

Periprosthetic Joint Infection

©2021

All rights reserved

Pfiedler Education, a Division of AORN,
2170 S. Parker Rd., Suite 125, Denver, CO 80231

www.pfiedler.com

Phone: 720-748-6144

CONNECT WITH US FOR UPDATES!



OVERVIEW

Periprosthetic joint infection (PJI) is the most challenging complication associated with total joint arthroplasty in the 21st century.¹ PJI following total joint arthroplasty is potentially a limb and life-threatening condition, which becomes even more difficult to treat when bacteria form a biofilm on the implant and adjacent tissue. Because traditional irrigation and debridement results in unsatisfactory outcomes, two-stage revision surgery has become the treatment of choice in most institutions in the United States. These two-stage procedures often include the use of adjunct materials, such as antibiotic-loaded polymethylmethacrylate (PMMA) bone cement or calcium sulfate bone grafts, to improve the outcomes of revision surgery.

LEARNER OBJECTIVES

After completing this continuing education activity, the participant should be able to:

1. Explain how periprosthetic joint infection (PJI) affects patients and the healthcare system.
2. List risk factors for PJI and actions that can be taken to reduce those risks.
3. Discuss the properties of biofilms and why they are particularly challenging to treat.
4. Identify ways to diagnose PJI.
5. Describe prevention and treatment options for PJI.

INTENDED AUDIENCE/EDUCATIONAL NEED

This continuing education activity is intended for a perioperative nurse or other healthcare professional who wants to learn more or needs to gain knowledge and skills in periprosthetic joint infection (PJI).

TEACHING METHODOLOGIES

This continuing education activity is governed by principles of adult learning. PowerPoint images will be used to augment the speaker's presentations and a supportive study guide with content and references is provided to each participant. Attendees will have an active role in discussion as well as opportunities to ask questions and share experiences.

STEPS FOR SUCCESSFUL COURSE COMPLETION

To earn continuing education credit, the participant must complete the following steps:

1. Attend the course presentation, view course content and review learner objectives.
2. Log into the link provided during the presentation.
3. Finish course evaluation to complete and receive credit for this activity.
4. Upon course completion of the above requirements, a Certificate of Attendance is awarded. This Certificate is found in your MyLearning profile on the Pfiedler Education website.

ACCREDITATION INFORMATION

California Board of Registered Nursing

Association of periOperative Registered Nurses is provider-approved by the California Board of Registered Nursing, Provider Number CEP 13019 for **2.0 contact hours**.

Obtaining full credit for this offering depends upon attendance, regardless of circumstances, from beginning to end. Licensees must provide their license numbers for record keeping purposes.

The certificate of course completion issued at the conclusion of this course must be retained in the participant's records for at least four (4) years as proof of attendance.

EXPIRATION DATE

This continuing education activity was planned and provided in accordance with accreditation criteria. This material was produced in March 2021 and expires after March 2023.

COMMERCIAL SUPPORT

Healthcare organizations engaged in continuing medical, nursing and allied health education have adopted standards to promote balanced and evidence-based content. This course is supported by funding provided by a commercial entity and complies with the intent of these standards. Pfiedler Education gratefully acknowledges educational funding provided by: **Biocomposites**.

DISCLAIMER

Pfiedler Education does not endorse or promote any commercial product that may be discussed in this activity.

ACTIVITY PLANNING COMMITTEE

Terry Aitable MSN, RN, CNOR

President

Pfiedler Education

Denver, CO

No conflict of interest

Lizette Girado, MSN, RN, CNOR

Senior Clinical Program Manager

Pfiedler Education

Denver, Co

No conflict of interest

Sandra Lindahl, MS, RN-BC, CNOR

Clinical Program Manager

Pfiedler Education

Denver, CO

No conflict of interest

Melinda T. Whalen, MSN, RN, CEN

Director of Education & Live Events

Pfiedler Education

Denver, CO

No conflict of interest

AUTHOR

Linda R. Sexton, BS

Medical Writer/Consultant

Sexton Medical Communications, LLC

Golden, CO

No conflict of interest

Disclosure of Relationships with Commercial Entities for Those in a Position to Control Content for this Activity

Pfiedler Education has a policy in place for identifying and resolving conflicts of interest for individuals who control content for a Nursing or Allied Health Professional activity. Information is provided to participants, so that a determination can be made if identified external interests or influences pose potential bias in content, recommendations or conclusions. The intent is full disclosure of those in a position to control content, with a goal of objectivity, balance, and scientific rigor in the activity. For additional information regarding Pfiedler Education's disclosure process, visit our website at:
<http://www.pfiedler.com/disclosure>

Disclosure includes relevant financial relationships with commercial interests related to the subject matter that may be presented in this continuing education activity. "Relevant financial relationships" are those in any amount, occurring within the past 12 months that create a conflict of interest. A commercial interest is any entity producing, marketing, reselling, or distributing healthcare goods or services consumed by, or used on, patients.

Facilitator/Presenter Disclosure

The facilitator will verbally disclose his/her affiliation with the commercial support organization prior to the onset of the activity and will identify off-label or investigational information.

HIPAA COMPLIANCE

Pfiedler Education makes every effort to be in compliance with HIPAA. To protect patient privacy, faculty and participants have been requested to de-identify patient related material.

INTRODUCTION

Nearly a million total hip arthroplasties (THAs) and total knee arthroplasties (TKAs) are performed annually in the United States (US), and that number is expected to rise in the near term with the aging of the population.² Artificial joints improve the quality of life for many patients, but insertion of any device into the body carries a risk of infection.³

Periprosthetic joint infection (PJI) is potentially a limb and life-threatening complication of joint arthroplasty in which the prosthesis and adjacent tissue become infected. The outcome of PJI is related to many factors, including:⁴

- the health of the patient,
- the condition of the local soft tissues, and
- the length of time the infection is present within the joint.

