycin powder alone. The vancomycin will be sourced as standard practice at each institution. After the final lavage with 1 L of isotonic sodium chloride solution without antibiotics, a total of 2 grams of vancomycin powder will be applied to the wound and will be distributed so that approximately 1 gram is administered deep to the fascia and 1 gram superficial to the fascia. The wound will then be closed in standard layered closure. The use of subfascial and subcutaneous drains will be left to the discretion of the operating surgeon. No dilute povidone iodine lavage would be utilized in this cohort

3.3.1.4. STUDY GROUP #4

Patients in Group #4 will be the control cohort. No additional steps in management are required for the control arm of the study besides lavage with 1 L of isotonic sodium chloride solution without antibiotics. No vancomycin powder or dilute povidone iodine lavage would be utilized in this cohort

3.3.2. RANDOMIZATION

Once TJA candidates are successfully screened, patients meeting eligibility criteria will be placed into one of four treatment cohorts: povidone iodine and vancomycin powder, povidone iodine alone, vancomycin powder alone, and conventional (neither povidone iodine, vancomycin powder, nor polymyxin/bacitracin irrigation). After informed consent is obtained and the screening interview is conducted, the principle investigator/sub- investigator or research assistant will electronically randomize a patient to a study group intervention using the REDCap database (web-based secure database application maintained by the NYU Investigators).The NYU Statistics Department will provide the randomization scheme that will be used within the REDCap database to randomly assign patients to one of the four treatment groups. A block randomization scheme stratified by site will be used in order to preserve treatment group balance within site. The block size will be undisclosed. Each patient who qualifies for entry into the study will be assigned a unique study number in chronological order within the participating site (i.e., site ID + patient ID).

4. STUDY POPULATION

The study population will include patients undergoing elective total joint arthroplasty by surgeons from the participating sites. All patients who present for evaluation for primary total joint arthroplasty will be screened to determine their study eligibility. Only patients who meet inclusion criteria based on the study screening protocol will be eligible for study participation.

We anticipate needing to enroll 3,350 patients per group into this study based on the following sample size calculations. If we assume rates of infections to be 1.5% in patients at high-risk for PJI, in order to demonstrate a 50% risk reduction from baseline, 3,100 patients would need to be enrolled into each arm of the study (power of 80% [alpha =0.05]).[11] To allow loss of follow-up of roughly 8% of patients in each arm, we allowed an additional 250 patients in each arm of the study, giving a recruitment of 3,350 in each arm and 13,400 patients in total.

4.1. INCLUSION CRITERIA

1. Patient is ≥ 18 years of age
2. Patient has no open wounds on operative leg
3. Patient is scheduled to undergo elective primary total joint arthroplasty for posttraumatic, osteoarthritis, avascular necrosis, and/or inflammatory arthritis
4. Patient does not have active infection on the operative leg, the operative joint
5. Patient are identified as high risk for the development of PJI which is determined by the presence of one or more of the following characteristics: over 75 years old, BMI >35, active smoker, ASA ≥ 3, immunosuppressed (i.e. being treated with chemotherapy, diagnosis of HIV, diagnosis of HCV, being treated with chronic steroids), diagnosis with diabetes mellitus, or established colonization with S. aureus

6. Patient understand the risks and benefits associated with TJA and willing to cooperate and follow study protocol and visit schedule

4.2. EXCLUSION CRITERIA

1. Patient is ≤ 18 years of age
2. Patient is pregnant
3. Patient is unable to provide written consent
4. Patient has psychiatric disorder that precludes safe study participation or that necessitates confinement in a custodial environment at home or in a chronic care facility
5. Patient does not have the mental capacity to participate and comply with the study protocol
6. Patient has active infections in the operative leg/joint
7. Patient has severe dementia
8. Suspicion of illicit drug abuse by patient
9. ASA score of 5 & 6
10. History of prior native septic joint arthritis
11. Has planned procedure within 90 days of surgery
12. Known allergy to vancomycin
13. Known iodine sensitivity

5. STUDY PROCEDURES/DATA COLLECTION

5.1. SCREENING STUDY PROCEDURES

Patient demographics and screening

Once a patient is deemed a surgical candidate for elective total joint arthroplasty, age, gender, and anthropometric assessment will be recorded in the electronic data management system. This is an essential part of the screening process and includes documentation of body weight, height, BMI, age, gender, and race.

