
# Peer Review and Public Commentary Report

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## Diagnosis and Prevention of Periprosthetic Joint Infections Clinical Practice Guideline

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## Overview of Peer Review and Public Commentary

The reviews and comments related to this clinical practice guideline are reprinted in this document and posted on the AAOS website. All peer reviewers and public commenters are required to disclose their conflict of interests. Names are removed from the forms of reviewers who requested that they remain anonymous; however, their COI disclosures still accompany their response.

## Peer Review

AAOS contacted 13 organizations with content expertise to review a draft of the clinical practice guideline during the two-week peer review period in January 2018.

- Six individuals provided comments via the electronic structured peer review form. No reviewers asked to remain anonymous.
- All six reviews were on behalf of a society.
- The work group considered all comments and made some modifications when they were consistent with the evidence.

## Public Comment

The new draft was then circulated for a two-week public comment period ending on February 22, 2018.

- AAOS received five comments.
- If warranted, and based on evidence, the guideline draft is modified by the work group members in response to the public comments.

## Peer Reviewer Key

Each peer reviewer was assigned a number (see below). All responses in this document are listed by the assigned peer reviewer's number.

Table 1. Peer Reviewers

| Reviewer Number | Name of Reviewer | Society Being Represented |
|---|---|---|
| 1 | Javad Parvizi, MD | American Association of Hip and Knee Surgeons (AAHKS) |
| 2 | Elie Berbari, MD | Infectious Diseases Society of America (IDSA) |
| 3 | Alice Ha, MD | American College of Radiology (ACR) |
| 4 | Alexis Vosooney, MD | American Academy of Family Physicians (AAFP) |
| 5 | Alex McLaren, MD | Musculoskeletal Infection Society (MSIS) |
| 6 | Robert Sautter, PhD, HCLD (ABB) CC | American Society of Microbiology (ASM) |

## Peer Reviewer Demographics

Table 2. Reviewer Demographics

| Reviewer Number | First Name | Society you are representing | Please list your primary specialty | Please list your work setting |
|---|---|---|---|---|
| 1 | Javad Parvizi, MD | American Association of Hip and Knee Surgeons (AAHKS) | Total Joint | Academic Practice |
| 2 | Elie Berbari, MD | Infectious Diseases Society of America (IDSA) | Other | Academic Practice |
| 3 | Alice Ha, MD | American College of Radiology (ACR) | Radiology | Academic Practice |
| 4 | Alexis Vosooney, MD | American Academy of Family Physicians (AAFP) | Family Medicine | Private Group or Practice |
| 5 | Alex McLaren, MD | Musculoskeletal Infection Society (MSIS) | MSK infection | Other |
| 6 | Robert Sautter, PhD, HCLD (ABB) CC | American Society of Microbiology (ASM) | Microbiology; Infectious disease | Consultant |

## Peer Reviewer's Disclosure Information

Table 3. Disclosure Question Key

| Disclosure Question | Disclosure Question Details |
|---|---|
| A | A) Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? |
| B | B) Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? |
| C | C) Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? |
| D | D) Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? |
| E | E) Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? |
| F | F) Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds)? |
| G | G) Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? |
| H | H) Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? |
| I | I) Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? |
| J | J) Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? |

Table 4. Peer Reviewer's Disclosure Information

| Reviewer Number | First Name | Disclosure Available via AAOS Disclosure System | A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Javad Parvizi, MD | Yes | | | | | | | | | | |
| 2 | Elie Berbari, MD | | No | No | No | No | No | No | Yes (STRIVE S aureus vaccine Spine trial by Pfizer) | No | No | No |
| 3 | Alice Ha, MD | | No | No | No | No | No | No | No | No | No | No |
| 4 | Alexis Vosooney, MD | | No | No | No | No | No | Yes (3M - 10 shares) | No | No | No | No |
| 5 | Alex McLaren, MD | Yes | | | | | | | | | | |
| 6 | Robert Sautter, PhD, HCLD (ABB) CC | | No | Yes (Speaker for Roche Diagnostics) | No | Yes (Advisory Board for QuantaMatrix and consultant for Roche Diagnostics) | No | Yes (Stocks in Mckesson Merck and Amgen) | No | No | No | No |

## Peer Reviewer Responses to Structured Peer Review Form Questions

All peer reviewers are asked 16 structured peer review questions which have been adapted from the Appraisal of Guidelines for Research and Evaluation (AGREE) II Criteria*. Their responses to these questions are listed on the next few pages.

Table 5. Peer Reviewer Responses Questions 1-4

| Reviewer Number | First Name | Society you are representing | 1. The overall objective(s) of the guideline is (are) specifically described. | 2. The health question(s) covered by the guideline is (are) specifically described. | 3. The guideline's target audience is clearly described. | 4. There is an explicit link between the recommendations and the supporting evidence. |
|---|---|---|---|---|---|---|
| 1 | Javad Parvizi, MD | American Association of Hip and Knee Surgeons (AAHKS) | Agree | Agree | Strongly Agree | Neutral |
| 2 | Elie Berbari, MD | Infectious Diseases Society of America (IDSA) | Agree | Agree | Agree | Agree |
| 3 | Alice Ha, MD | American College of Radiology (ACR) | Agree | Agree | Agree | Agree |
| 4 | Alexis Vosooney, MD | American Academy of Family Physicians (AAFP) | Agree | Agree | Strongly Agree | Agree |
| 5 | Alex McLaren, MD | Musculoskeletal Infection Society (MSIS) | Agree | Agree | Agree | Strongly Disagree |
| 6 | Robert Sautter, PhD, HCLD (ABB) CC | American Society of Microbiology (ASM) | Strongly Agree | Strongly Agree | Strongly Agree | Strongly Agree |