PJI can present acutely and/or persist chronically for years following surgery.² Patients affected often must endure additional surgeries and lengthy exposure to systemic antibiotics, neither of which is certain to resolve the infection.² Prolonged periods of lost function and time away from work may also result.⁵

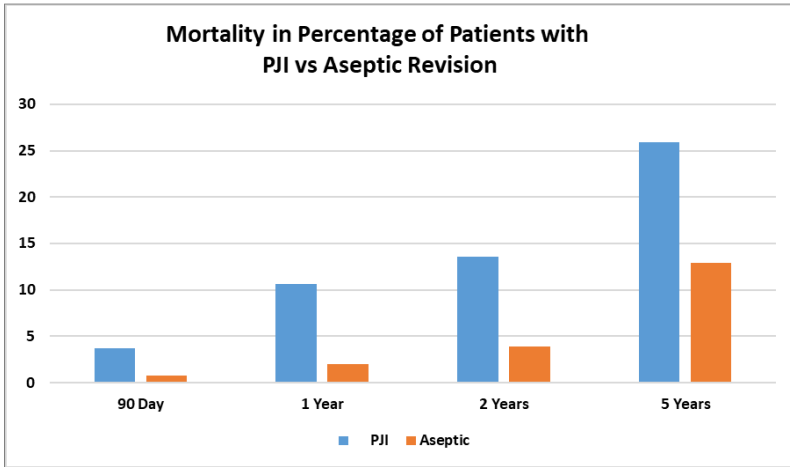
Incidence of PJI

According to an analysis of data from the Nationwide Inpatient Sample (NIS) which is a nationally representative inpatient database, there were 127,193 infected hip replacements and 238,133 infected knee replacements treated in US hospitals between 2002 and 2017. The relative incidence of PJI was 2.1% and 2.3% for THA and TKA, respectively, and this incidence is expected to increase over time.⁶ It is estimated that PJI is responsible for 15% of all revision hip and 25% of all revision knee procedures.⁶

Mortality

Mortality rates for patients with revisions secondary to PJI have been shown to be higher than rates for patients with aseptic revisions. In one study, when 436 patients with at least 1 surgical intervention secondary to confirmed PJI were compared with 2,342 patients undergoing revision arthroplasty for aseptic failure, PJI revisions were associated with five times the risk of death.⁷ (See Table 1) The relative five-year survival rate for patients with PJI was 87.3%, which is lower than reported survival rates for prostate cancer, melanoma, and breast cancer.⁸

Table 1 – Five Year Mortality Rate of Patients with PJI vs Aseptic Revision



Economic Burden

In addition to patient morbidity and mortality, PJI is associated with significant hospital costs and charges:¹

- Based on NIS data, the estimated hospital cost in 2017 of treating PJI following THA was \$32,100; the average cost of treating PJI following TKA patients was \$28,161.⁶
- The average charges in 2009 for an infected THA revision were \$93,600, compared to \$74,900 for an infected TKA revision.
- From 2002 to 2017, the estimated total annual cost to US hospitals of PJI for the hip and knee increased from \$372.7 million to \$902.9 million, and this figure is projected to reach \$1.85 billion by 2030.⁶

A study of the Healthcare Cost and Utilization Project (HCUP) State Inpatient Databases (Medicare admissions from 2009 to 2013 for Florida, Massachusetts, and California) found a 30-day readmission rate of 3.9% to 4.7% following THA or TKA. Of those patients, approximately 33% to 35% were readmitted because of infection.⁹

Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA) are significantly associated with an increased length of stay (LOS) due to readmission. Typically, developing post-orthopedic surgical site infections (SSIs) results in two to three times higher LOS in infected patients, and as a result, costs up to three times more compared with noninfected patients. Costs and LOS are compounded if SSIs result in hospital readmissions.¹⁰ Specifically, postoperative MRSA leads to an average of 23 days of additional hospitalization and is independently predictive of readmission within 90 days compared to noninfected patients.¹¹

The Hospital Readmissions Reduction Program (HRRP) is a value-based purchasing program by the Centers for Medicare and Medicaid Services (CMS) that can penalize hospitals up to 3% of their Medicare Part A payments for higher-than-expected

readmissions for specific clinical conditions, including elective THA and TKA. The Bundled Payments for Care Improvement was an initiative that set payments to health care providers according to predetermined expected costs of a grouping of related healthcare services. The Bundled Payments for Care Improvement Initiative ended in 2018. BPCI Advanced Model is a new iteration of the program and a continuation of efforts to implement episode-based payment models - bundled payments.

Among other things, bundled payments hold participating providers financially accountable for the quality and cost of a joint replacement episode of care, beginning with hospital admission of a beneficiary who is ultimately discharged after major joint replacement and ending 90 days post-discharge.^{12,13}

PATHOGENESIS

Two major routes and time scales are associated with the entry of pathogenic bacteria into a joint:²

- In the perioperative period, most commonly via the surgical incision, the source is either: 1) the patient's endogenous flora, or 2) bacteria from the personnel or environment of the operating room.
- The second route of entry is hematogenous spread (through the bloodstream), which is generally thought to occur during the postoperative period.