Clinical Data Collection/Submission

Study data will be collected on specific REDCap forms that can be printed directly from the database

Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) assesses an individual's comorbidity level by documenting both the number and severity of pre-defined comorbid conditions. [25] It provides a weighted score of a patient's comorbidities which can be used to predict short- and long-term outcomes such as function, hospital length of stay, and mortality rates. The CCI is one of the most widely used scoring systems for comorbidities (see table). This information will be collected at the baseline screening.

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

5.2. PERIOPERATIVE STUDY PROCEDURAL/DATA COLLECTION

The following data points will be collected during the index procedure and recorded in the electronical data management system

1. Type of anesthesia
2. Surgical approach (Knee: medial parapatellar, midvastus, subvastus, lateral, Hip: Anterior, lateral, posterior)
3. Use of tourniquet including tourniquet time
4. Use of tranexamic acid/aminocaproic acid/desmopressin and route of administration (intravenous, oral, topical), dosage
5. Length of surgery
6. Units of blood transfused
7. Used of closed suction versus reinfusion drain versus no drain
8. Intraoperative complications
9. Type of wound closure (e.g. running subcuticular, nylon, staples)
10. Type of wound dressing used (incisional negative pressure dressing, hydrofiber silver-impregnated dressing, occlusive/island wound dressing, cotton-based absorbent dressings, etc.).
11. Type of antibiotic given (time and route), antibiotic redosed? (yes/no, time)
12. Use of antibiotic cement (yes/no, type)
13. ASA Score

American Society of Anesthesiologists (ASA) physical status score

The ASA physical status classification system is a system for assessing the fitness of patients before surgery.[45] In 1963 the American Society of Anesthesiologists (ASA) adopted the five-category physical status classification system; a sixth category was later added. These are:

1. Healthy person.
2. Mild systemic disease.
3.Severe systemic disease.

4. Severe systemic disease that is a constant threat to life.
5. A moribund person who is not expected to survive without the operation.
6. A declared brain-dead person whose organs are being removed for donor purposes.

5.3. FOLLOW-UP EVALUATION

5.3.1. Post-operative hospital course

Post-operative variables will be obtained from the outpatient visit. Variable collected at this time will include initial postoperative CBC and BMP, length of stay, anticoagulant used, wound drainage, fistula, or excessive joint pain.

5.3.2. FOLLOW-UP EVALUATION (90-day)

Surgical Site Infection/Periprosthetic Infection Status

The primary outcome measure will be the rate of periprosthetic infection (PJI) after elective total joint arthroplasty. For each enrolled and randomized subject, the 90-day PJI rate and causing organism if PJI occurred will be reported. The definition of periprosthetic infection exists when the following criteria are met

- NEW MSIS criteria for PJI: 1 major criteria (2) or 6 minor criteria (6) [26–28]
- Major Criteria: [1] sinus tract [2] + Cx from 2 separate aspirations
- Minor Criteria: [1] ESR >30 mm/hr (1 point), [2] D-dimer >860 ng/mL or CRP >1 mg/dL [2] increased synovial WBC (>3000 cells/microliter) [4] alpha-defensin (signal-to-cutoff ratio>1) [5] leukocyte esterase (++) [6] increased synovial PMNs of >80% [7] synovial CRP >6.9 mg/L

Major criteria (at least one of the following)	Decision
Two positive cultures of the same organism	Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis	

		Minor Criteria	Score	Decision
Preoperative Diagnosis	Serum	Elevated CRP *or* D-Dimer	2	≥6 Infected
		Elevated ESR	1	
	Synovial	Elevated synovial *WBC count or LE*	3	2-5 Possibly Infected [a]
		Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	0-1 Not Infected
		Elevated synovial CRP	1	

	Inconclusive pre-op score *or* dry tap [a]	Score	Decision
Intraoperative Diagnosis	Preoperative score	-	≥6 Infected
	Positive histology	3	4-5 Inconclusive [b]
	Positive purulence	3	
	Single positive culture	2	≤3 Not Infected

5.3.3. LONGTERM FOLLOW-UP EVALUATION (12-months and 24-months)

We will review the subject medical records for documented infection, hospital readmissions, and reoperations. No study procedures will be performed at these visits.