Table 6. Peer Reviewer Responses Questions 5-8

| Reviewer Number | First Name | Society you are representing | 5. Given the nature of the topic and the data, all clinically important outcomes are considered. | 6. The patients to whom this guideline is meant to apply are specifically described. | 7. The criteria used to select articles for inclusion are appropriate. | 8. The reasons why some studies were excluded are clearly described. |
|---|---|---|---|---|---|---|
| 1 | Javad Parvizi, MD | American Association of Hip and Knee Surgeons (AAHKS) | Neutral | Agree | Strongly Agree | Strongly Agree |
| 2 | Elie Berbari, MD | Infectious Diseases Society of America (IDSA) | Neutral | Strongly Agree | Agree | Agree |
| 3 | Alice Ha, MD | American College of Radiology (ACR) | Agree | Agree | Agree | Agree |
| 4 | Alexis Vosooney, MD | American Academy of Family Physicians (AAFP) | Agree | Strongly Agree | Agree | Agree |
| 5 | Alex McLaren, MD | Musculoskeletal Infection Society (MSIS) | Agree | Agree | Strongly Disagree | Strongly Disagree |
| 6 | Robert Sautter, PhD, HCLD (ABB) CC | American Society of Microbiology (ASM) | Neutral | Strongly Agree | Strongly Agree | Strongly Agree |

Table 7. Peer Reviewer Responses Questions 9-12

| Reviewer Number | First Name | Society you are representing | 9. All important studies that met the article inclusion criteria are included. | 10. The validity of the studies is appropriately appraised. | 11. The methods are described in such a way as to be reproducible. | 12. The statistical methods are appropriate to the material and the objectives of this guideline. |
|---|---|---|---|---|---|---|
| 1 | Javad Parvizi, MD | American Association of Hip and Knee Surgeons (AAHKS) | Strongly Agree | Strongly Agree | Strongly Agree | Strongly Agree |
| 2 | Elie Berbari, MD | Infectious Diseases Society of America (IDSA) | Agree | Agree | Strongly Agree | Agree |
| 3 | Alice Ha, MD | American College of Radiology (ACR) | Neutral | Agree | Agree | Agree |
| 4 | Alexis Vosooney, MD | American Academy of Family Physicians (AAFP) | Agree | Agree | Strongly Agree | Agree |
| 5 | Alex McLaren, MD | Musculoskeletal Infection Society (MSIS) | Neutral | Agree | Agree | Agree |
| 6 | Robert Sautter, PhD, HCLD (ABB) CC | American Society of Microbiology (ASM) | Strongly Agree | Strongly Agree | Strongly Agree | Strongly Agree |

Table 8. Peer Reviewer Responses Questions 13-16

| Reviewer Number | First Name | Society you are representing | 13. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed. | 14. Health benefits, side effects, and risks are adequately addressed. | 15. The writing style is appropriate for health care professionals. | 16. The grades assigned to each recommendation are appropriate. |
|---|---|---|---|---|---|---|
| 1 | Javad Parvizi, MD | American Association of Hip and Knee Surgeons (AAHKS) | Agree | Agree | Agree | Agree |
| 2 | Elie Berbari, MD | Infectious Diseases Society of America (IDSA) | Neutral | Agree | Agree | Agree |
| 3 | Alice Ha, MD | American College of Radiology (ACR) | Agree | Agree | Agree | Neutral |
| 4 | Alexis Vosooney, MD | American Academy of Family Physicians (AAFP) | Agree | Agree | Agree | Agree |
| 5 | Alex McLaren, MD | Musculoskeletal Infection Society (MSIS) | Agree | Neutral | Neutral | Agree |
| 6 | Robert Sautter, PhD, HCLD (ABB) CC | American Society of Microbiology (ASM) | Strongly Agree | Strongly Agree | Strongly Agree | Strongly Agree |

## Peer Reviewer's Recommendation for Use of this Guideline in Clinical Practice

Table 9. Would you recommend these guidelines for use in clinical practice?

| Reviewer Number | First Name | Society you are representing | Would you recommend these guidelines for use in clinical practice? | Additional Comments regarding this CPG? |
|---|---|---|---|---|
| 1 | Javad Parvizi, MD | American Association of Hip and Knee Surgeons (AAHKS) | Recommend | |
| 2 | Elie Berbari, MD | Infectious Diseases Society of America (IDSA) | Recommend | |
| 3 | Alice Ha, MD | American College of Radiology (ACR) | | |
| 4 | Alexis Vosooney, MD | American Academy of Family Physicians (AAFP) | Recommend | While, I am reviewing the guideline as a member of the AAFP, it does not imply endorsement by the organization. A separate request will need to be sent to AAFP leadership requesting a review for potential endorsement. This request can be directed to the attention of Melanie Bird, PHD at mbird@aafp.org. |
| 5 | Alex McLaren, MD | Musculoskeletal Infection Society (MSIS) | Unsure | The CPG in its present form needs attention in enough places (as noted) that we cannot make this determination without seeing the updated version following incorporating peer review comments. While we strongly agree with the need for this CPG and appreciate the tremendous amount of work that was done to produce this document the noted concerns need to be addressed before we can reconsider endorsing and recommending it. |
| 6 | Robert Sautter, PhD, HCLD (ABB) CC | American Society of Microbiology (ASM) | Strongly Recommend | |