Once bacteria have gained entry to the surgical site, they can persist in the body in the planktonic form or as a biofilm.²

- In the planktonic (free-floating) form, bacteria behave as unicellular organisms. They can adhere to periprosthetic tissue or to the surface of the implant, where they begin to undergo replication. Planktonic bacteria often can be identified and cleared by the host's natural defenses or antibiotic therapy.
- As bacteria in the joint multiply, they become more firmly attached to the implant and periprosthetic tissue, secrete a protective extracellular polymeric substance, and become organized. The result is a highly structured biofilm that is resistant to destruction by antibiotics or natural immune mechanisms.

The microbiological causes of PJI in 14 large studies involving more than 2,400 patients with hip or knee arthroplasty infection found that Gram-positive cocci were involved in the majority of hip and knee PJIs. *Staphylococcus aureus* (*S. aureus*) and coagulase-negative staphylococci contributed to 50% to 60% of PJIs. Streptococci and enterococci together accounted for approximately 10% of cases, and aerobic Gram-negative bacilli were involved in approximately 10% of cases.¹⁴

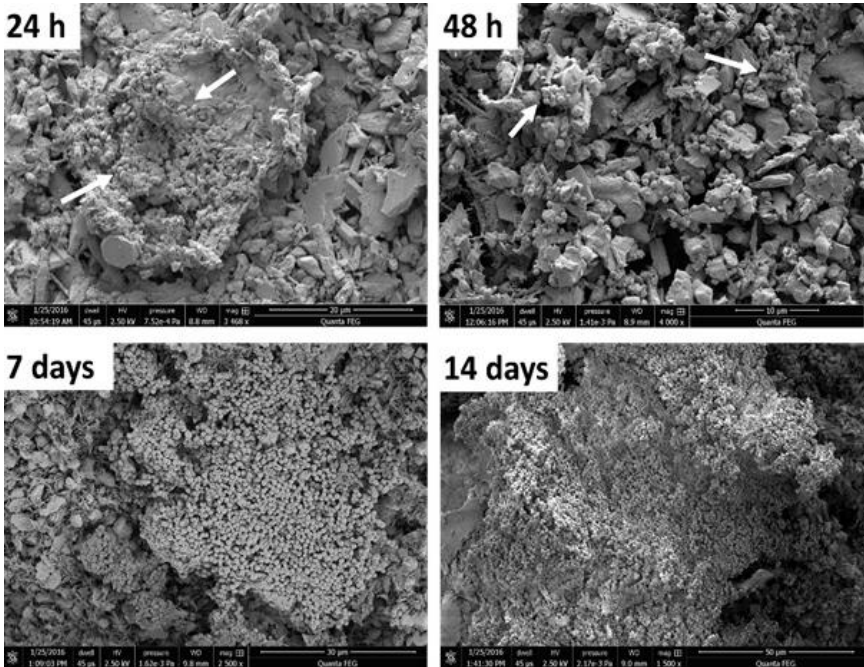
Biofilms

A growing body of evidence suggests that bacterial biofilms are the underlying cause of PJI.¹⁵ More than 30 years ago, in a review of published studies on the composite science of cells and surfaces, Gristina noted that progression to clinical infection in biomaterial-related disease may involve the maturation of an inoculum of pathogens to a septic focus of adhesive, virulent organisms.¹⁶ More recently, direct microscopic examination and

indirect techniques (eg, culturing following hardware sonication) have supported the hypothesis that biofilm formation is a major cause of PJI.²

Figure 1 shows scanning electron microscopy images illustrating surface colonization and biofilm formation on the surface of a commercially available bone void filler with *Staphylococcus epidermidis*. Surface colonization can be observed at 24 and 48 hours (indicated by white arrows), with extensive microcolony and biofilm formation observed at 7 and 14 days.

Figure 1 – Colonization of MRSA



Maturation

Structurally, a biofilm is a complex microbial community in which bacteria are embedded in a layer of sugars and proteins. Biofilms tend to form in the following stages.^{2,17}

1. Free-floating planktonic bacteria attach to a surface (eg, implant components, cement, bone, and/or periprosthetic tissue).
2. The bacteria multiply, become more firmly attached, and form micro-colonies.
3. The bacteria in these micro-colonies secrete a protective extracellular matrix made up of polysaccharides, extracellular deoxyribonucleic acid (DNA), and proteins. It can recruit and increase the adhesion of other microbes in the vicinity. Only 15% of the total mature biofilm is cellular, as the matrix components make up a large majority of the total biomass. The close proximity of these bacterial cells, their high density, and limited transport through the biofilm creates an environment conducive to a form of cell-to-cell communication known as “quorum

sensing,” a regulatory mechanism that allows bacteria to modify gene transcription based on cell density.

4. As the biofilm grows and matures, the bacteria on the outside of the biofilm consume the available nutrients (eg, oxygen and glucose), leaving the center of the biofilm relatively devoid of these nutrients. These centrally situated bacteria become metabolically inactive, entering a dormant “persister” state. Because of their lack of metabolic activity, these persister cells can survive exposure to high levels of antibiotics.
5. In addition to its role in the developing biofilm, quorum sensing can play a role in the detachment of bacteria from a mature biofilm in order to spread infection within the host. This coordinated dispersal is thought to allow bacteria to colonize new surfaces once nutrients and space have been depleted.

A typical timeline for the development and maturation of a biofilm is outlined in Table 2.

