# The Connection

Oct 2017

**Inside this issue:**


| | |
|---|---|
| *National Meeting by Luke Huff Towle* | 2 |
| *Region V info* | 3 |
| **Prosthetic Joint Infection** | 4 |
| *2022-23 Developing Professional* | 6 |


## President's Message

Hello everyone, I would like to introduce myself. I am Sharon Reistad, ASCLS-ND president for 2022-23. I am honored to serve you. I retired from the UND Center for Family Medicine in 2019. I live in Minot with my husband, Art (who is also retired). I have 2 fabulous boys who will be 34 in Nov. and an amazing daughter in law. One son lives here in Minot and the other, with his wife, live in Florida. I have 4 grand kitties and a grand dogder. I love them all.

There are many changes coming in the next year. At the Joint Annual Meeting (JAM) the House of Delegates voted to remove the "regional" from the directorship. What this means is the board of directors will no longer be made up of one director from each region. It will still be made up of 10 directors, but they can be from any region. Also decided by the Board of Directors, the only requirement for being a director is to have been a member of ASCLS for 5 consecutive years. There is still a lot of unanswered questions about how this will all work but they are working on it.

We also want to work on expanding our membership. Talk to you co-workers, MLS and phlebotomy friend about becoming a member of ASCLS.

I will keep everyone updated on changes as I find out about them. If you have any questions, concerns, or ideas please contact me.

Here is to a great year. Sharon Reistad sreistad@srt.com

# MY FIRST JAM

## By Luke Huff Towle
## Ascending Professional

2022 Joint Annual Meeting (JAM)

I recently had the wonderful experience of attending the 2022 JAM in Grand Rapids, Michigan. This is the annual meeting for laboratory science and was attended by members of three organizations: American Society for Clinical Laboratory Scientists (ASCLS), Association of Genetic Technologists (AGT), Society of American Federal Medical Laboratory Scientists (SAFMLS). As a first time attendee, I was not sure exactly what I was getting myself into. It was a mixed format where both in-person and virtual attendees were present. The conference was five days and consisted of networking events, continuing education seminars, and a rather lengthy and contentious House of Delegates session.

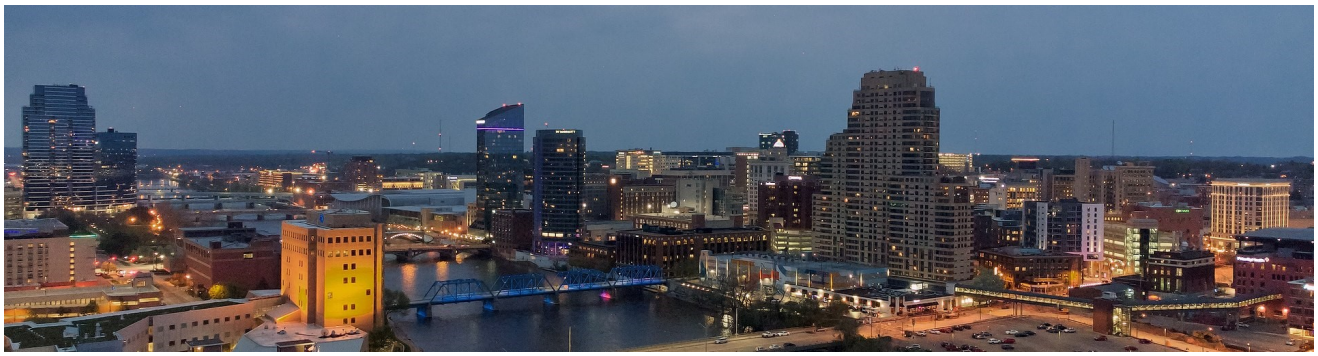
The work for this meeting did not begin on the day it began. My first ASCLS meeting was the pre-JAM Region V meeting. Here I got to meet many new faces and see the passions and ideas about the upcoming topics in the House of Delegates. After this, we held a North Dakota meeting to finalize what we thought of the proposed changes. It was at this meeting where I truly got to see how important the work of ASCLS-ND is. We discussed the changes and how they might affect us and our state. Once that was sorted, all we had left was to fly to Michigan.

