

# Diagnosis and Prevention of Periprosthetic Joint Infections

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## Abstract

The *Diagnosis and Prevention of Periprosthetic Joint Infections Clinical Practice Guideline* is based on a systematic review of current scientific and clinical research. Through analysis of the current best evidence, this guideline seeks to evaluate strategies to mitigate the risk of periprosthetic joint infection (PJI) in hip and knee arthroplasty and identify best practices in the diagnostic evaluation for these infections. Twenty-five recommendations related to prevention and diagnosis of PJI are presented. In addition, the work group highlighted areas for needed additional research when evidence proved lacking on the topic and carefully reviewed the rationale behind the recommendations while also noting potential harms or risks associated with implementation.

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This clinical practice guideline was approved by the American Academy of Orthopaedic Surgeons Board of Directors on March 11, 2019.

The complete document, *Diagnosis and Prevention of Periprosthetic Joint Infections Clinical Practice Guideline*, includes all tables, figures, and references used and is available at [www.aaos.org/pjguideline](http://www.aaos.org/pjguideline).

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prosthetic joint infection requiring revision surgery.<sup>4</sup>

Defining the incidence and prevalence of PJI has been difficult with unclear definitions for diagnosis of PJI in the literature until recently.<sup>5,6</sup> The reported prevalence of PJI out to 2 years after hip replacement is 1.63%<sup>7</sup> and after knee replacement is 1.55%.<sup>8</sup> Both procedures likely have a prevalence over 2% at 10 years.<sup>7,8</sup>

PJI for the individual patient is devastating with increased rate of mortality,<sup>9</sup> increased risk of morbidity,<sup>10</sup> decreased quality of life,<sup>11</sup> and potential for decreased level of mobility and ambulation.<sup>12</sup>

In addition, the economic burden (represented by hospital costs) of periprosthetic joint infection in the United States is estimated at an annual cost of \$1.62 billion (confidence interval \$1.53 to 1.72 billion) in 2020.<sup>13</sup> These data did not include the cost of surgeon or other provider services nor the postacute care or patient's lost work productivity, making the societal costs for PJI remarkably high.

The American Academy of Orthopaedic Surgeons (AAOS), with input from representatives from the American Association of Hip and Knee Surgeons, the American Society for Clinical Pathology, the American Society for Microbiology, the Infectious Disease Society of America, The Hip Society, The Knee Society, the Society of Nuclear Medicine and Molecular Imaging, the College of American Pathologists, and the American College of Radiology, recently published their clinical practice guideline (CPG), Diagnosis and Prevention of Periprosthetic Joint Infections (PJI).<sup>1</sup> This CPG was approved by the AAOS Board of Directors in March, 2019. The purpose of this CPG is to provide recommendations for preventive strategies and diagnostic tools for PJI based on current best evidence.

With the aging cohort and continued advancement in joint arthroplasty, the demand for hip and knee replacement is expected to continue to rise.<sup>2,3</sup> With the demand for these surgeries is also an expectation for an increased prevalence of peri-

## Guideline Development

The AAOS assembled a team of clinical experts and analysts to build off the foundation of the original *Diagnosis of Periprosthetic Joint Infection* guideline published in 2013. The group of physician experts defined the scope of this updated CPG by creating PICO Questions (population, intervention, comparison, and outcome) that directed the literature search. The intent was to not only update the understanding of diagnosing PJI from the original guideline but to also build on this by looking into preventive measures.

The *Diagnosis and Prevention of PJI* guideline involved reviewing more than 9,300 abstracts and more than 1,280 full-text articles to develop 25 recommendations supported by 248 research articles meeting stringent inclusion criteria. Each recommendation is based on a systematic review of the research-related topic which resulted in 3 recommendations classified as strong, 6 as moderate, 10 as limited, and 6 as consensus. Strength of recommendation is assigned objectively based on the quality of the supporting evidence. The recommendations underwent a rigorous internal and external peer review process resulting in the final approved CPG with the entire process adhering to the strict evidence-based methodology.