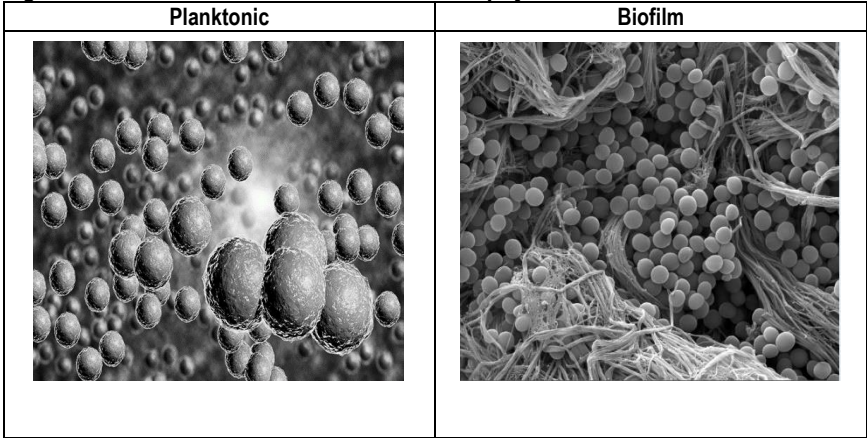
Table 2 – Timeline for Biofilm Development and Maturation

	Timeline
Free-floating planktonic bacteria attach to the implant	minutes
Firmly attached microcolonies form	2-4 hours
Extracellular matrix develops	6-12 hours
Fully mature biofilm colonies entering a dormant “persister” state	2-4 days
Biofilm re-forms after dispersion	24 hours
Source: Fehring TK, Odum SM, Berend KR, et al. Failure of irrigation and debridement for early postoperative periprosthetic infection. <i>Clin Orthop Relat Res.</i> 2013;471(1):250-257.	

Biofilms may be present on prosthesis components, surface tissue, subsurface tissue or joint fluid and can migrate among these locations. If bacteria in one niche are eradicated by debridement or antibiotic therapy, there is still potential for repopulation of pathogens from the other locations.²

Figure 2 shows planktonic and biofilm forms of *Staphylococcus aureus* under a microscope. The left image shows unicellular free-floating *S. aureus* which is seen in the early stages of infection. There is no structural organization between the individual cells as well as no development of chemical gradients and accompanying microniches.⁵ The image on the right is *S. aureus* bacteria visible in collagen matrix with some bacteria-produced extracellular matrix. This biofilm matrix offers protection as well as provides an organizing scaffold, which can facilitate the metabolic activity and even communication between its members within.⁵

Figure 2 – Planktonic and Biofilm Forms of *Staphylococcus aureus*



Resistance to Antibiotics

In a biofilm, bacteria can tolerate antibiotics at concentrations that are orders of magnitude greater than that needed to kill planktonic bacteria.⁵ The biofilm protects bacteria against antibiotics in three ways:^{2,3}

- Its material properties. The polysaccharide network in the extracellular matrix has local negative charges that can interact with positively charged regions of antibiotics and prevent them from affecting the bacteria. Extracellular DNA also plays a major role in the organization and transfer of genes that confer antibiotic resistance within the biofilm. In addition, the polymers that make up the extracellular matrix can bind to and thereby deactivate antibiotic molecules.
- Its ability to avoid the body's immune defenses. Evidence indicates that biofilms provide resistance against both the antibodies of the adaptive immune system and the neutrophils and macrophages of the innate immune response.³
- The ability of persister cells to avoid antibiotics. The metabolically dormant persister cells that exist inside the biofilm may allow for survival and repopulation after antibiotics eliminate the majority of other biofilm bacteria.

Acute vs. Chronic PJI

PJI may be classified as acute or chronic. For example, according to one classification scheme used by Segawa et al in a retrospective study of infected total knee arthroplasty:^{5, 18}

- Early acute postoperative PJI occurs within four weeks after the index procedure, usually accompanied by pain, poor healing, erythema, and prolonged wound drainage.
- Late acute PJI may occur years after surgery, at the site of a previously well-functioning joint replacement. Late acute infections are thought to result from the hematogenous spread of infection from another location in the body. They are accompanied by acute onset of pain, erythema, and joint effusion.
- Late chronic PJI occurs more than four weeks postoperatively. It is often more indolent, and chronic pain may be the only clinical symptom.

Another classification scheme was popularized by Tsukayama in the 1990s^{19,20} which divides PJIs into four categories, based partly on the time elapsed since the operation and also on the presumed mode of infection.¹¹

- The first category is positive intraoperative cultures, in which a patient undergoing revision for presumed aseptic failure is found to have a positive intraoperative culture. Some patients falling into this category do not truly have PJI. For example, in one paper using this classification scheme, only 1 out of 31 patients with this type of infection had acute inflammation determined by histopathology.¹⁹
- The second category is an early postoperative infection that occurs within the first month after surgery.
- The third category is late chronic PJI, which occurs >1 month after the index operation and is typically associated with an insidious clinical course.
- The final category of infection is acute hematogenous infection. This classification scheme is useful in determining medical and surgical management. Both early postoperative infection and acute hematogenous infection may be amenable to a debridement and implant retention procedure, while a two-stage revision arthroplasty would be preferable for late chronic infection.

Whether the infection is acute or chronic influences its treatment. Acute infection has been treated with irrigation and debridement with or without joint replacement. For chronic infections, the two-stage revision arthroplasty procedure is considered the gold standard with success rates of 80-100%. It should be noted that a chronic infection involves biofilm which needs to be removed or the two-stage revision arthroplasty procedure will fail.⁵

In general, early infections are typically caused by high-virulence bacteria, while those that develop later tend to be caused by low-virulence bacteria.²

RISK FACTORS

A 2017 review by Eka and Chen identified multiple medical risk factors that may predispose a patient to PJI, including:

- morbid obesity,
- uncontrolled diabetes mellitus,
- smoking,
- malnutrition,
- hyperglycemia,
- rheumatoid arthritis,
- preoperative anemia,
- cardiovascular disorders,
- chronic renal failure,
- alcohol abuse, and
- depression.