My initial impression as I met up with Region V in Minneapolis was how quickly and seamlessly I was accepted into the group. As someone who is new to ASCLS, this was somewhat of a concern for me as I think it would/will be for others looking to join. North Dakota, Region V, and all the other laboratorians I met over that week were helpful, insightful, and very excited to help me on my journey of laboratory medicine. This was especially true once I reached the conference. The first day, I attended the Ascending/Developing Professionals forum. At this, I met other first time attendees who were in the same place as me career-wise. We were all new and some of us were still students. This was extremely important for me as most people I met in Michigan have been active in ASCLS for many years and already knew everyone. This meeting provided an early way of getting to know people. I ended up attending most of the continuing Education (CE) seminars with my table from that forum and are still in contact with them in a group chat. They have helped me with ideas coming from the perspective of a student and I have been able to assist them in the transition from student to professional. I also had the pleasure of meeting many experienced professionals including professors, past presidents, board members, supervisors. They had all been where I was at one point. I got invaluable advice on steps to negotiate contracts, how to manage and lead, how to move into different roles, and how to move the profession forward. While there were many facets to the conference, the networking was the most important to me.

The CE seminars were fantastic. Not only did I gain valuable knowledge ranging from up and coming technologies to how to lead a multigenerational team, I pretty much covered my ASCP and ND ASCLS license renewals coming up. These seminars provided a great learning environment and invited questions that could be asked directly to a knowledgeable source. The talks also prompted discussions and gave me different perspective to consider and grow from.

The last day of the conference was the House of Delegates meeting. This four hour meeting (which I later learned is never quite four hours in length) consist of the voting delegates, in-person and virtual, from every state. Here, we were given an update on ASCLS as an entity. After this, we moved into the proposed changes. It was here where I was able to witness the intense passion laboratory professionals have for our field. Regardless of how any members' stance on an issue, they always spoke with how they felt a change might benefit or harm our ability to provide our essential role to the healthcare team. I was interesting and informative to see how the rules and laws of ASCLS are set and how those inform and affect our profession.

I learned a great deal about my profession and how it works at the 2022 JAM. I met many incredible people from my state, region, and across the United States. I made important connections that will help me become a better Labradorian. I look forward to hopefully attending next year's meeting in Providence, Rhode Island and would encourage everyone, and especially students and new grads, to attend as well.



Grand Rapid, Michigan

# 2022 Region V Symposium "WILD UP NORTH"

**Mark YOUR Calendars !**

Calling All Clinical Laboratory Professionals and Industry Partners!
Mark your 2022 Calendars Region V
2022 Fall Symposium
Hosted by ASCLS -MN, ASCLS-SD, ASCLS-ND & ASCLS-WI
Save the Date!
September 29-30, 2022
Mayo Health Event Center
1 Civic Center Plaza
1-507-389-3000
Mankato Minnesota

We invite you to join us in-person
"WILD UP NORTH"
Where laboratory students and professionals meet industry partners for Education, Networking, and Entertainment!

Region V of the American Society for Clinical Laboratory Science is comprised of the state constituent societies that includes:

ASCLS Minnesota
ASCLS North Dakota
ASCLS South Dakota
ASCLS Wisconsin

*ASCLS Region V* embraces the mission of ASCLS for our Region, our States, but most importantly our member

# Prosthetic Joint Infection

Katie Riese
arch 31, 2022

MLS 515 Capstone in Medical Laboratory Science

Instructor: Mary Coleman

## OBJECTIVES

After reading this paper, the reader should be able to:

1. State the growing healthcare burden of prosthetic joint infections.
2. Discuss the clinical features, pathogenesis, and microbiology of prosthetic joint infections.
3. Outline the criteria for the diagnosis of prosthetic joint infections and discuss laboratory testing used to achieve this diagnosis.
4. Identify strategies to improve detection of the causative microorganism(s) in culture-negative prosthetic joint infections.
5. Briefly discuss treatment of prosthetic joint infections.

## INTRODUCTION

Prosthetic joint infection (PJI) is a devastating complication of joint arthroplasty surgeries, a significant challenge for physicians, and a tremendous burden to public healthcare.[1] Although PJI occurs in only a small fraction of joint arthroplasty cases, the incidence of PJI is predicted to increase in the future proportionate to the growing demand for joint arthroplasty surgeries.[2] Diagnosis and identification of the causative microorganism(s) are key to effectively managing PJIs and improving patient outcomes.[1] Culture-negative PJI (CN-PJI) represents a particular diagnostic challenge.[3] However, new testing strategies hold promise to improve the diagnosis of PJIs.