This CPG provides orthopaedic surgeons and other healthcare providers evidence-based principles in

understanding risk and preventive strategies for PJI as well as guiding the diagnostic process. From analysis of the literature, there are two important overarching themes:

- (1) Comprehensive understanding of the interplay between patient risk factors and systems in place to mitigate risk for PJI is lacking.
- (2) The diagnostic process for PJI should involve a thoughtful, multipronged approach evaluating blood, synovial fluid, and tissue specimen tests with other test methods available in more unclear settings.

Recognizing the inherent limitation of any guideline at completely accounting for every unique clinical scenario, judgment and expertise of the rendering provider takes precedence and cannot be overstated. The intent of this overview is to facilitate the understanding of the recommendations through highlighting key elements of the guideline. The reader is encouraged to explore the full guideline with embedded rationales and explanations for potential harms and areas for additional research.

## Prevention of Periprosthetic Joint Infection

The principle of providing value in health care underscores the importance of trying to prevent periprosthetic joint infection occurrences. As such, this guideline sought to evaluate current

evidence on risk factors for infection and perioperative care methods used to mitigate risk. The evidence related to patient-specific risk factors for infection is quite limited. Much has been written, but few studies provide the quality of evidence to draw firm conclusions with possibly the exception of obesity which moderate quality evidence does suggest increases PJI risk in hip and knee arthroplasty. The guideline highlights the various risk factors grouping them by quality of evidence available. The reader is highly encouraged to review the “Possible Risks and Harms” section in particular on this topic. An ethical fine line exists with improved understanding of patient-related risk factors for infection; this guideline is not to be taken as prescriptive in determining access to care to two of the most successful procedures at improving quality of life. As the evidence continues to unfold, the guideline has taken care to identify shortcomings in knowledge to ensure the recommendations serve to guide constructive communication between provider and patient regarding options for care and associated individualized risks with and circumstances related to that care. It should be noted that it is unclear, based on the current literature, “if modification of any risk factor, including obesity, actually reduces the risk of PJI.”<sup>1</sup>

Paucity of quality evidence also exists to support the myriad of perioperative tactics used to mitigate risk with limited or conflicting evidence for modalities such as decolonization

Dr. Tubb or an immediate family member serves as a board member, owner, officer, or committee member of American Academy of Orthopaedic Surgeons and American Association of Hip and Knee Surgeons. Dr. Polkowski or an immediate family member serves as a consulting activity in DJO Surgical and serves as a board of directors in American Association of Hip and Knee Surgeons. Neither Ms. Krause nor any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article.

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protocols, delaying surgery after intra-articular injection, the use of antibiotic impregnated cement, and antiseptic intraoperative lavage. Certainly, this area is ripe for additional high-quality research to better define the value and importance of these practices. Strong evidence does support administering a preoperative prophylactic antibiotic before any revision hip or knee arthroplasty in which periprosthetic infection is not suspected or when this diagnosis has been already made and appropriate cultures obtained. Although evidence available at the time of this guideline does not clearly define a preferred preoperative prophylactic antibiotic, future updates may as new evidence becomes available.

## Diagnosis of Periprosthetic Joint Infection

Evidence surrounding diagnostic tools for PJI was generally more robust. This is not to say that the diagnosis of PJI is particularly easy; in fact, the diagnostic process typically requires a multipronged strategy of blood, synovial fluid, and tissue specimen tests. This should be approached methodically so as to maximize diagnostic accuracy. The reader is encouraged to explore the rationales and cited evidence on the topic. The guideline found serum C-reactive protein (CRP),<sup>14,15</sup> erythrocyte sedimentation rate,<sup>14,15</sup> and/or interleukin-6<sup>16-18</sup> are supported by strong evidence as useful “ruling out” tests in the evaluation process while moderate evidence suggests that a peripheral blood leukocyte count or serum tumor necrosis factor  $\alpha$  does not have clinical utility.<sup>16,18-23</sup> Synovial fluid tests such as leukocyte count<sup>14,20,23-26</sup> and neutrophil percentage,<sup>14,20,23-26</sup> aerobic and anaerobic cultures, leukocyte esterase,<sup>27-29</sup> CRP,<sup>30-33</sup>  $\alpha$ -defensin, and nucleic acid amplification techniques for