It is important that each of these underlying factors be evaluated and optimized prior to joint replacement surgery. For example, in people with diabetes, blood glucose control should be improved when possible. Smoking cessation should be strongly encouraged, and infections at other body sites should be diagnosed and managed prior to surgery.¹⁴

PREVENTION

As with any infection, prevention is the preferred control option. Prevention of PJI focuses on infection-control measures in the operating room environment, the use of prophylactic antibiotics, and refinements to the implants themselves.

Environmental Controls

The first line of defense against PJI is infection control in the operating room environment. Measures taken to protect the sterile field include, but are not limited to:²

- use of high-efficiency particulate air (HEPA)-filtered air handling;
- limiting personnel and traffic in the operating room;
- use of “spacesuit” scrubs (see Figure 3);
- skin disinfection;
- use of surgical drapes; and
- limiting number of door openings.

Figure 3 – Spacesuit Scrubs



Prophylactic Antibiotics

Prophylactic antibiotics can be an effective method for reducing the likelihood of infection following surgery, but their window of effectiveness is narrow. It has been reported that antibiotics are not beneficial if they are given less than 30 minutes before incision.²

Implant Characteristics

Strategies to prevent the development of biofilms by modifying the surface or other characteristics of implanted materials continue to evolve.³

- In the past, materials scientists examined the propensity of implants to become infected based on bulk composition, surface topography, and implant dimensions.
- Currently, promising strategies involve antibiotic incorporation and delivery via various carriers, including protein-based materials, bone graft-based materials, and polymer-based materials.
- As antibiotic resistance becomes more common, future strategies may involve new dispersal agents, bacteriophage-releasing materials, surface modifications and coatings, and bacterial interference approaches.

DIAGNOSIS

In most medical settings, diagnosis of infection involves the isolation of an infecting organism from tissue or fluid that is cultured in a broth or on a solid growth medium. Once isolated, the pathogen can be identified and the sensitivity of the pathogen to various antimicrobial agents can be determined. The sensitivity of a bacterium to an antibiotic is described in terms of the antibiotic's minimum inhibitory concentration

(MIC)—the concentration of that antibiotic required to inhibit visible growth of that particular pathogen.

In most cases, this approach is effective. However, biofilm bacteria generally do not culture well using traditional techniques.⁵ In multiple studies, *in vitro* culturing of bacteria detected biofilms only 30% of the time, compared with 80% to 90% using histology and microscopy.¹

Often, chronic periprosthetic infection has to be diagnosed using indirect methods that are basically measures of the immune response to the infection rather than a direct identification of the infecting organism. Such methods may include:⁵

- erythrocyte sedimentation rate,
- C-reactive protein level,
- synovial fluid cell count,
- synovial fluid neutrophil percentage, and
- analysis of leukocyte esterase levels in aspirated fluid.

In addition, recent studies have used molecular methods that involve polymerase chain reaction (PCR) amplification and sequencing of a nucleic acid mix isolated from clinical samples using either microbe-specific or broad-range primers, often derived from bacterial 16S recombinant DNA (rDNA) sequences. This approach can allow for the simultaneous identification of multiple microbes and has shown several advantages over cultures alone.²

In 2018, the Musculoskeletal Infection Society (MIS) published diagnostic criteria for PJI. Two positive cultures or the presence of a sinus tract are considered major criteria and diagnostic of PJI. Other diagnostic criteria are each assigned a numerical score, as detailed in Table 3. Patients with an aggregate score of 6 or greater in steps 1 and 2 are considered infected, while a score of 2 to 5 requires the inclusion of intraoperative findings to confirm or refute the diagnosis.²¹

Table 3 – MIS Criteria for PJI

Step	Criterion	Score
Step 1		
	Serum C-reactive protein >1 mg/dL	2
	Serum D-dimer >860 ng/mL	2
	Serum erythrocyte sedimentation rate >30 mm/h	1
Step 2		
	Synovial white blood cell count >3000 (cells/ μ L)	3
	Synovial alpha-defensin	3
	Synovial leukocyte esterase (++)	3
	Synovial polymorphonuclear % >80%	2
	Synovial C-reactive protein >6.9 mg/L	1
Step 3	(intraoperative findings)	
	Histology	3
	Purulence	3
	Single culture	2
Source: Parvizi J, Tan TL, Goswami K, et al. The 2018 definition of periprosthetic hip and knee infection: An evidence-based and validated criteria. <i>J Arthroplasty</i> . 2018;33(5):1309-1314 e1302.		

TREATMENT

The goal of treating PJI is a pain-free, functional joint. This can best be achieved by eradication of the infection. A combination of various therapeutic approaches have been used, including:⁵

- systemic antibiotics,
- irrigation and debridement with component retention;
- irrigation and debridement with removal of the prosthetic components and the immediate placement of new components (a single-stage exchange); and
- irrigation and debridement with removal of the prosthetic components, placement of an interim antibiotic cement spacer, and placement of new prosthetic components, usually weeks to months later (a two-stage revision arthroplasty).

The optimal treatment approach depends on whether or not a bacterial biofilm is present.⁴

- In an acute infection, before a biofilm is established, treatment focuses on implant preservation, with radical debridement, modular bearing exchange, copious lavage with antibiotic solution, and systemic antibiotic therapy.
- When a biofilm is present, the infection is considered chronic. Because the biofilm impedes the eradication of bacteria, implants must be removed, along with radical debridement of bone and soft tissue. Resection of implants most commonly is performed in a two-stage revision arthroplasty protocol. At some centers that focus on PJI, one-stage protocols may be utilized.