## DISEASE OVERVIEW

### Epidemiology

Joint arthroplasty surgeries are frequently performed procedures that improve quality of life for patients by providing pain relief and restoring function to affected joints.[1] Millions of joint arthroplasties are performed worldwide each year. In the U.S. alone, 2.5 million individuals were living with total hip arthroplasty (THA) and 4.7 million individuals were living with total knee arthroplasty (TKA) as of 2010. Together these numbers represent

over 2% of the U.S. population.[4] Furthermore, the incidence of joint arthroplasties is predicted to rise substantially in the future as the population ages and demand for surgery to improve mobility and quality of life grows.[4]

While joint arthroplasty surgeries have high success rates, complications do occur. In 2014, 50,220 revision THAs and 72,100 revision TKAs were performed in the U.S. to remediate failures of primary arthroplasties.[5] Infection ranks as the most common cause of failure requiring surgical revision in TKA and the third most common cause in THA.[5,6] One study estimated the combined rate of PJI within two years of primary TKA and THA surgeries to be 1.5% for U.S. patients.[7] Another study, which analyzed Medicare inpatient data from 2005-2015, found the risk of PJI within five years of primary TKA and THA surgeries to be 1.38% and 1.09%, respectively.[2] The study further showed no substantial decline in incidence of PJI over time. Therefore, PJI incidence is expected to continue to rise in the U.S. proportionate to the growing demand for TKA and THA surgeries.[2,5]

PJI is a tremendous burden for individual patients, as well as for the healthcare sector. Patients with PJIs experience lower health-related quality of life than patients with uncomplicated arthroplasties and do not return to the functionality enjoyed by their un-infected counterparts.[8] PJI is also associated with a 5-year mortality rate higher than that of melanoma, breast cancer, and Hodgkin's lymphoma.[2] The financial burden of PJI is significant as well. By 2030, the combined annual hospital costs of TKA and THA PJIs in the U.S. is estimated to be $1.85 billion.[9]

Several factors increase patients' risk of developing PJIs. Patient factors include obesity, diabetes, heart disease, male gender, tobacco use, and malnutrition.[2,8,10] Surgical factors associated with increased risk of PJI are previous surgery on the joint, longer length of hospital stay, and preoperative administration of high dose steroids.[2,10]

**Clinical Presentation and Classification**

Common signs and symptoms of PJIs include pain, swelling, erythema, warmth around the joint, fever, drainage, and the presence of a sinus tract communicating with the surgical site. However, clinical presentation and timing of PJI depends on a variety of factors, including the mode of initiation of infection, the virulence of the organism, the host immune response, and the joint involved.[1]

PJIs are commonly classified as early, delayed, or late-onset based on the time from the last surgery to manifestation of the infection. Early-onset PJI occurs within three months of surgery. Patients present with pain, edema and effusion, wound drainage, and erythema around the surgical site.[8] Early-onset PJI is typically initiated through intraoperative contamination and the causative organisms are relatively virulent.[1] Delayed-onset PJI occurs 3-12 (or 24, according to some authors) months after surgery. These infections are also usually acquired at the time of surgery, but the causative microorganisms are less virulent.[1,8] Persistent pain is a common symptom.[8] Finally, late-onset PJI occurs greater than 12 (or 24) months after surgery. Patients present with acute onset of symptoms in a joint that was previously asymptomatic.[8] Late-onset PJI is frequently initiated by hematogenous spread from another site, although it may also be due to a very indolent infection from the time of surgery.[1]

**Pathogenesis**

PJI can be initiated through three mechanisms: intraoperative contamination, contiguous spread from an adjacent site, and hematogenous seeding. The majority of PJIs are initiated at the time of surgery via direct contact or aerosolized contamination of the prosthetic device or periprosthetic tissue. The second mechanism, contiguous spread of infection, can occur in the early postoperative period when a superficial surgical site infection progresses to involve the prosthesis. Alternately, contiguous spread can also occur later if adjacent tissue is disrupted by trauma or surgery. Hematogenous seeding, although the rarest mechanism of PJI initiation, can occur any time after the prosthesis is placed. In most PJIs with hematogenous origin, bacteremia and symptoms of PJI occur together.[1]