bacteria can play an important diagnostic role with moderate supporting evidence. This is not to say that all tests are required, and this may be site and resource dependent. Even with a stricter interpretation of how evidence is graded in this current guideline, moderate strength evidence finds that Gram stain should not be used as a “rule out” test for PJI.<sup>20,34,35</sup> If preoperative evaluation with serum and synovial fluid tests does not secure a diagnosis, strong evidence does support frozen section tissue histopathology to help make the diagnosis.<sup>14,36,37</sup> Although imaging modalities can play an important role in the evaluation of a potentially failed arthroplasty, conflicting evidence still exists with respect to their role in diagnosing PJI. This highlights an important lack of high quality and conclusive evidence on the topic. The practitioner may interpret the limited evidence as an area where these diagnostic tools may be helpful in complex scenarios with conflicting data from other tests.

A particular area of ongoing confusion is the management of antimicrobials during the evaluation of a patient with possible PJI. This guideline has separated these recommendations out to hopefully provide some clarity. When presented with a patient in which PJI is a possibility, evidence is clear that there are blood and serum tests that can aid in the diagnosis as stated above. Moderate evidence supports obtaining these tests, particularly synovial fluid cultures, before initiating antimicrobial treatment. This recommendation is subject to clinical judgment and may not be appropriate in the case of life-threatening septic episodes. If a patient is suspected of having a PJI and previous antimicrobials have already been administered before obtaining synovial fluid cultures, limited evidence would support a minimum 2-week antimicrobial

“holiday” (if clinically feasible) to maximize the yield in the culture results. However, in the patient in which PJI is not suspected or has already been clearly established with appropriate cultures, strong evidence argues for administering preoperative prophylactic antibiotics at the time of revision surgery.

## Conclusion

This guideline builds on the previous work on this topic with the goal to identify best practices in prevention and diagnosis of PJI and underscores gaps in knowledge that may spur additional research. The consequence of PJI is quite severe at the patient as well as the healthcare system level. The growing demand for orthopaedic care and shift toward a more value-based system frames the importance of these guidelines. But be clear, the guideline is a tool and a packaged, comprehensive understanding of the literature on this topic. Practitioners must rely on their judgment and experience, available resources, and their patients’ preferences and values when making clinical decisions.

## Recommendations

This Summary of Recommendations of the AAOS *Diagnosis and Prevention of Periprosthetic Joint Infections Clinical Practice Guideline* contains a list of evidence-based treatment recommendations. Discussions of how each recommendation was developed and the complete evidence report are contained in the full guideline at <https://www.aaos.org/pjiguideline>. Readers are urged to consult the full guideline for the comprehensive evaluation of the available scientific studies. The recommendations were established using methods of evidence-based medicine that rigorously control for

Strength	Overall Strength of Evidence	Description of Evidence Strength	Strength Visual
Strong	Strong	Evidence from two or more "High" strength studies with consistent findings for recommending for or against the intervention.	
Moderate	Moderate	Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.	
Limited	Low strength evidence or conflicting evidence	Evidence from two or more "Low" strength studies with consistent findings or evidence from a single study for recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.	
Consensus	No evidence	There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion. Consensus recommendations can only be created when not establishing a recommendation could have catastrophic consequences.	

bias, enhance transparency, and promote reproducibility.

The Summary of Recommendations is not intended to stand alone. Medical care should be based on evidence, a physician's expert judgment, and the patient's circumstances, values, preferences, and rights. For treatment procedures to provide benefit, mutual collaboration with shared decision-making between patient and physician/allied healthcare provider is essential.