## Peer Reviewer Detailed Responses

Reviewer #1

| Reviewer Number | First Name | Society you are representing | Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: |
|---|---|---|---|
| 1 | Javad Parvizi, MD | American Association of Hip and Knee Surgeons (AAHKS) | Following comments refer to the "Diagnostic Imaging" section starting Line 1264. These comments also refer to this section summarized in the beginning of the document.<br>A. Most important reference is the ACR Appropriateness Criteria after Total knee arthroplasty. (J Am Coll Radiol. 2017 Nov;14(11S):S421-S448. doi: 10.1016/j.jacr.2017.08.036. PMID: 29101982)<br>B. Although radiographs are usually first line imaging before aspiration is performed for suspected infection, radiographic appearance of periprosthetic infection is nonspecific. Nonetheless, it is recommended as the first imaging study before aspiration is done to see if there are any other pathologies such as fractures, dislocations, etc.<br>C. In addition, none of the other imaging modalities are recommended by the ACR as first line imaging.<br>D. Of note, there are recent studies on MR with metal artifact reduction techniques (Plodkowski AJ, Hayter CL, Miller TT, Nguyen JT, Potter HG. Lamellated hyperintense synovitis: potential MR imaging sign of an infected knee arthroplasty. Radiology. 2013;266(1):256-260. Li AE, Sneag DB, Greditzer HGt, Johnson CC, Miller TT, Potter HG. Total Knee Arthroplasty: Diagnostic Accuracy of Patterns of Synovitis at MR Imaging. Radiology. 2016;281(2):499-506.) that showed that specific appearance of synovium can distinguish infection from non-infected TKA. Further studies are needed.<br>E. Line 1268: must specify CT with or without contrast? CT with contrast can be useful in finding periprosthetic abscesses or fistulae in some cases. CT can also help to define the extent of periprosthetic lucency before surgery.<br>F. Line 1285: Bone scan or PET/CT (either type) are good for excluding infection when negative, but nonspecific when positive.<br>G. Zhuang et al (Zhuang H, Duarte PS, Pourdehnad M, et al. The promising role of 18F-FDG PET in detecting infected lower limb prosthesis implants. J Nucl Med. 2001;42(1):44-48.) studied 36 painful knee prostheses using FDG-PET and identified 10 of 11 infected cases but had false-positive results in 7 cases (sensitivity of 90.9%, specificity of 72%, and accuracy of 77.8% for detecting infection). This was a lower accuracy than found in assessment of hip prostheses. |

| | | | |
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| | | | H. Line 1640 Aksoy SY et al reference should not be described as ordinary FDG uptake PET/CT. This study looked at combined WBC labeling and PET/CT.<br>I. Line 1320: important to distinguish White blood cell labeling used with Marrow labeling with sulfur colloid. WBCs may be radiolabeled in vitro with In-111 oxine or Tc-99m exametazime (Tc-99m-hexamethylpropyleneamineoxime [HMPAO]. Love et al examined 150 failed joint prostheses with histopathologic correlation and found that leukocyte/marrow imaging yielded sensitivity of 96%, specificity of 87%, and accuracy of 91%. They found that leukocyte/marrow imaging was significantly more accurate than bone scan (50%), bone/gallium scan (66%), and leukocyte/bone imaging (70%) in their population.<br>J. Love C, Tronco G, Yu A, Marwin S, Nichols K, Palestro C. Diagnosing lower extremity (LE) prosthetic joint infection: Bone, gallium & labeled leukocyte imaging. Journal of Nuclear Medicine. 2008;49(supplement 1):133P. |

Workgroup Responses to Reviewer #1

A. Based on the methodology for development of the AAOS guidelines, we are unable to include other reviews in our guidelines; however, we do screen their bibliographies for primary articles that meet our inclusion criteria. Additionally, since appropriateness criteria are at least partially based on consensus, we cannot use their conclusions in our CPGs.
B. We would agree that plain radiographs would be appropriate in the general evaluation of total knee arthroplasty but focused this guideline more directly to the evaluation for infection.
C. See above
D. Plodkowski, et al. presented a case control study with a control group with no evidence of infection at aspiration or histopathologic exam. Diagnostic studies enrolling healthy controls who typically would not receive the test in clinical practice are automatically excluded from our CPGs due to patient spectrum bias. The study by Li, et al. was included in this guideline.
E. A referenced study by Cyteval (2002) did not use CT scans with contrast. The authors from that paper acknowledged that contrast may have improved sensitivity. However, since no other studies met the inclusion criteria for CT with contrast for specifically diagnosing PJI, we cannot make a definitive evidence based statement about this imaging modality.
F. We were unable to uncover sufficient evidence from primary studies to make this recommendation.
G. This study was excluded because it was appraised as very low quality due to not using the same reference standard for all patients (differential verification bias) and lack of blinding.
H. Aksoy, et al. evaluated ordinary FDG PET / CT and FDG-labelled leucocyte PET/CT. The work group elected to exclude the labelled WBC PET/CT data because it is not commercially available and the study only looked at patients with positive FDG PET results.
I. AAOS CPG methodology only includes full text article publications as possible sources for evidence in our CPGs and therefore automatically excludes conference abstracts that do not become full publications.
J. See above