A low inoculum of microorganisms is often sufficient to establish infection in the presence of a prosthetic implant. A study of hip arthroplasty in a rabbit model found that $<10^2$ CFU of *Staphylococcus aureus* were necessary to establish infection in the presence of an implant, while $10^4$ CFU were required to establish infection in the absence of an implant.[11] Another study found that the in vivo interaction between neutrophils and a foreign body, like a prosthetic implant, can induce a complex defect in neutrophils, thus increasing the host's susceptibility to infection.[12]

Once microorganisms are introduced into the periprosthetic site, they adhere to the surface of the prosthetic and begin to form a biofilm.[1,13] Biofilms are complex communities of microorganisms that form on surfaces, including prosthetic implants. Biofilm formation is a key virulence factor in PJIs as biofilms promote survival of microorganisms against antibiotics and the host immune system, allowing even traditionally non-pathogenic normal flora organisms to establish infection in the presence of a prosthetic implant.[1,14,15]

Biofilm growth occurs in four stages: adherence to the surface of the prosthetic, cell proliferation, biofilm maturation, and detachment and dissemination.[1,15] Some microorganisms possess species-specific mechanisms to facilitate biofilm growth. For example, *Staphylococcus* species express microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) on their cell surface, which play an important role in initiating attachment.[14,15] Once attached, microorganisms form microcolonies. As the initial cells in the microcolonies proliferate, they form an extracellular matrix composed of polysaccharides, proteins, and extracellular nucleic acids.[1,15] The extracellular matrix provides mechanical stability, prevents penetration of the biofilm by antimicrobial agents, and retains essential nutrients and enzymes for survival of the microorganisms.[13,15] Surrounded by the extracellular matrix, biofilms mature into complex, nonhomogeneous communities in which subpopulations of cells perform different functions and cells communicate with one another via quorum sensing.[1,13] Mature biofilms can also shed component microorganisms, allowing migration and dissemination to other sites in the body.[13]

Apart from the protective effects of the extracellular matrix, biofilms also promote immune evasion and pathogenesis by PJI-causing microorganisms. For example, *S. aureus* biofilms, harbor an extensive collection of proteins for immune evasion, such as leukocidins (lyse neutrophils, monocytes, and macrophages), staphylokinase (cleaves complement factor C3b), and nucleases (inactivate neutrophil extracellular traps). *S. aureus* biofilms also harbor virulence factors that promote pathogenesis, such as toxic shock syndrome toxin (TSST).[15] The summative effect of biofilm formation in

PJI is to create a persistent infection that is difficult to eradicate, either by the host immune system or clinical management. Indeed, surgical intervention including removal of the prosthesis is often required to achieve a cure.[1]

**Microbiology**

Many types of microorganisms have been implicated in PJI. The most common microorganisms in TKA and THA PJI are *S. aureus* (27%), coagulase-negative *Staphylococcus* (27%), aerobic Gram-negative bacilli (9%) and *Enterococcus* sp. (8%).[1] The majority of PJI cases are monomicrobial, although 10-15% are polymicrobial. *Staphylococcus epidermidis* is the most frequently detected microorganism in polymicrobial infections (59%), but *Enterococcus* sp. (28%) and other coagulase-negative *Staphylococcus* sp. (25%) are also common in polymicrobial PJI.[16] Anaerobic bacteria, mycobacteria, and fungi are infrequent causes of PJI; together they make up approximately 7% of TKA and THA PJI. *Cutibacterium acnes* is an important exception. While *C. acnes* is rare in TKA and THA PJI, it is found in 24% of shoulder PJI.[1]

The causative microorganism impacts the timing and course of PJI. More virulent, "typical pathogen" organisms predominate in early-onset PJI, while low virulence "normal flora" predominate in PJI cases with later onset. For example, *S. aureus* causes 27% of all TKA and THA PJI, but 38% of early-onset PJI. Similarly, while aerobic Gram-negative bacilli cause 9% of TKA and THA PJI over all time periods, they are responsible for 24% of early-onset PJI cases. *Enterococcus* sp. is most commonly detected in early-onset polymicrobial infections.[1] Furthermore, polymicrobial infections generally manifest symptoms sooner after surgery than monomicrobial infections.[16] On the other hand, low virulence organisms like coagulase-negative *Staphylococcus* and *C. acnes* PJI cases follow more indolent courses and commonly manifest as delayed- and late-onset PJI.[1]