The primary outcome measure will be the rate of periprosthetic infection (PJI) after elective total joint arthroplasty. For each enrolled and randomized subject, the 90-day PJI rate and causing organism if PJI occurred will be reported. The definition of periprosthetic infection exists when the following criteria are met

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- Minor Criteria: [1] ESR >30 mm/hr (1 point), [2] D-dimer >860 ng/mL or CRP >1 mg/dL [2] increased synovial WBC (>3000 cells/microliter) [4] alpha-defensin (signal-to-cutoff ratio>1) [5] leukocyte esterase (++) [6] increased synovial PMNs of >80% [7] synovial CRP >6.9 mg/L

Major criteria (at least one of the following)	Decision
Two positive cultures of the same organism	Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis	

		Minor Criteria	Score	Decision
Preoperative Diagnosis	Serum	Elevated CRP *or* D-Dimer	2	≥6 Infected
		Elevated ESR	1	
	Synovial	Elevated synovial *WBC count or LE*	3	2-5 Possibly Infected [a]
		Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	0-1 Not Infected
		Elevated synovial CRP	1	

	Inconclusive pre-op score *or* dry tap [a]	Score	Decision
Intraoperative Diagnosis	Preoperative score	-	≥6 Infected
	Positive histology	3	4-5 Inconclusive [b]
	Positive purulence	3	
	Single positive culture	2	≤3 Not Infected

5.4. SCHEDULE OF ACTIVITIES

Study Interval	Preoperative	Peri-operative	Long-term Follow-Up		
	Screening	Date of Surgery	3 months	1 year	2 year
Review of demographics and preoperative variables (Table 1)	X				
Measurement of height, weight and BMI	X	X	X		
Screening—using eligibility criteria	X				
Patient Consent	X				
Review of Preoperative labs (e.g. CBC, BMP, HbA1c)	X				
Perioperative Values (Table 2)		X			

Postoperative Variables (Table 2)		X	X	X		
Review of subject medical record for joint infection, hospital readmission, re-operation					X	X

Table 2. Collected peri- and post-operative variables

Perioperative Variables
Type of anesthesia Approach Length of tourniquet (in TKAs) TXA use, type (topical vs IV vs oral), dosage Length of surgery Units transfused Intraoperative complications Perioperative analgesics (morphine equivalents) Closure (Staples vs Sutures) Dressing (Aquacel versus Wound Vacs) Initial postoperative CBC and BMP
Postoperative Variables
Length of stay Anticoagulant Used Postoperative complications - Infection requiring intervention - Wound drainage - Fistula formation - PJI-related death Revision procedures for infection Revision procedures for any reason 30/90 day ED visits and hospital readmissions Any extended antibiotic therapy Use of chronic antibiotic suppression therapy Presence of persistent wound drainage

Abbreviations
BMI – body mass index
BMP – basic metabolic panel
CBC – complete blood count
HbA1c- hemoglobin A1c
EMR – electronic medical record
THA – total hip arthroplasty
TKA – total knee arthroplasty
TJA – total joint arthroplasty (including hip and knee)
PJI – periprosthetic joint infection
VPIP – vancomycin and povidone iodine protocol

A member of the research team will ensure that all necessary data points (Table 3) are collected.

6. STUDY DURATION

This study is designed as a prospective longitudinal study with participants remaining in the study for 2 years after TKA surgery. Data collection for each individual study participant will be concluded at the 90-day post- surgical follow-up visit. In addition, there is long-term follow-up for subjects up to 2 years for follow-up assessment of the periprosthetic joint infection rate (PJI).

7. DATA MANAGEMENT

Data will be collected and managed using REDCap. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture. REDCap was developed by Vanderbilt's CTSA Standard operating procedures will be developed to ensure data quality. Monthly performance reports will summarize: patients recruited, patients successfully randomized, and the extent of follow-up for the enrolled patients. The reports also will evaluate the completeness of collected study data and 90-day periprosthetic joint infection rate if available.