## Peer Reviewer Detailed Responses

Reviewer #2

| Reviewer Number | First Name | Society you are representing | Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: |
|---|---|---|---|
| 2 | Elie Berbari, MD | Infectious Diseases Society of America (IDSA) | The attached guidelines on the diagnosis and prevention of PJI are an extensive document that outlines important papers in the field and provide an exhaustive evidence based recommendations. The guidelines can be improved by addressing the following:<br>A. It is unclear as to why certain important risk factors such as prior joint surgery, prior arthroplasty and superficial SSI are not discussed.<br>B. The presence of a concomitant distant infection such as UTI and soft tissue infection is a risk factor for PJI. This has been assessed in a published case control study (Berbari et al, CID 2010 while studying the topic of dental procedures as risk factors for PJI)<br>C. The increased risk of PJI in patients with HIV is not well documented. Most of the dated studies where the risk was assessed did not control for viral suppression and immunologic recovery.<br>D. It is important to distinguish between a diagnosis of PJI and microbiologic confirmation.<br>E. Joint fluid analysis for cell count or markers need to highlight accuracy and cost. Studies of cell count and differential is a reliable and cheap method of establishing the diagnosis of PJI. Others, such as IL6 and Alpha defensin are costly and add very little to the diagnosis of PJI. An ongoing FDA approved study will provide some insight on the utility of alpha defensin.<br>F. It is important to highlight the COI that exists on most published studies looking at the utility of alpha defensin in the diagnosis of PJI.<br>G. The use of abx prophylaxis prior to arthroplasty is highly supported by a number of high quality trials. The duration of antibiotic prophylaxis post-surgery is not discussed and would be of benefit. Recent CDC guidelines (JAMA 2017) on this topic highlight the need to discontinue antibiotics after wound closure .<br>H. The use of Chlorhexidine Cloth prior to arthroplasty is favored in the guidelines. There is limited data supporting the use of cloth vs solution. The cloth is much more expensive and does not convey additional benefit.<br>I. On the topic of nasal s aureus screening and decolonization, there is a number of high quality trials that included a number of type I surgeries (including ortho) that showed a significant benefit of the use of mupirocin. It is important that this be highlighted.<br>J. 10- Page 15 should be Osmon 2013 instead of "Osman"; the definition of PJI was first described/published at the Mayo Clinic in the early 1990's by the work of Drs Hanssen, Osmon and Wilson.<br>K. Page 27 : Prior Joint infection should distinguish between prior native septic arthritis and prior PJI. The risk of subsequent PJI in patients with prior PJI is well documented in numerous cohort studies looking at the outcome of patients that are treated with 2 stage surgery. In this patient population the risk of PJI is 10-20% compared to 1-2 % for primary arthroplasty. |

## Workgroup Responses to Reviewer #2

A. One of the risk factors evaluated in the PICO question format [Population, Intervention, Comparison, Outcome] was recent infection, which was a broad category intended to catch all types of recent infection. Unfortunately, no study met the inclusion criteria for superficial SSI. We did uncover one study that evaluated if treatment for active infection before surgery increased the risk of PJI, but it is unclear if that variable included any patients with superficial SSI. The strength of evidence from this single observational study was not sufficient to make an evidence based recommendation. We also looked at prior joint infection as a risk factor for future joint infection, but this would have excluded prior superficial SSIs. Prior joint surgery was not considered when the PICO questions were written. We agree that this aspect would be worth including when this guideline is updated in the future.
B. This was excluded from the current guideline because UTI was listed under post-operative factors in the Berbari study, and the PICO question addressed factors present at or before surgery. Therefore, we only included studies that evaluated history of UTI that was present before joint replacement surgery.
C. The work group agreed and did downgrade the recommendation from limited to consensus due to lack of control or stratification by important confounding factors.
D. Agreed. This issue was discussed in the recommendation on the effect of antibiotics on diagnosis, starting on page 43.
E. Agreed. A similar statement was made in the rationale. The evidence said the tests were informative, but it is unclear if they provide additional information to what other tests already provide, and cost is an important consideration in many health care settings. The guideline did not specifically compare cost between diagnostic or prevention strategies but recognize its importance and sought to address cost concerns in the rationales provided.
F. A sentence was added to line 1166 on page 35 highlighting the conflict of interest.
G. Agreed. The workgroup decided that Periprosthetic Joint Infection treatment and management was too broad a topic to be lumped in with prevention and diagnosis. We felt this aspect of care would be better covered in a separate future CPG.
H. We were unable to find any studies that met our inclusion criteria comparing chlorhexidine cloth to solution and consider this an important area for additional research.
I. The literature search did uncover data regarding nasal screening and decolonization protocols. Studies that were not specific to hip / knee arthroplasty patients did not meet our inclusion criteria.
J. You are correct, and this has been corrected. Thank you for pointing that out.
K. Both included studies looked at patients with prior prosthetic joint infection, rather than native septic joint arthritis. Therefore, on line 916 on page 27, “history of prior joint infection” was changed to “history of prior prosthetic joint infection.”

## Peer Reviewer Detailed Responses

Reviewer #3

| Reviewer Number | First Name | Society you are representing | Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: |
|---|---|---|---|
| 3 | Alice Ha, MD | American College of Radiology (ACR) | A. Line 523: Would they consider referencing the recent publication related to the definition of PJI (Parvizi JOA May 2018). As they claim that all publications up to June 2018 are included, the readers may be surprised to see a May 2018 publication missing<br>B. Line 620-622: The voting methodology appears unclear (at least to me). Would the workgroup consider including the details of the voting (%Agree, %disagree) or are we to assume that EVERY voting member of the workgroup agreed with EVERY recommendation that is included?<br>C. Line 693-694: I assume they are deliberately making a distinction between diabetes and uncontrolled diabetes. Some (Namba study from Kaiser for example and some European studies) however suggest that diabetes per se is not a risk factor for PJI. It is the uncontrolled hyperglycemia and the co-presence of diabetes related conditions (such as renal disease, anemia, peripheral vascular disease and so on) that leads to the increase in this risk. In light of recent evidence, some of which is discussed in the document (line 825-827 and again line 832-833), would the workgroup be prepared to include hyperglycemia (with or without the diagnosis of diabetes) as a risk factor for PJI?<br>D. Line 763- the unit is kg/m2<br>E. Line 773- It is correct that there are no orthopedic studies evaluating this issue. But a level study by Tonnesen H et al BMJ 1999 on patients undergoing colorectal surgery did find that abstinence from alcohol (for four weeks0 did reduce the incidence of infection.<br>F. Line 825: In favor? I would replace “in favor” with “for”<br>G. Line 837- need unit for 292<br>H. Line 870- I am surprised to see that the study by Huang R et al J Arthroplasty 2013 Sep;28(8 Suppl):21-4. PMID: 23993346 was not included<br>I. Line 891: The influence of untreated hepatitis C on the incidence of PJI is better studies and mechanistic explanations for this association has been offered by some of the studies (Eslam Pour A,. Total joint arthroplasty in patients with Hepatitis C. J Bone Joint Surg 93(15): 1448-1454,2011). The workgroup has the opportunity to highlight the issue of hepatitis C and the importance of its treatment (in light of curative therapies being available now).<br>J. Line 930: The discussion on the effect of smoking on PJI is somewhat superficial and appears to have missed some relevant publications (Singh J Arth Care Res 2011, Khan LA et al Hip Int J Clin Exp Res 2008, Bedard JOA 2018). It is certainly true to state that |