A Strong recommendation means that the quality of the supporting evidence is high. A Moderate recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the quality/applicability of the supporting evidence is not as strong. A Limited recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm. A Consensus recommendation means that expert opinion supports the guideline recommendation, although there is no available empirical evidence that meets the inclusion criteria of the guideline's systematic review.

### Strength of Recommendations Descriptions

#### Risk Factors for PJI

- (1) Moderate strength evidence supports that obesity is associated with increased risk of periprosthetic joint infection (PJI).

#### Strength of Recommendation:

##### Moderate

Implication: Practitioners should generally follow a Moderate recommendation but remain alert to new information and be sensitive to patient preferences.

- (2) Limited strength evidence supports that patients in which one or more of the following criteria are present are at an increased risk of periprosthetic joint infection (PJI) after hip and knee arthroplasty:
  - Cardiac disease (arrhythmia, coronary artery disease, congestive heart failure, and other);
  - Immunocompromised status (other than HIV), including transplant and cancer;
  - Peripheral vascular disease;

- Inflammatory arthritis;
- Previous joint infection;
- Renal disease;
- Liver disease (hepatitis, cirrhosis, and other);
- Mental health disorders (including depression);
- Alcohol use;
- Anemia;
- Tobacco use;
- Malnutrition;
- Diabetes;
- Uncontrolled diabetes.

#### Strength of Recommendation:

##### Limited

Implication: Practitioners should feel little constraint in following a recommendation labeled as Limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

- (3) In the absence of reliable evidence, it is the opinion of this work group that in the case that one or more of the following conditions are present, the practitioner should carefully consider

the risk before proceeding with surgery:

- Active infection (strongly caution against proceeding with surgery given the risks);
- Anticoagulation status, active thromboprophylaxis (proceed only after careful consideration of the risks);
- Autoimmune disease (proceed only after careful consideration of the risks);
- HIV status (proceed only after careful consideration of the control and risks);
- Institutionalized patients (proceed only after careful consideration of the risks);
- Previous bariatric surgery (proceed only after careful consideration of the risks).

#### Strength of Recommendation: Consensus

Implication: In the absence of reliable evidence, practitioners should remain alert to new information as emerging studies may change this recommendation. Practitioners should weigh this recommendation with their clinical expertise and be sensitive to patient preferences.

- (4) In the absence of reliable evidence, it is the opinion of this work group that the following conditions have an unclear effect on risk of PJI:
  - Age (conflicting evidence);
  - Dementia (imprecise effect estimates);
  - Poor dental status (inadequate evidence for a recommendation);
  - Asymptomatic bacteriuria (conflicting evidence).

#### Strength of Recommendation: Consensus

Implication: In the absence of reliable evidence, practitioners should remain alert to new information as emerging studies may change this recommendation. Practitioners should weigh

this recommendation with their clinical expertise and be sensitive to patient preferences.

### Injections Before Arthroplasty

Limited evidence suggests intra-articular injection done before total joint arthroplasty may have a time-dependent association for increased risk of PJI.

#### Strength of Recommendation: Limited

Implication: Practitioners should feel little constraint in following a recommendation labeled as Limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

### Blood Tests for Preoperative Diagnosis

- (1) Strong evidence supports the use of the following to aid in the preoperative diagnosis of periprosthetic joint infection (PJI):
  - Serum erythrocyte sedimentation rate;
  - Serum CRP (C-reactive protein);
  - Serum interleukin-6.

#### Strength of Recommendation: Strong

Implication: Practitioners should follow a Strong recommendation unless a clear and compelling rationale for an alternative approach is present.

- (2) Moderate strength evidence does not support the clinical utility of the following to aid in the diagnosis of PJI:
  - Peripheral blood leukocyte count;
  - Serum tumor necrosis factor- $\alpha$ .

#### Strength of Recommendation:

##### Moderate

Implication: Practitioners should generally follow a Moderate recommendation but remain alert to new information and be sensitive to patient preferences.