Each site will be responsible for data entry and the following steps should be followed while completing the CRFs:

1. Complete data carefully and accurately
2. Complete header information consistently across all case report forms for each individual study subject
3. Ensure that all fields are completed

Data Submission

Completed CRFs will be submitted directly to the Coordinating Center by REDCap, every effort must be made to ensure data submission to coordinating center is made within 30 days of the visit completion. The use of disclosure of all protected health information will comply with the Health Insurance Portability and Accountability Act (HIPAA).

Reporting Requirements

Investigator Reporting Responsibilities

The investigator will be responsible for the accuracy, completeness, and timeliness of data reported to the Coordinating Center in accordance with this protocol. The Investigator or Designee will ensure timely reporting to their IRB/IEC as required by their local institution to maintain the approval throughout the study, and will provide any required final reporting upon study completion/termination. A copy of all IRB or EC re-approval letters must be submitted to the Coordinating Center.

REDCap Features

- HIPAA-compliant and secure. Data are stored on a NYU server behind firewall.
- Intuitive, web-based interface for database build, data entry, and reporting
- Data validation, audit trail, branching logic, and calculated fields
- Data dictionary for easy project edits and duplication
- Automated data export (.csv, SPSS, SAS, Stata, R)
- Data import from external sources
- Ability to add users external to NYU

8. STATISTICAL ANALYSIS

Data will be summarized and presented using the mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum for continuous variables and counts with percentages for non-missing categorical variables unless otherwise stated. All analyses will be performed as intention-to-treat with sensitivity analyses for subjects lost to follow-up. Descriptive statistics will be used to report baseline characteristics, as well as primary and secondary outcomes for the four prospective cohorts. Outcomes and baseline characteristics will be compared between each of the cohorts using chi-square tests. A Kaplan-Meier analysis will be used as a sensitivity analysis to include subjects lost to follow-up. Comparisons between continuous variables at baseline will use either a t-test or Wilcoxon rank sum test, dependent on the variable distribution. Univariable and multivariable logistic and/or Cox proportional hazards regression models will be used to adjust for the effects of possible baseline confounders (ASA, CCI, age, tourniquet use and time, drain use, TXA/amicar/desmopressin, wound dressing, skin closure modality) on the occurrence of infection. Statistical analysis will be performed using SPSS statistical software (International Business Machines, Version 24.0, Armonk, NY). A p-value < 0.05 will be considered statistically significant unless otherwise specified.

These estimates will be based on only those patients who are treated with the study medication to which they were randomized (a per-protocol approach). Thus, for example, if a patient was randomized to vancomycin only and was treated with iodine instead, they will not be included in the per-protocol analysis.
In a secondary analysis, we will also perform an "as-treated" analysis. In this analysis, patients will be included in the group based on the study medication they actually received. Thus, for example, if a patient is randomized to vancomycin but receives iodine, they will be included in the iodine group. This approach will include "crossover" patients and provide more precise estimates but will need to be interpreted with caution as this approach has more potential to result in a lack of representativeness of the groups.

9. PRIVACY AND CONFIDENTIALITY

Participant Confidentiality

• Any information that could identify study participants (i.e. names or medical record numbers) will not be included on study data forms. Instead each study participant will be given a study number. Only the study staff will be able to link the study numbers to the names of study participants.
• Data forms will be stored in a cabinet in a locked office.
• Data collected during the study will be stored electronically in REDCap, a cloud based electronic data management system that is password protected. Only personnel on the study team will have access to this data.
• The names, medical record numbers, or any other unique identifiers of study participants will not be included in any publications resulting from this study. To protect data stored on computers, passwords will be used and will be changed regularly.
• Backup copies of all data stored on the computer will be made at specified time intervals
• Research records will be stored in a research study file separate from the study participants' medical records.

9.1. INFORMED CONSENT

Written informed consent will be obtained from all subjects before any study related procedures are performed. The investigator(s) has both ethical and legal responsibility to ensure that each subject under consideration for enrollment is given a full explanation of the study. This process must be documented on a written Informed Consent Form (ICF) that has already been reviewed and approved by the same Institutional Review Board and/or Independent Ethics Committee (IRB/IEC) responsible for approval of the protocol. Each ICF shall include the elements required by Food and Drug Administration (FDA) regulations in 21 (CFR) Part 50 and International Committee on Harmonization (ICH) Good Clinical Practice (GCP).