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| | | | smoking has been shown to result in higher rate of SSI, though the association between smoking and PJI remains unclear.<br>K. Line 936: The issue of active infection needs to be clarified. Are we talking about active infection in the affected joint (that is about to undergo arthroplasty), the extremity or any type of active infection like oral disease? I assume the recommendation relates to active infection in the affected joint but this needs to be clarified.<br>L. Line 939: Would it be useful to make a clarification here regarding a couple of issues. First is that this recommendation relates to patients who are undergoing TJA and were on anticoagulation and not patients who have undergone TJA and placed on anticoagulation for VTE prophylaxis. As you know there is ample evidence to suggest that patients who are placed on aggressive anticoagulation after TJA are higher risk of PJI (multiple studies). The other issue relates to the connection between arrhythmia and PJI. It is anticipated and shown in a few studies that the reason for a higher rate of PJI in patients with arrhythmia may indeed relate to the effect of anticoagulation. It may be important to also make a mention of the fact that "bridging" patients who are on anticoagulation prior to TJA is not required (NEJM 2016)<br>M. Line 945: It has become clear that management of HIV patients with the HAART has lead to a rapid decline in the high rate of infection that used to be seen in this patients population (Parvizi et al JOA 2003). A recent systematic review did confirm the beneficial role of HAART for patients with HIV in terms of reduction of the risk for PJI (Enayatollahi et al JOA 2016). It may be important to make a mention of this issue here so that the practitioners recognize the importance of treatment of HIV.<br>N. Line 980: I am somewhat worried about the recommendation related to poor dental health. Although a direct association between dental health and PJI has not been disclosed in any studies and some have shown that routine screening for dental disease is not needed, this recommendation could be potentially dangerous. The statement at the end of this section (lines 985-987) is excellent and draws the attention of the practitioner to seek an association between oral disease and other comorbidities. However, it falls short of drawing attention to the fact that arthroplasty in patients with poor oral health is not a great idea and potentially carries the risk of subsequent SSI/PJI. May be the rationale could highlight the group of patients who are likely to have poor dental health and subsequently require preoperative clearance and/or optimization. One study identified important risk factors for poor dental health (Tokarski AT, Dental clearance prior to elective arthroplasty may not be needed for everyone. J Arthroplasty. 2014;29:1729–1732.)<br>O. Line 1086-87: This statement does not appear to be true any more. With better diagnostic methods and the recognition of the fact that slow growing organisms do not elicit inflammatory response that can be picked up by serological markers, many believe that a normal ESR/CRP DOES NOT rule out infection. In fact there was a 100% agreement among the delegates regarding this issue during the recent consensus meeting. You have |

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| | | | missed many studies that show a high false negative rate with both ESR and CRP being normal. Johnson et al reported a 11.1% false negative rate for combined ESR and CRP when MSIS criteria were considered for diagnosis of PJI (Johnson et al Int Orthop 2011). Saleh et al stated that ESR/CRP combination increase specificity at the cost of sensitivity (Saleh A et al Bone Jt Res 2018). Another recent study showed a relatively poor sensitivity (84%) and specificity (47%) for combination of ESR/CRP for diagnosis of PJI (Shahi A et al JBJS 2017). The latter study also demonstrated that the level of ESR and CRP is affected by administration of antibiotics. The stated sensitivity and specificity (as poor as they are) apply to diagnosis of CHRONIC PJI. The issue is even more worrisome when it comes to diagnosis of acute PJI, when these serological markers are elevated anyway. Thus, different thresholds for ESR/CRP has been offered for diagnosis of PJI during acute PJI (Yi et al COR 2014). I think it is important to mention the fact that normal ESR and CRP DO NOT rule out PJI and great attention needs to be given to patients who may have PJI and normal serology. Line 1099-1103 captures the issues with ESR/CRP but could be strengthened by discussing the above studies that have shown poor sensitivity and specificity for ESR and CRP in the body of the text for this section<br>P. Line 1111: what about calprotectin? There are two moderate level studies (from the same group of investigators)(Wouthuyzen-Bakker M bone Joint J 2017 and Wouthuyzen-Bakker M J Arthroplasty 2018) that demonstrate very high sensitivity and specificity for the test. I realize that the second publiacation may have been outside the window for the literature search and perhaps having one publication only did not qualify the test for inclusion<br>Q. Line 1260- I realize that the studies related to the role of next generation sequencing, that are recent, could not be included in the search. I wonder if in this line a mention of NGS should be made<br>R. Line 1110 (section on diagnosis of infected joint replacements): No mention of ALTR and the complexity that it poses for diagnosis of PJI has been made. This may be deliberate but perhaps in the section regarding over-diagnosis of PJI (line 1250-1254) a mention of ALTR should be made.<br>S. Line 1563-1566: What about the considerable cost of ABLC?<br>T. Line 1578-1580: There are some issues related to the use of mupirocin. It appears that up to 20% of Staph in the US are now resistant to mupirocin and the use of the drus may lead to the emergence of higher rate of resistance (Hetem CID 2016). In addition, the efficacy of mupirocin is being questioned. Despite compliance with the regimen, up to 20% of patients undergoing decolonization with mupirocin have persistent colonization (Kalmeijer MD CID 2002, Baratz MD et al CORR 2015, Kim DH JBJS 2010). Would the workgroup consider mentioning non-antibiotic decolonization strategies such as povidine iodine, CHG or others non-antibiotic agents. There is plenty of studies related to the use of the latter agents also. |