Between 5-42% of PJI cases are culture-negative (CN-PJI).[1,3] Patients with CN-PJI have nonmicrobiological evidence of infection, such as a sinus tract communicating with the joint, acute inflammation determined by histopathology, elevated inflam-

**Alissa Volk**
**ASCLS ND Developing Professional for 2022-23**

matory biomarkers, or periprosthetic purulence, in the absence of an identified pathogen. CN-PJI may result from an inability to recover an organism in culture because of prior antimicrobial administration, inadequate culture media and protocols, or limitations of current diagnostic testing methods.[1,3] However, new strategies and diagnostic testing methods hold promise to improve the identification of the causative microorganism in CN-PJIs.

## DIAGNOSIS AND LABORATORY TESTING

### Diagnostic Criteria for PJI

The diagnosis of PJI can be challenging as no test exists with absolute accuracy. Therefore, the diagnosis of PJI requires a multi-disciplinary approach incorporating clinical findings, microbiological culture, laboratory testing from peripheral blood and synovial fluid, histological evaluation of periprosthetic tissue, and intraoperative findings.[1]

To standardize the diagnosis of PJI, the Musculoskeletal Infection Society (MSIS) created diagnostic criteria in 2011.[17] These criteria were updated in 2013, and again in 2018 to address limitations of the previous criteria, establish threshold values, and incorporate novel tests.[18,19] The 2018 criteria and threshold values are listed in Tables 1 and 2, respectively. These criteria were designed to allow clinicians to be confident in their diagnosis of PJI, but certain true infections with low virulence organisms may not meet the criteria.[19] For example, a study of *C. acnes* PJI found that only 26% of patients had an elevated erythrocyte sedimentation rate (ESR), 39% had an elevated C-reactive protein (CRP) level, and 17.8% had positive histology.[20] The criteria also have the limitation that they may provide an inconclusive diagnosis, in which case molecular testing may be considered.[19]

Table 1. 2018 Diagnostic criteria for PJI[19]

| **Major Criteria** | **Decision** | |
|---|---|---|
| Two positive cultures with the same organism | Infected if at least one is met | |
| Presence of a sinus tract with evidence of communication to the joint or visualization of the prosthesis | | |
| **Minor Criteria (Preoperative Diagnosis)** | **Score** | **Decision** |
| Elevated serum CRP or D-dimer | 2 | ≥6 Infected<br>2-5 Possibly Infected<br>0-1 Not Infected |
| Elevated ESR | 1 | |
| Elevated synovial WBC or LE | 3 | |
| Positive alpha-defensin | 3 | |
| Elevated synovial PMN (%) | 2 | |
| Elevated synovial CRP | 1 | |
| **Intraoperative Criteria (If Preoperative Score Inconclusive)** | **Score** | **Decision** |
| Preoperative minor criteria score | - | ≥6 Infected<br>4-5 Inconclusive<br>≤3 Not Infected |
| Positive histology | 3 | |
| Positive purulence | 3 | |
| Single positive culture | 2 | |

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LE, leukocyte esterase; PMN, polymorphonuclear cell; WBC, white blood cell

Table 2. Threshold values for 2018 diagnostic criteria for PJI[19]

| Marker | Chronic (>90 d) | Acute (<90 d) |
|---|---|---|
| Serum CRP (mg/dL) | 1.0 | 10 |
| Serum D-dimer (ng/mL) | 860 | 860 |
| Serum ESR (mm/h) | 30 | - |
| Synovial WBC count (cells/μL) | 3000 | 10,000 |
| Synovial PMN (%) | 80 | 90 |
| Synovial CRP (mg/L) | 6.9 | 6.9 |
| Synovial alpha-defensin (signal-to-cutoff ratio) | 1.0 | 1.0 |

**Laboratory Diagnosis**

Clinical suspicion of PJI should be raised when a patient experiences persistent pain after joint replacement with no pain-free interval, the patient experiences acute onset of pain in a prosthetic joint that was previously asymptomatic, or there is drainage from the scar or a draining sinus tract.[21] Imaging studies can also help to guide diagnosis. Once PJI is suspected, an appropriate diagnostic approach must be chosen using available tests. The general approach to PJI diagnosis seeks to answer two questions. First, is the joint infected? Second, what is the causative microorganism and what is its antimicrobial susceptibility pattern?[1]