### Diagnosis of Infected Joint Replacements

#### Synovial Fluid Tests

- (1) Moderate strength evidence supports the use of the following to aid in the diagnosis of prosthetic joint infection (PJI):
  - Synovial fluid leukocyte count and neutrophil percentage;
  - Synovial fluid aerobic and anaerobic bacterial cultures;
  - Synovial fluid leukocyte esterase;
  - Synovial fluid alpha-defensin ( $\alpha$ -defensin);
  - Synovial fluid CRP;
  - Synovial fluid nucleic acid amplification testing (eg, polymerase chain reaction) for bacteria.

#### Strength of Recommendation:

##### Moderate

Implication: Practitioners should generally follow a Moderate recommendation but remain alert to new information and be sensitive to patient preferences.

#### Intraoperative Tests

- (2) Strong evidence supports the use of histopathology to aid in the diagnosis of PJI.

#### Strength of Recommendation:

##### Strong

Implication: Practitioners should follow a Strong recommendation unless a clear and compelling rationale for an alternative approach is present.

- (3) Moderate strength evidence supports the use of the following

to aid in the diagnosis of prosthetic joint infections (PJI):

- Multiple aerobic and anaerobic bacterial periprosthetic tissue cultures;
- Implant sonication fluid aerobic and anaerobic bacterial cultures;
- Implant sonication fluid nucleic acid amplification testing (eg, polymerase chain reaction) for bacteria.

#### Strength of Recommendation:

##### Moderate

Implication: Practitioners should generally follow a Moderate recommendation but remain alert to new information and be sensitive to patient preferences.

- (4) Limited strength evidence supports that periprosthetic tissue nucleic acid amplification testing for bacteria is not useful in the diagnosis of PJI.

#### Strength of Recommendation:

##### Limited

Implication: Practitioners should feel little constraint in following a recommendation labeled as Limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

## Diagnostic Imaging

- (1) Limited strength evidence supports the use of the following to aid in the diagnosis of PJI:
  - <sup>18</sup>F-Fluorodeoxyglucose positron emission tomography/CT;
  - <sup>18</sup>F-NaF positron emission tomography/CT;
  - CT.

#### Strength of Recommendation:

##### Limited

Implication: Practitioners should feel little constraint in following a rec-

ommendation labeled as Limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

- (2) Limited strength evidence supports the clinical utility of nuclear imaging to aid in the diagnosis of PJI.

#### Strength of Recommendation:

##### Limited

Implication: Practitioners should feel little constraint in following a recommendation labeled as Limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

- (3) In the absence of reliable evidence for gallium-67 imaging, it is the opinion of this work group that this radiopharmaceutical does not have a role in the workup of PJI.

#### Strength of Recommendation:

##### Consensus

Implication: In the absence of reliable evidence, practitioners should remain alert to new information as emerging studies may change this recommendation. Practitioners should weigh this recommendation with their clinical expertise and be sensitive to patient preferences.

## Gram Stain

### Update of 2009 CPG Recommendation

Moderate strength evidence supports that the practitioner avoid the use of intraoperative Gram stain to rule out periprosthetic joint infection.

#### Strength of Recommendation:

##### Moderate

Implication: Practitioners should generally follow a Moderate recom-

mendation but remain alert to new information and be sensitive to patient preferences.

## Avoiding Antimicrobials 2 Weeks Before Obtaining Intra-articular Culture to Identify a Pathogen for the Diagnosis of PJI

### Update of 2009 Recommendation

Limited evidence supports withholding antimicrobials for a minimum of 2 weeks before obtaining intra-articular culture to establish the diagnosis of PJI.

#### Strength of Recommendation:

##### Limited

Implication: Practitioners should feel little constraint in following a recommendation labeled as Limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

## Avoiding Initiating Antimicrobials Before Obtaining Intra-articular Culture in Patients Suspected of Having PJI

### Update of 2009 Recommendation

Moderate strength evidence supports avoiding administration of antimicrobials in patients suspected of having a periprosthetic joint infection until cultures have been obtained and a diagnosis has been established.