Treatment approaches vary between surgeons and can involve physician-directed applications. Physician-directed application refers to use of a medical product in a manner that is not specified in the labeling approved by the Food and Drug Association (FDA) for that particular indication.²² It is the responsibility of the physician to be well informed about the product, and the scientific basis and medical evidence for such usage.¹⁹ Patients need to be informed of alternative treatments and to provide consent.¹⁹ In addition, institutions/facilities may have policies which govern the use and documentation of physician-directed application of prescription drugs, biologics and medical devices.²²

Systemic Antibiotics Alone

Curative antibiotic treatment alone is sometimes attempted, but it is not recommended. Nonsurgical management should be considered only for patients who are unable to undergo a surgical procedure (eg, due to multiple comorbidities) or are unwilling to undergo surgery and who have a well-fixed prosthesis and infection with microorganisms that are susceptible to oral antibiotics.¹⁴

Once a patient develops a PJI that cannot be cleared by antibiotic therapy, the only viable course of action may be to irrigate and debride the area, often with removal and replacement of the affected implant.²

Irrigation and Debridement with Component Retention

Irrigation and debridement (I&D) entails reopening the joint through the original incision, removal of unhealthy tissues, thorough lavage with antibiotic-laden saline, and exchange of modular components, while retaining fixed components. Most clinicians use intravenous antibiotics for the first two to six weeks following the procedure.¹⁴

I&D with component retention is a time-honored procedure for dealing with orthopedic surgical-site infections. It can be successful if the infection is treated quickly enough so that a biofilm either has not been established on the prosthesis or the biofilm is adequately removed from the prosthesis. It also assumes that other infected tissue has been adequately debrided.⁵ Unfortunately, I&D does not satisfactorily control arthroplasty-related infections in more than two-thirds of patients.¹⁴ The literature has also documented its inability to control chronic infections (100% failure rate), infections caused by resistant organisms (89% failure rate), and even infections from susceptible organisms such as *Streptococcus* (69% failure rate).¹⁴

Multiple surgical debridements followed by long-term parenteral antibiotics are often required for effective therapy. However, high concentrations of long-term parenteral antibiotics are frequently required, which can lead to unwanted side effects and systemic toxicity, as well as further pathogenic resistance.²³

One-Stage Revision Arthroplasty

For a one-stage revision, the prosthesis is removed, and a new device is implanted during the same procedure. One-stage arthroplasty exchange procedures are less frequently performed in the United States than two-stage arthroplasty exchanges. Open arthrotomy and debridement are performed, followed by complete removal of the prosthesis and any polymethylmethacrylate (PMMA) present. Aggressive debridement in

the hands of a skilled surgeon is critical. A new device is implanted during the same procedure, typically using antimicrobial-loaded PMMA to fix the new implant in place.¹⁴

The most commonly used antimicrobial strategy for a one-stage arthroplasty exchange includes 4 to 6 weeks of intravenous (IV) therapy antibiotics, followed by 3 to 12 months of oral antibiotics.⁹

In general, a one-stage arthroplasty exchange offers results comparable to those of a two-stage exchange and is superior to I&D.¹⁴

Two-Stage Revision Arthroplasty

Two-stage revision arthroplasty procedures have generally been considered the gold standard in the US for treatment of chronic PJI after THA or TKA.⁵ These two-stage procedures often include the use of adjunct materials, such as antibiotic-loaded PMMA bone cement or calcium sulfate bone grafts, to help improve surgical outcomes.

In the first surgery, cultures are obtained, all infected tissue is debrided, and prosthesis components and PMMA are removed. The two-stage procedure typically requires the use of a spacer to maintain the joint space that results after prosthesis and PMMA removal. The product of choice with regards to spacer material use will vary according to product availability within the facility, surgeon preference as well as the condition of the patient. Some examples of spacer materials include PMMA cement and antimicrobial-impregnated PMMA cement.

Pathogen-directed antimicrobial therapy is usually given intravenously for 4 to 6 weeks after the first stage, followed by at least a 2- to 6-week antibiotic-free time period, during which the patient is evaluated for any signs of ongoing infection. When there is no evidence of ongoing infection, the second-stage of the revision can be performed. In the second surgery, the spacer is removed, a new prosthesis is implanted, and synthetic bone grafts are utilized as needed to fill remaining dead space. Patients are often treated with IV antibiotics until the reimplantation culture is negative.¹⁴

Reported success rates for two-stage revision hip and knee arthroplasty procedures range from 87-100% and 72-95%, respectively.¹⁴

PMMA Bone Cement

For many years, the controlled release and local delivery of antibiotics from a carrier which can be loaded with single or multiple antibiotics, has formed part of a surgeon's treatment plan. During two-stage revision arthroplasty procedures, an antibiotic-impregnated cement spacer is often implanted prior to closure to maintain the joint space that results after removal of the prosthesis, while also providing a high local concentration of antibiotics with low serum levels.⁴ Local delivery can also help to minimize problems with systemic toxicity and avoid wasting expensive antibiotics.³ One of the most widely adopted materials for local release of antibiotics is PMMA bone cement.²³ PMMA beads have also been used to pack into wounds as an antimicrobial delivery system.² It is important to follow the manufacturer's instructions for use with regards to all products used on patients during a surgical procedure.