***Non-microbiological testing***

Non-microbiological testing includes serum and synovial fluid biomarkers that provide evidence for infection. Serum CRP and ESR are frequently-used inflammatory markers. CRP and ESR tests are widely available, inexpensive, and have rapid turnaround times. However, they lack specificity and may be elevated in patients with underlying inflammatory conditions, such as rheumatoid arthritis.[1] They also lack sensitivity and should not be used to rule out PJI, especially when a low-grade infection may be present or there was prior antibiotic administration.[13,19,22] Other serum biomarkers, including interleukin-6 and procalcitonin, may be used although they are not included in the diagnostic criteria.[1,13]

Synovial fluid analysis provides valuable diagnostic data following examination, plain imaging studies, and CRP and ESR tests. Preoperative synovial white blood cell count (WBC) and polymorphonuclear cell percentage (PMN%) have high sensitivity and specificity for PJI.[1] They can also help to distinguish true-positive from false-positive culture results. Furthermore, PMN% is

unaffected by antibiotic treatment. However, synovial WBC and PMN% must be interpreted with caution as they can also be elevated in other scenarios, such as hemarthrosis, rheumatoid arthritis, and postoperative inflammation.[1,22] Synovial leukocyte esterase (LE) may be used as an alternative to synovial WBC. The LE strip test is a rapid and inexpensive immunochromatographic method that detects LE enzyme secreted by neutrophils, and thus reflects the concentration of neutrophils in synovial fluid.[13]

Alpha-defensin was added to the PJI diagnostic criteria in 2018.[19] Alpha-defensins are antimicrobial and anti-inflammatory cationic peptides released by neutrophils as a defense mechanism. The sensitivity and specificity of alpha-defensin testing for PJI diagnosis approach 100%.[13] Alpha-defensin values are not affected by prior antibiotic administration, other inflammatory conditions, the type of microorganism, or the presence of blood in a synovial fluid specimen.[13] However, the test is costly and can have a turnaround time of 24-hours.[21] Alpha-defensin values may also be elevated due to metallosis, but synovial fluid CRP can be used to exclude false positives.[13]

***Microbiological testing***

Microbiological culture is one of the most valuable components of PJI diagnostic testing as positive cultures allow the identification of the causative microorganism(s) to be determined and yield viable microorganism(s) for antimicrobial susceptibility testing (AST). Many specimen types may be cultured, with varying sensitivities. Cultures should be incubated in both aerobic and anaerobic conditions.[1,13,17] Mycobacterial and fungal cultures are not recommended for routine diagnosis, except in high-risk scenarios.[17]

Synovial fluid cultures collected preoperatively can provide early identification of the causative pathogen(s) and allow for determination of AST results. However, the sensitivity is low; one study found the sensitivity of synovial fluid culture to be 45.7%.[23] Overreliance on preoperative synovial fluid cultures to detect pathogens can miss cases of PJI, but sensitivity may be improved by inoculating aspirated fluid into blood culture bottles rather than conventional solid and/or liquid media.[1,13,22]

Intraoperative periprosthetic tissue culture is a staple of the microbiological diagnosis of PJI. Like synovial fluid culture, periprosthetic tissue culture has low sensitivity when using conventional plate and broth media; one study found the sensitivity to be 62.6% when specimens were cultured on conventional media.[24] However, the same study found that by homogenizing tissue specimens in brain heart infusion broth and inoculating the homogenized specimen into blood culture bottles, the sensitivity of periprosthetic tissue culture improved to 92.1%. Culture in blood culture bottles also shortened the time to microorganism detection for periprosthetic tissue cultures.[24]

Number of specimens is another important consideration for periprosthetic tissue culture. In order to meet the 2018 PJI major diagnostic criteria, at least two cultures must be positive with the same organism.[19] A single positive culture, especially with a low virulence organism, is often regarded as a contaminant.[1,17] Therefore, it is generally recommended that three to five periprosthetic specimens be collected.[1,17,22] One study determined the greatest accuracy of PJI diagnosis was obtained with three periprosthetic tissue specimens inoculated into blood culture bottles or four specimens cultured on standard broth and plate media. Culturing five or more specimens did not improve diagnostic accuracy.[25] Individual specimens should be collected using separate, sterile instruments to prevent cross-contamination between specimens. Specimens should be sampled from a variety of areas where signs of infection are evident.[17,22]