#### Strength of Recommendation:

##### Moderate

Implication: Practitioners should generally follow a Moderate recommendation but remain alert to new information and be sensitive to patient preferences.

## Antibiotics With Low Preoperative Suspicion of PJI or Established PJI With a Known Pathogen

### Update of 2009 Recommendation

Strong evidence supports that preoperative prophylactic antibiotics be given before revision surgery in patients at low preoperative suspicion for periprosthetic infection and those with an established diagnosis of periprosthetic joint infection of a known pathogen who are undergoing revision surgery.

#### Strength of Recommendation: Strong

Implication: Practitioners should follow a Strong recommendation unless a clear and compelling rationale for an alternative approach is present.

## Perioperative Antibiotic Selection

- (1) Limited strength evidence supports the use of any of the following perioperative antibiotics in reducing risk of PJI, although no studies reviewed were powered to detect a notable difference among those listed:
  - First-generation cephalosporin (eg, cefazolin);
  - Second-generation cephalosporin (eg, cefuroxime);
  - Glycopeptide (eg, vancomycin).

#### Strength of Recommendation:

#### Limited

Implication: Practitioners should feel little constraint in following a recommendation labeled as Limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

- (2) In the absence of reliable evidence comparing other antibiotics

and antibiotic combinations, including those listed in the guideline, it is the opinion of this work group that perioperative antibiotics should be selected based on principles of responsible stewardship, balancing the risk of PJI and antibiotic resistance. Selection should reflect the antibiogram of the individual institution, the individual risk factors of the patient, and multidisciplinary support of institutional infection control experts. There is no current reliable evidence to support one antibiotic versus the other (examples provided in the rationale).

#### Strength of Recommendation: Consensus

Implication: In the absence of reliable evidence, practitioners should remain alert to new information as emerging studies may change this recommendation. Practitioners should weigh this recommendation with their clinical expertise and be sensitive to patient preferences.

## Antibiotic Cement

- (1) Limited evidence suggests the routine use of antibiotics in the cement does not reduce the risk of periprosthetic joint infections for patients undergoing cemented total knee arthroplasty.

#### Strength of Recommendation:

#### Limited

Implication: Practitioners should feel little constraint in following a recommendation labeled as Limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

- (2) Limited evidence suggests the use of antibiotics in the cement

may reduce the risk of periprosthetic joint infections for patients undergoing cemented total hip arthroplasty (THA).

#### Strength of Recommendation:

#### Limited

Implication: Practitioners should feel little constraint in following a recommendation labeled as Limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

## Preoperative Screening and Decolonization

- (1) Limited strength evidence supports the use of universal preoperative chlorhexidine cloth decolonization to reduce PJI after THA and total knee arthroplasty.

#### Strength of Recommendation:

#### Limited

Implication: Practitioners should feel little constraint in following a recommendation labeled as Limited, exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

- (2) In the absence of reliable evidence for screening and nasal decolonization, it is the opinion of this work group that preoperative nasal mupirocin decolonization is a low-risk, reasonable option before hip and knee arthroplasty in patients who are methicillin-resistant *Staphylococcus aureas* (MRSA) carriers.

#### Strength of Recommendation:

#### Consensus

Implication: In the absence of reliable evidence, practitioners should remain

alert to new information as emerging studies may change this recommendation. Practitioners should weigh this recommendation with their clinical expertise and be sensitive to patient preferences.

## Intraoperative Technical Factors

In the absence of reliable evidence for the use of an antiseptic wash during hip or knee arthroplasty, it is the opinion of this work group that dilute betadine lavage be used as a method to decrease infection risk in hip or knee arthroplasty.

## Strength of Recommendation: Consensus

Implication: In the absence of reliable evidence, practitioners should remain alert to new information as emerging studies may change this recommendation. Practitioners should weigh this recommendation with their clinical expertise and be sensitive to patient preferences.

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References printed in **bold type** are those published within the past 5 years.

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