Once the investigator or designated research personnel have fully explained the study and answered all the potential questions the participant may have and it is agreed that the participant understands the implications of participating, the IRB approved informed consent form should be signed and dated by all applicable parties in accordance to the IRB/IEC requirements. Study team should give a copy of the signed consent form to the participant and the original should be kept in study subject binder or regulatory binder. Explanation of study and the signing of the informed consent must occur prior to the subject's participation in the trial.

If the patient meets the study entry criteria, the study will be introduced to them by study personnel. A thorough explanation of the study will be provided to the patient and sufficient time will be provided for the potential subjects to thoroughly read the consent form, ask and have all questions about study participation answered, and make an informed decision to participate. The prospective participants will be encouraged to discuss the study and their potential participation in the study with their family members or significant others. The patient must be able to read the consent form in order to participate in the study. The patient will either provide a written signature to signify their agreement to participate in the study or they will decline study participation. In cases in which the patient decides not to participate in the study, they will be provided with the standard of care at the institution for their surgical procedure.

During the informed consent process, potential study participants will be informed that they may discontinue study participation at any time. If a study participant chooses to withdraw from the study, they will be asked to notify the principal investigator or a member of the study staff of their intentions.

Potential study participants also will be told that the principal investigator may choose to withdraw a study participant from the study for reasons related to noncompliance with the study protocol or if an event occurs that would warrant this decision. In such cases, the principal investigator will provide an explanation for the decision and the reason why the decision was made. Specific data forms will be completed to document the reasons for study participant withdrawal from the study.

9.2. RISK AND BENEFITS

Benefits

Subjects may or may not benefit from participation in this study. The knowledge gained from this study may help others in the future.

Risks

Risks of Povidone Iodine

Povidone Iodine may cause skin irritation, allergic skin reaction, redness of skin, acneiform eruptions, and thyroid imbalances.

Risks of Vancomycin Powder

Vancomycin powder may cause fever, rash, and reversible neutropenia. Rare side effects include ototoxicity, thrombophlebitis nephrotoxicity, and nonimmune hypersensitivity reaction.

Risks of Vancomycin Powder and Povidone Iodine Combined

Additional risks of these two treatments in combination have not been explored.

Risks of conventional method

No risks have been reported.

10. ADVERSE EVENTS/REACTIONS

Adverse event means any untoward medical occurrence associated with the use of the antibiotic drug in humans, whether or not considered antibiotic related.

Adverse reaction means any adverse event caused by any antibiotic drug used in the study.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the antibiotic drug used caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction"

Reasonable possibility. For the purpose of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the antibiotic drug used and the adverse event.

Life-threatening, suspected adverse reaction. A suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator), its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.

Serious, suspected adverse reaction. A suspected adverse reaction is considered "serious" if, in the view of the Investigator (i.e., the study site principal investigator), it results in any of the following outcomes: death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Unexpected, suspected adverse reaction. A suspected adverse reaction is considered "unexpected" if it is not listed in the general investigational plan, clinical protocol, or elsewhere; or is not listed at the specificity or severity that has been previously observed and/or specified.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

• The test finding is accompanied by clinical symptoms
• The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.

Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

• The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study.
• The test finding is considered an adverse event by the Investigator.

11. DATA SAFETY MONITORING

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the antibiotic administration will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained in order to permit: 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event and; 2) an assessment of the casual relationship between the adverse event and the antibiotic administration.

Adverse events or abnormal test findings felt to be associated with the antibiotic administration /drug will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Investigator. In addition, a Data Safety Committee will review cases with adverse events and monitor overall infection rate on a quarterly basis.

Unexpected, suspected rise of infection rates/study suspension. An unexpected rise in postoperative infection rate greater than 3% in total per enrolling site or among all enrolling sites will warrant a review of site specific and overall data. The finding may lead to a change in study drug dosing or discontinuation of administration and/or suspension of the study.