Other miscellaneous microbiological tests include swab culture and intraoperative Gram stain. Swab cultures are not recommended for PJI diagnosis. Swabs of tissue have low sensitivity and swab samples from draining wounds may be contaminated with skin flora, leading to false-positive results.[1,22] Finally, intraoperative Gram stains, although they may provide rapid microbiological evidence of PJI, have very low sensitivity (0-27%) and are not routinely recommended.[1]

***Culture-negative PJI***

It is possible to reach the diagnosis of PJI without identifying the causative microorganism(s). These cases are termed culture-negative PJI (CN-PJI) and they account for 5-42% of PJI.[1,3] Cultures may be negative due to several factors, including antibiotic administration prior to specimen collection, improper culture handling, inadequate culture media for atypical organisms, inadequate incubation times, suboptimal number of tissue specimens, and delayed transport to the laboratory.[3] CN-PJI may also result from limitations of current diagnostic tests. Without the causative microorganism(s) identified, treatment of CN-PJI is challenging. Patients with true CN-PJI should be treated with broad spectrum antibiotics with activity against both Gram-positive and Gram-negative organisms.[3]

Improved culture protocols may improve the detection of organisms and reduce the proportion of CN-PJI. Sonication of removed prosthetic implants has been shown to improve microbiological diagnosis.[1,13,26] Especially in delayed- and late-onset PJIs, microorganisms are concentrated in biofilms on the surface of the prosthesis and are not easily dislodged from that sur-

face. With sonication, the prosthetic implant is submerged in liquid and low-frequency ultrasound waves are passed through the liquid, creating microscopic bubbles that release energy and liberate bacteria from the surface of the prosthetic.[1] A study of sonication culture for PJI diagnosis found that, while 57% of cases were positive by tissue culture, 93% were positive on sonication culture.[26] Sonication is especially valuable when only a small amount of viable tissue is available for culture or the patient was administered antibiotics prior to specimen collection.[26] Extending culture incubation may also improve detection of organisms, although this is a matter of debate.[1,3,13] One study found that lengthening PJI culture incubation from five days to fourteen days did not improve overall culture yield, except for *C. acnes*.[27]

Molecular testing may also be used to identify the causative microorganism(s) in CN-PJI. While it is not directly included in the 2018 diagnostic criteria for PJI, molecular testing is mentioned in a footnote stating that clinicians may "consider further molecular diagnostics" in the case of an inconclusive diagnosis.[19] Polymerase chain reaction (PCR) of synovial fluid has high sensitivity, but its clinical utility is limited by the concern for false-positive results and the need for organism-specific primers, which requires clinicians to have a strong suspicion for specific pathogens prior to testing.[3] Next-generation sequencing (NGS) is a promising diagnostic tool for PJI. Studies have shown the sensitivity of NGS to be 63-96% and the specificity to be 73-100%. However, more research is needed to confirm the clinical utility of NGS for PJI diagnosis.[28]

## TREATMENT

The goals of treatment of PJI are three-fold: eliminate the infection, minimize PJI-related morbidity and mortality, and restore pain-free function in the infected joint. Achieving all three goals may not be possible for all patients. Therefore, a treatment strategy must be chosen with respect to the chronicity of the infection, the condition of the joint and implant, and the patient's priorities for pain relief, function, and ability and willingness to undergo surgery.[1,29]

Treatment of PJI consists of medical and surgical interventions. Successful medical therapy requires identification of the cause of the infection, permitting the selection of narrow spectrum antimicrobial therapy. Several surgical treatment strategies exist, including two-stage arthroplasty exchange, one-stage arthroplasty exchange, debridement with implant retention, resection without reimplantation and arthrodesis (i.e., immobilization of the joint), and amputation. However, all surgical strategies include the same components: debride infected tissue, completely resect or replace components of the prosthetic device to eradicate biofilm-related infection, and maintain adequate soft tissue to permit healing. Some patients may be managed with antimicrobial therapy without surgery, but this is not recommended and is reserved for patients who are unable to undergo a surgical procedure. Algorithms exist to assist selection of an appropriate treatment strategy.[29]

## CONCLUSION

PJI is a devastating, though infrequent complication of joint arthroplasty surgeries. Diagnosis of PJI requires fulfillment of diagnostic criteria incorporating clinical findings, microbiological testing, non-microbiological laboratory testing, histological analysis, and intraoperative findings. CN-PJI poses special challenges for diagnosis and treatment. However, new testing strategies are available that may improve the diagnosis of PJI.