## Workgroup Responses to Reviewer #3

A. Our guideline literature search was updated through December 12, 2017; any article past December 2017 was not included.
B. AAOS voting methodology for the guideline allows for a simple majority. However, this work group did not wish to settle on the final recommendation until the entire work group was satisfied with the wording of the recommendation. In this case 100% approval was achieved for the recommendations.
C. The PICO question originally set out to evaluate diabetes and uncontrolled diabetes separately. Preoperative hyperglycemia in the absence of diabetes was not part of the original PICO question, and so we cannot be confident that we have captured all relevant literature on hyperglycemia in the absence of diabetes. Also, given the fact that the studies were mostly retrospective, the methods for measuring diabetes and especially uncontrolled diabetes were variable and often unclear. The variable, ill-defined measurement methodologies of the included studies would not allow us to single out hyperglycemia. However, the point is valid. Given the results of the Jamsen, et al. study that you mentioned, it would be worthwhile to look for literature on hyperglycemia alone as a risk factor when this guideline is updated in the future.
D. Changed
E. We did find low quality observational studies for hip/knee replacement patients, but no RCTs. An RCT in hip/knee patients using similar methodology as the Tonnesen study would be useful if conducted and may result in a higher strength recommendation when this guideline is updated.
F. Changed to “for”
G. Unit was added
H. The study was not originally recalled because the abstract appeared as if the study was not specific to deep infection/PJI. On further review, it does meet the inclusion criteria. Thank you for the attention. The study was appraised as low quality due to the exploratory nature of the study (e.g. use of stepwise regression models), so the results will not change the strength or the wording of the recommendation since most of the studies still say malnutrition is a risk factor.
I. Agreed. The Eslam Pour study evaluated surgical complications following total hip and knee arthroplasty in Hepatitis C patients. It was appraised as additional low strength evidence and thus does not further alter the recommendation that hepatitis has limited strength evidence to suggest an increased risk for PJI. We have tried to highlight in the rationale the critical need to carefully evaluate medical optimization and have called for additional research to further understand the impact of optimization / treatment of comorbidities on the risk for PJI.
J. The Singh study did not meet our inclusion criteria because the infection outcomes were not specific to deep SSI/PJI. We could not find the referenced Kahn study to assess its level of evidence. The Bedard study was published after the final literature search (December 12, 2017) and therefore cannot be included for this guideline. Studies published after our final literature search will be important to future updates of this guideline.
K. The study described it as infection at other anatomical sites. Therefore, line 941 on page 28 was changed to “evaluated active infection at other anatomical sites.”
L. The title for Anticoagulation/active thromboprophylaxis was changed to Anticoagulation/active thromboprophylaxis status at the time of surgery. We couldn’t track down the NEJM study because no author was provided.
M. The Parvizi 2003 study was excluded due to the sample size being less than 25 patients Our methodology does not allow for the use of other systematic reviews in our CPGs, although we do screen their bibliographies for relevant primary studies.
N. The Tokarski study was not specific to total joint patients so was excluded from our assessment of available evidence based on our methodology.
O. The Yi study has been reviewed and added to the recommendation. There were a few other studies of acute PJI that were already included, but their results were not originally summarized in the rationale. We added a summary of results of those studies, along with the positivity thresholds used. A description of studies in patients with inflammatory conditions was added as well. The possible harms and future research sections briefly describe the potential problems of the tests, and say that the tests should not be used alone. It should also be noted that the recommendation is that the listed biomarkers can be used to aid in diagnosis, which does not necessary mean they should be the only test used for diagnosis. However, the body of the rationale originally was

not clear on this point, and it is our hope that the additions to the rationale make it clearer. Although these tests can be of some value in diagnosis, they are not gold standard tests on their own.

   a. Reasons for exclusion of the other studies listed: Consensus based guidelines from other groups are automatically excluded from AAOS CPGs. The Saleh study was published after the last literature search. The Shahi study was not best available evidence due to high risk of patient spectrum bias, since they included a subgroup of patients getting primary arthroplasty as a healthy control group. The Johnson study is excluded due to the patient spectrum not being generalizable, which decreased its quality rating. The authors note in their limitations section that the specificity in their study was lower than previously published studies as ESR and CRP were not routinely tested at the authors' institution when there was low clinical suspicion of infection. The inclusion criteria of the study were for patients with clinical and radiographic suspicion of PJI. The authors stated that "Consequently, a negative test is more likely to be a false negative, generating a low ability of a negative test to disprove infection (specificity)." Because of the inclusion criteria, the prevalence of PJI in the Johnson study's patient population was 92.9%, whereas the prevalence of PJI in the two included combined ESR/CRP studies was 27.4% and 29.8%.

P. The 2017 study within the search window was excluded because the patient population was not specific to hip and knee replacement patients.
Q. A comment about NGS was added to the future research section
R. There was one study by Kwon that evaluated ESR and CRP in people with hip dual taper corrosion with ALTR. The results of this study have been added to the rationale
S. CPG methodology assesses evidence based effectiveness research and does not currently allow cost to be included in the recommendation statements.
T. We did not find sufficient quality data on these topics from studies that met our inclusion criteria. The Hatem study was partially a literature review and was unclear whether the data used for their model was specific to hip and knee patients. Similarly, the Kalmeijer and Kim studies were not specific to hip and knee replacement patients. The Baratz study was appraised as very low-quality due to its historical controlled trial design.