PMMA cement spacers or beads for local release of antibiotics at the surgical site have demonstrated a significant reduction in infection rates in THA and TKA.¹⁵ Antibiotic-loaded PMMA provides weight bearing strength and offers advantages compared to systemic antibiotic therapy.²³

However, PMMA is a dense and non-resorbing material and a second surgery is generally required for removal. PMMA is also not suitable for delivery of thermosensitive antibiotics due to high temperatures generated during curing.²³ The literature has documented that antibiotic release from PMMA quickly falls below the MIC, creating a selection pressure that may cause multi-drug resistant organisms to predominate, and if prolonged, PMMA itself may become colonized with biofilm on its surface.²⁴ Furthermore, the addition of antibiotics to commercially available cements and the mixing procedure itself can affect the microstructure of the cement, which in turn influences its mechanical properties and elution characteristics.²

Calcium Sulfate Bone Grafts

Calcium sulfate, an inorganic, naturally occurring compound with the formula CaSO_4 , has been used as a bone graft material since 1892.²⁴ Calcium sulfate products for use in orthopedic surgery have evolved from first-generation natural materials to today's medical grade synthetic products. Synthetic calcium sulfate is used to fill bone voids and defects in a variety of clinical applications, including two-stage revision arthroplasty procedures.

Synthetic calcium sulfate products are naturally absorbed and biodegrade completely. They do not require a second procedure for surgical removal and do not provide a permanent artificial surface for bacterial colonization.²

Because synthetic calcium sulfate products dissolve relatively quickly, they are not present for long enough to provide any significant long-term mechanical support.¹⁸

SUMMARY

Artificial joints improve the quality of life for many patients, but insertion of any device into the body carries a risk of infection.³ Nearly a million total hip and total knee arthroplasties are performed annually in the US, and that number is expected to rise in the near term with the aging of the population.² The evidence increasingly points to bacterial biofilms as the underlying cause of PJI, and traditional approaches have been unsatisfactory in eradicating infection once an organized biofilm is established.

The treatment choice continues to be two-stage revision surgery, although alternative and complementary strategies continue to be explored to improve the outcomes of revision surgery.

GLOSSARY

Biofilm	A colony of bacteria in which the cells stick to each other and often also to a surface. These adherent cells become embedded within a slimy extracellular matrix composed of extracellular polymeric substance.
Debridement	The removal of dead, damaged, or infected tissue to improve the healing potential of the remaining healthy tissue.
Hematogenous Spread	Distribution via the bloodstream.
Minimum Inhibitory Concentration (MIC)	The lowest concentration of an antibacterial agent necessary to inhibit visible growth.
Osteomyelitis	Infection in a bone.
Periprosthetic Joint Infection (PJI)	The invasion and multiplication of microorganisms involving an orthopedic implant and adjacent tissue.
Persister Cell	A bacterial cell in a dormant state that survives killing by antibiotics; persister cells usually comprise about 1% of the bacterial cells in a biofilm.
Planktonic Bacteria	A microorganism that is free-flowing in suspension, as opposed to being sessile in a biofilm.
Polymethylmethacrylate (PMMA)	A synthetic, self-curing acrylic material used as a bone cement to fill up a cavity or create mechanical fixation.

Quorum Sensing

The ability of bacteria to detect and to respond to cell population density by gene regulation.

REFERENCES

1. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. *J Arthroplasty*. 2012;27(8 Suppl):61-65 e61.
2. McConoughey SJ, Howlin R, Granger JF, et al. Biofilms in periprosthetic orthopedic infections. *Future Microbiol*. 2014;9(8):987-1007.
3. Shah SR, Tatara AM, D'Souza RN, Mikos AG, Kasper FK. Evolving strategies for preventing biofilm on implantable materials. *Materials Today*. 2013;16(5):177-182.
4. McPherson EJ, Dipane MV, Sherif SM. Dissolvable antibiotic beads in treatment of periprosthetic joint infection and revision arthroplasty: The use of synthetic pure calcium sulfate (Stimulan(r)) impregnated with vancomycin & tobramycin. *Reconstructive Review*. 2013;March 2013:32-43.
5. Arnold WV, Shirliff ME, Stoodley P. Bacterial biofilms and periprosthetic infections. *J Bone Joint Surg Am*. 2013;95(24):2223-2229.
6. Premkumar A, Kolin D, Farley KX, Wilson JM, McLawhorn S, Cross M, Sculco K. Projected Economic Burden of Periprosthetic Joint Infection of the Hip and Knee in the United States. *The Journal of Arthroplasty* online December 9, 2020. <https://doi.org/10.1016/j.arth.2020.12.005>.
7. Zmistowski B, Karam JA, Durinka JB, Casper DS, Parvizi J. Periprosthetic joint infection increases the risk of one-year mortality. *J Bone Joint Surg Am*. 2013;95(24):2177-2184.
8. American Cancer Society. Cancer facts and figures 2020. - <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf>. Accessed February 8, 2021.
9. Zawadzki N, Wang Y, Shao H, et al. Readmission due to infection following total hip and total knee procedures: A retrospective study. *Medicine (Baltimore)*. 2017;96(38):e7961.
10. Patel H, Khoury H, Girgenti D, et al. Burden of surgical site infections associated with arthroplasty and the contribution of staphylococcus aureus. *Surg Infect (Larchmt)* 2016;17:78-88.
11. Anderson DJ, Kaye KS, Chen LF, et al. Clinical and financial outcomes due to methicillin resistant staphylococcus aureus surgical site infection: a multi-center matched outcomes study. *PLoS One*. 2009 Dec 15;4(12):e8305. doi: 10.1371/journal.pone.0008305
12. Hospital Readmissions Reduction (HRRP) CMS <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program->. Accessed February 8, 2021.