Members of the Data Safety Committee are:

1. PI
2. Statistician
3. Research Manager
4. Orthopedic Surgeon (not involved in the study)
5. Site representative from at least 3 sites

In accordance with applicable policies of the New York University Institutional Review Board (IRB) the Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) associated with the antibiotic administration; 2) serious; and 3) unexpected. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator's receipt of the respective information. Adverse events which are 1) associated with the antibiotic administration; 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting, the Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days after the determination was made.

Data will be reviewed on an ongoing basis by the site PIs. All study data will be reviewed on a yearly basis by Dr. Schwarzkopf to ensure the study is safe to proceed. If there is cause for stopping the study it will be discussed at that time. A yearly statement from the lead site, NYU Langone Health, allowing the study to proceed will be emailed to all sites.

12. Subject Costs and Payments

Subjects will not incur any additional costs associated with this research study. All visits and procedures are part of standard clinical care. The medications used in this study are also standard clinical care. Patients and/or their insurance will be responsible for their total joint replacement surgery.

Patients will not be compensated for their participation in this study. This study uses standard of care visits and we expect most patients to comply with the visit schedule.

13. ETHICS/CONFLICT OF INTEREST

The clinical research study will be conducted in accordance with the current IRB-approved clinical protocol; International Conference of Harmonization (ICH) Good Clinical Practice (GCP) Guidelines adopted by the FDA; and relevant policies, requirements, and regulations of the New York University IRB, State of New York, and applicable federal agencies.

None of the principal investigators, co-investigators or study team members should perform, for any personal gain, services to any supplier of goods or services, as employee, consultant, or in any other capacity which promises compensation of any kind, unless the fact of such transaction or contracts are disclosed in good faith, and the board or committee authorizes such a transaction. Similar association by a family member of principal investigators, co-investigators or study team members or by any other close relative may be inappropriate.

Currently, there are no consultative relationships that the principal or co-investigators have with any entity related to the protocol that might be considered a conflict of interest.

14. PUBLICATION & PRESENTATION PLAN

The dissemination of clinical data will include the timely presentation of results at the following scientific congresses and orthopaedic society meetings:

- American Association of Hip and Knee Surgeons (AAHKS) Annual Meeting, Dallas, Texas
- American Academy of Orthopaedic Surgeons (AAOS) Annual Meeting

In addition, the primary investigators and co-investigators will submit a full-length manuscripts summarizing the results of the study to the following peer reviewed medical and specialty journal. Sub-analyses of other variables and the impact on the primary outcome measures will be published as deemed scientifically appropriate.

15. Potential Limitations

The potential limitations of this study include the requirement of a large sample size in order to power the study and achieve potential significance. Adequate resources and adherence to protocol over an extended period of time will be required for the study to be carried out to completion. An additional potential limitation to the study is physician buy-in to the protocol. Physicians caring for high-risk TJA patient may be hesitant to enroll patients into the control arm of this study. Deviating from the protocol for patients enrolled in this group would skew the results. As such, physician buy-in and adherence to the protocol is paramount to the success of this study.

Project Timeline

Specific Aims	6 months	12 months	24 months	36-48 months
Aim 1: To assess the need for surgical intervention for infection within three months following the index arthroplasty in each of the treatment arms (povidone iodine and vancomycin combined and alone) and the control arm.	• Database (REDCap) developed • Enroll patients in study	• Continue enrollment of patients • Begin short-term analysis of data	• Continue enrollment • Continue data analysis	• Patients continued to be monitored as standard of care—1 and 2-year data will be collected and analyzed for all patients
Aim 2: To evaluate the development of persistent wound drainage, fistula formation, chronic infection and excessive joint pain following the index arthroplasty in each of the treatment arms and the control arm.	• Database (REDcap) developed • Enroll patients in study	• Continue enrollment of patients • Begin short-term analysis of data	• Continue enrollment • Continue data analysis	• Patients continued to be monitored as standard of care—1 and 2-year data will be collected and analyzed for all patients
Aim 3: To study the incidence of death related to a PJI in each of the treatment arms and the control arm.	• Database (REDcap) developed • Enroll patients in study	• Continue enrollment of patients • Begin short-term analysis of data	• Continue enrollment • Continue data analysis	• Patients continued to be monitored as standard of care—1 and 2 year data will be collected and analyzed for all patients

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