## Peer Reviewer Detailed Responses

Reviewer #4

| Reviewer Number | First Name | Society you are representing | Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: |
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| 4 | Alexis Vosooney, MD | American Academy of Family Physicians (AAFP) | A. In the first line of the second paragraph of the Methods section it states that this is a guideline for acute compartment syndrome (page 19).<br>B. In the first recommendation, "Risk Factors for PJI", the first line of the "Rationale" section state that there were 143 articles that met criteria for inclusion while above it says 248 articles met inclusion. I believe they mean only 143 articles met inclusion for this topic but I think they need to state the 143 figure is just for this topic area.<br>C. On page 25, under "limited strength", in the "Alcohol section" they list alcohol consumption in grams per week - this would be more understandable listed in either ounces or examples (i.e. 4 beers per week, three 6 oz glasses of wine per week) as that is more translatable to how patients/providers consider consumption.<br>D. On page 25, under "limited strength", in the "Anemia" section; it's not clear to me if they mean pre-op anemia, post-op anemia or if both were used in the study data.<br>E. On page 32, in the "Injections Prior to Arthroplasty" section, under "rationale", the first line of the second paragraph discuss that two studies showed increased risk of infection with steroid injection prior to surgery but didn't define the timeline of "prior to surgery" for those studies. This would be helpful information to include<br>F. On page 45, under "Avoiding Antibiotics When Diagnosis Has Not Been Established" recommendation, in the second line of the "possible harms" section they state that with a hemodynamically stable patient there are no potential risks for withhold antibiotics. I think you need to take into account the risk of progression from isolated PJI to sepsis/systemic illness - either specifically state the risk to systemic illness is low or state that risk of progression is unknown. While they cited sepsis as a possible reason to not withhold antibiotics they may want to consider if other populations should be excluded, like immunocompromised patients.<br>G. On page 46, under "Avoiding Initiating Antibiotics" recommendation, the "possible harms" section states that there is no risk to withholding antibiotics. I think this is a reasonable statement to make if it also includes language like, "the chance of PJI progressing to systemic illness is X%, so there is very little harm from withholding antibiotics until a culture is obtained/diagnosis established".<br>H. On page 52, under "Antibiotic Cement", in the "Rationale B" section - the data, as it's presented, does not seem convincing as to why the overall recommendation is that you |

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| | | | could use antibiotics in cement for THA - needs further explanation as to why the studies that show potential benefit were strong enough to over come the studies with no benefit.<br>I. On page 53, under "Preoperative screening and Decolonization", in the "Rationale" section, regarding the chlorhexidine wipes, since they are citing just a few studies, it may be helpful to include the study protocol (i.e. wipes night prior to surgery or twice in week before surgery) with language that it may not be the ideal protocol but it is the one with data.<br>J. 10. I also couldn't find the COI listings in the main guideline or the 500 page appendix. This is important information that is missing and hinders an comprehensive review. |

## Workgroup Responses to Reviewer #4

A. Changed
B. Changed. Out of 143 studies which met inclusion criteria for this recommendation
C. Addition made
D. It is preoperative. The section title was changed from “Anemia” to “Preoperative anemia”
E. Was changed to “With respect to injections prior to knee arthroplasty, two low strength studies (Papavasiliou et al. 2006, Bedard et al. 2017) reported on an increased risk for deep infection if the patient had received an intra-articular steroid injection within six months or within 12 months prior to surgery.”
F. This sentence is in the harms section “However, it is recommended that patients remain closely monitored to ensure no worsening of their clinical status during the antibiotic free period.”
G. The harms section was changed to “There may be scenarios where withholding antibiotic treatment may not be appropriate, such as in the case of sepsis. However, in a hemodynamically stable patient, there are no known associated risks or harms with this recommendation. It is important to note that there is not clear evidence as to the risk of delaying antibiotic treatment in the patient with suspected but undiagnosed periprosthetic infection which argues for expeditious evaluation to make the diagnosis.”
H. Thank you for bringing this to our attention. The wording of the rationale does send a mixed message, due to an incorrect reporting of the Dale 2012 study in the rationale. In regard to that study, the rationale incorrectly stated they found “increased infection rates with the use of antibiotic cement (Dale, 2012).” The Dale 2012 study actually showed revision for infection was reduced with antibiotic cement compared to cement with antibiotics. This error makes the evidence seem more conflicting than it actually is. We have fixed the error, and moved the results discussion of the Dale 2012 study to the next paragraph, that discusses revision risk with abx cement.
I. All 3 studies were by the same lead author and had the wipes applied the night before and preoperatively in the hospital. The specifics of each treatment can be found in the evidence tables. Also, the orthoguidelines.org web page in which people will be able to view the guideline provides links to the included studies for a recommendation. Therefore, if a reader wants to get more information on each study, they can click the hyperlink underneath the rationale, which will connect them to the study on pubmed.
J. COI is provided in the final document, but author details are blinded to peer reviewers for unbiased review