-
13. CMS BPCI Advanced. <https://innovation.cms.gov/innovation-models/bpci-advanced>. Accessed February 8, 2021.
 14. Tande AJ, Patel R. Prosthetic joint infection. *Clin Microbiol Rev*. 2014;27(2):302-345.
 15. Howlin RP, Brayford MJ, Webb JS, Cooper JJ, Aiken SS, Stoodley P. Antibiotic-loaded synthetic calcium sulfate beads for prevention of bacterial colonization and biofilm formation in periprosthetic infections. *Antimicrob Agents Chemother*. 2015;59(1):111-120.
 16. Gristina AG. Biomaterial-centered infection: microbial adhesion versus tissue integration. *Science*. 1987;237(4822):1588-1595.
 17. Fehring TK, Odum SM, Berend KR, et al. Failure of irrigation and debridement for early postoperative periprosthetic infection. *Clin Orthop Relat Res*. 2013;471(1):250-257.
 18. Segawa H, Taukayama DT, Kyle RF, Becker DA, Gustilo RB. Infection after total knee arthroplasty: A retrospective study of the treatment of eighty-one infections. *J Bone Joint Surg Am*. 1999 Oct; 81(10):1434-45.
 19. Tsukayama DT, Estrada R, Gustilo RB. 1996. Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. *J. Bone Joint Surg. Am*. 78:512–523 [PubMed]
 20. Tsukayama DT, Goldberg VM, Kyle R. 2003. Diagnosis and management of infection after total knee arthroplasty. *J. Bone Joint Surg. Am*. 85(Suppl 1):S75–S80. <https://pubmed.ncbi.nlm.nih.gov/12540674/>. Accessed February 4, 2021.
 21. Parvizi J, Tan TL, Goswami K, et al. The 2018 definition of periprosthetic hip and knee infection: An evidence-based and validated criteria. *J Arthroplasty*. 2018;33(5):1309-1314.
 22. AAOS American Academy of Orthopaedic Surgeons Position Statement Physician Directed Use of Medical Products. June 2009/revised February 2016. <https://www.aaos.org/about/bylaws-policies/statements--resolutions/position-statements/>. Accessed February 4, 2021.
 23. McConoughey SJ, Howlin RP, Wiseman J, Stoodley P, Calhoun JH. Comparing PMMA and calcium sulfate as carriers for the local delivery of antibiotics to infected surgical sites. *J Biomed Mater Res B Appl Biomater*. 2015;103(4):870-877.
 24. Ferguson J, Diefenbeck M, McNally M. Ceramic biocomposites as biodegradable antibiotic carriers in the treatment of bone infections. *J Bone Jt Infect*. 2017;2(1):38-51.

POST-TEST

Multiple choice/True or False.

Complete the test questions. Incorrect answers will offer the opportunity to re-read the question and answer choices. You may also revisit relevant content.

1. The effect that periprosthetic joint infections (PJIs) may have on patients and the healthcare system include:
 - a. Slightly lower mortality rates
 - b. Prolonged periods of lost function and time away from work
 - c. Cost savings to hospitals
 - d. Short-term exposure to antibiotics
2. Under the Hospital Readmissions Reduction Program (HRRP), the Centers for Medicare and Medicaid Services (CMS) can penalize US hospitals up to 3% of their Medicare Part A payments for higher-than-expected readmissions for total hip arthroplasty (THA) and total knee arthroplasty (TKA).
 - a. True
 - b. False
3. Which of the following is NOT considered a risk factor for PJI?
 - a. Morbid obesity
 - b. Prior joint surgery
 - c. Uncontrolled diabetes mellitus
 - d. Smoking
4. The majority of PJIs are associated with:
 - a. Gram-positive cocci
 - b. Gram-negative cocci
 - c. Bacilli
 - d. Viruses
5. Bacteria in a biofilm are protected by:
 - a. The material properties of the extracellular matrix
 - b. The biofilm's ability to evade the body's immune defenses
 - c. The existence of dormant persister cells inside the biofilm
 - d. All of the above

-
6. Cell-to-cell communication in a biofilm based on cell density is known as:
 - a. Quorum detection
 - b. Quorum sensing
 - c. Quota sensing
 - d. Persister evasion
 7. Biofilm bacteria generally are easy to identify using traditional laboratory culturing techniques.
 - a. True
 - b. False
 8. In multiple studies, biofilm bacteria *in vitro* culturing detected biofilms only ____ of the time compared to compared with 80% to 90% using histology and microscopy.
 - a. 51%
 - b. 2%
 - c. 30%
 - d. 75%
 9. Irrigation and debridement can be a successful approach to PJI if:
 - a. The infection is treated quickly and a biofilm has not been established
 - b. The organism is identified as one that is susceptible to antibiotic therapy
 - c. Long-term suppressive antibiotics are used
 - d. I&D is never an effective approach for PJI
 10. Chronic infections:
 - a. Develop later than acute infections
 - b. Have an established biofilm
 - c. Are harder to treat than acute infections
 - d. All of the above
 11. For chronic PJI with biofilm formation, the most common treatment approach is:
 - a. Nonsurgical treatment with systemic antibiotics only
 - b. Irrigation and debridement with implant retention
 - c. A single-stage exchange
 - d. A two-stage exchange

-
12. Antibiotic-loaded polymethylmethacrylate (PMMA) provides all of the following EXCEPT:
- a. Provides weight-bearing strength
 - b. Shows significant decrease in infection rates
 - c. Is suitable for thermosensitive antibiotics
 - d. Provides local delivery of antibiotics
13. Infection control measures include:
- a. Use of high-efficiency particulate air
 - b. Skin disinfectant
 - c. Limiting personnel and traffic in the operating room
 - d. All of the above

POST-TEST ANSWERS

1. b
2. a
3. b
4. a
5. d
6. b
7. b
8. c
9. a
10. d
11. d
12. c
13. d