## REFERENCES

1. Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev. 2014 Apr;27(2):302-45.

2. Kurtz SM, Lau EC, Son MS, Chang ET, Zimmerli W, Parvizi J. Are we winning or losing the battle with periprosthetic joint infections: Trends in periprosthetic joint infection and mortality risk for the Medicare population. J Arthroplasty. 2018 Oct;33(10):3238-45. Epub 2018 Jun 1.

3. Kalbian I, Park JW, Goswami K, Lee Y, Parvizi J, Koo K. Culture-negative periprosthetic joint infection: Prevalence, aetiology, evaluation, recommendations, and treatment. Int Orthop. 2020 Jul;44(7):1255-61. Epub 2020 May 24.

4. Kremers HM, Larson DR, Crowson CS, Kremers WK, Washington RE, Steiner CA, et al. Prevalence of total hip and knee replacement in the United States. J Bone Joint Surg Am. 2015 Sep 2;97(17):1386-97.

5. Schwartz AM, Farley KX, Guild GN, Bradbury Jr TL. Projections and epidemiology of revision hip and knee arthroplasty in the United States to 2030. J Arthroplasty. 2020 Jun;35(6S):S79-85. Epub 2020 Feb 19.

6. Koh CK, Zeng I, Ravi S, Zhu M, Vince KG, Young SW. Periprosthetic joint infection is the main cause of failure for modern knee arthroplasty: An analysis of 11,134 knees. Clin Orthop Relat Res. 2017 Sep;475(9):2194-201. Epub 2017 Jun 1.

7. Marang-van de Mheen PJ, Turner EB, Liew S, Mutalima N, Tran T, Rasmussen S, et al. Variation in prosthetic joint infection and treatment strategies during 4.5 years of follow-up after primary joint arthroplasty using administrative data of 41397 patients across Australian, European, and United States hospitals. BMC Musculoskelet Disord. 2017 May 22;18(1):207.

8. Kapadia BH, Berg RA, Daley JA, Fritz J, Bhave A, Mont MA. Periprosthetic joint infection. Lancet. 2016 Jan 23;387 (10016):386-94. Epub 2015 Jun 28.

9. Premkumar A, Kolin DA, Farley KX, Wilson JM, McLawhorn AS, Cross MB, et al. Projected economic burden of periprosthetic joint infection of the hip and knee in the United States. J Arthroplasty. 2021 May;36(5):1484-9. Epub 2020 Dec 9.

10. George DA, Drago L, Scarponi S, Gallazzi E, Haddad FS, Romano CL. Predicting lower limb periprosthetic joint infections: A review of risk factors and their classification. World J Orthop. 2017 May 18;8(5):400-11.

11. Southwood RT, Rice JL, McDonald PJ, Hakendorf PH, Rozenbilds MA. Infection in experimental hip arthroplasties. J Bone Joint Surg Br. 1985 Mar;67(2):229-31.

12. Zimmerli W, Lew PD, Waldvogel FA. Pathogenesis of foreign body infection. Evidence of a local granulocyte defect. J Clin Invest. 1984 Apr;73(4):1191-200.

13. Vaishya R, Sardana R, Butta H, Mendiratta L. Laboratory diagnosis of prosthetic joint infections: Current concepts and present status. J Clin Orthop Trauma. May-Jun 2019;10(3):560-5. Epub 2018 Oct 16.

14. Heilmann C, Ziebuhr W, Becker K. Are coagulase-negative staphylococci virulent?. Clin Microbiol Infect. 2019 Sep;25 (9):1071-80. Epub 2018 Nov 29.

15. Ricciardi BF, Muthukrishnan G, Masters E, Ninomiya M, Lee CC, Schwarz EM. Staphylococcus aureus evasion of host immunity in the setting of prosthetic joint infection: Biofilm and beyond. Curr Rev Musculoskelet Med. 2018 Sep;11