## Peer Reviewer Detailed Responses

Reviewer #5

| Reviewer Number | First Name | Society you are representing | Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: |
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| 5 | Alex McLaren, MD | Musculoskeletal Infection Society (MSIS) | MSIS Review committee: 3 ID docs, 2 MSK Infection surgeons, one Co-Chair of AAOS SSI management CPG. We understand the recommendations are based on the data extracted from a rigorous systematic review however many of our comments rely on the experience and wisdom of the work group to make certain that recommendations are not taken out of context or go against established/expected medical practice; if they do go against accepted practice, comprehensive irrefutable data should be cited and discussed. Also, in light of real world experience, there is a concern that any recommendation that relies on the rationale to be implemented appropriately runs the risk of inappropriate use by readers who only read the recommendation and not the supporting information.<br>A. Some of the cryptic recommendation titles are often poor, needing more accurate or better descriptive wording.<br>B. Much of the text throughout needs copy editing to resolve ambiguity, unclear statements, difficult flow of rationale and colloquialisms.<br>C. Also, we suggest using more correct terminology of antimicrobial (or antibacterial or antifungal where appropriate) instead of antibiotic and suggest the consistent use of microorganism (or pathogen where appropriate) throughout instead of organism<br>D. Included in the manuscript are obvious content from other documents, like Line 583. We also recognize other wording from other CPG overviews and methods<br>E. 135 Diabetes Perioperative Glucose control see below<br>F. 144 Ambiguous statement might be more specific to state “the risk of PJI” rather than “caution should be considered”<br>G. 145 – 150 Placing a patient with active infection in the same risk category as an “institutionalized patient” makes no sense; it is not obvious why the parenthetical phrase is included it does not seem to add anything<br>H. 158 In the <u>absence of reliable evidence</u>, it is the opinion of this work group that the following conditions <u>do not have enough evidence</u> ….. suggest rewording<br>I. 185-186 In light of the SSI Management CPG clarification would be appropriate …. Are these independent or in combination? |

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| | | | J. 226 Intraop histopathology requires the availability of skill set not present in all centers which warrants discussion in the rationale.<br>K. 255 MAVRIC/MARS technique MRI is missing, please see below<br>L. 257-8 While PET CT may there are data supporting PET-CT, the lack of availability/ coverage for clinical use make this recommendation impractical. We ask the work group to consider the wisdom of a recommendation that cannot be followed in most centers for most patients due to system limitations; perhaps diagnostic capabilities in the rationale balanced by system limitations<br>M. 266 “nuclear imaging is felt to be too generic; the recommendation should specify which studies<br>N. 292 Should this cryptic title and the recommendations read as follows: “pathogen has been identified” rather than “diagnosis has not been established”, as the diagnosis can be made without a positive culture<br>O. 306 consider deleting “and a diagnosis has been made” as a diagnosis does not require a positive culture and also consider adding “unless antibiotics are necessary for the safety of the patient”<br>P. 334 The issue of vancomycin alone as adequate prophylaxis warrants consideration related to several points: Vancomycin prophylaxis has not been shown to be ineffective; Vancomycin is less potent than 1st generation cephalosporins by in vitro studies against some strains of staphylococci. Stewardship- it is likely that if MIC’s continue to “creep” higher, vancomycin will become ineffective. The wording of the recommendation should be such that it does not promote an unacceptable practice<br>Q. 364-81 Differing recommendations for THR and TKR are fallout from alpha errors and interpretation of reported data. (A and B ) recommendations need attention. A Please see further comments below. More recent data does not show reduction in PJI and the risk of PJI resistant to loaded antimicrobial when it does o/reccur should be addressed.<br>R. 386 The cloths are made by a specific manufacturer and there are studies on CHG bathing that do not involve the cloths. Should just say ‘preoperative decolonization using chlorhexidine’ Please see further comments below.<br>S. 402 Is this nasal mupirocin for universal implementation or for positive carriers only? There are variations on protocol(s) that need discussion in rationale. (5 day protocol vs day prior to or day of surgery, Staph aureus carriers, Please see further comments below.\<br>T. 413 Other antiseptics like CHX should be discussed and it should be specified whether this is for primary, revision, conversion, DAIR or second stage post PJI reimplantation.<br>U. 493 it would be desirable to provide which PJI definition is being used<br>V. 495-505 Please provide references for the statistics stated.<br>W. 546 None of us could figure out what this sentence means.<br>X. 591 link loops to same document<br>Y. 622 entire in this table need to be defined/explained<br>Z. 646 ?? do you mean diagnosis and prevention not treatment |

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| | | | AA. 719, 968, 974 There is no such thing as an asymptomatic UTI. The correct term is asymptomatic bacteriuria'<br>BB. 1025 may usually expressed a permission, nevertheless, the wording leads to uncertainty related to the "dependent" relationship which usually means positive progressive (i.e. longer time more effect) relationship. The data does not give a progressive relationship, could be a threshold, and it is inverse.<br>CC. 1053 We are concerned that as written, there is risk that patients could be inappropriately be denied reconstruction of end stage joint disease if they had an injection within a year<br>DD. 1097-9 as in previous comment, CRP and ESR should not be sole tests and think this should be reflected in the recommendation<br>EE. 1302 We do not see MRI in the recommendation however think MAVRIC/MARS technique MRI should be both in the recommendation and the rationale.<br>FF. 1386, 1419 It is a very real possibility that a patient taken off ABX treatment could have progression or acceleration of their infection that requires urgent intervention. While it is agreed that to stop antimicrobials for 2 weeks (or some multiple of half-lives or efficacy times) prior to obtaining definitive culture specimens is appropriate, we believe it is prudent to actively follow/monitor the patient for timely detestation and intervention if clinical deterioration occurs. A statement regarding the need to monitor patients closely for worsening of their clinical status is needed here.<br>GG. 1444-5 Considering the above recommendation " AVOIDING ANTIBIOTICS WHEN DIAGNOSIS HAS NOT BEEN ESTABLISHED" and assuming the previous recommendation related to synovial aspirate preoperatively, please reconcile in the rationale the difference between preoperative synovial aspirate on full treatment and tissue/device cultures obtained at debridement after a single antimicrobial dose<br>HH. 1464 We have concern that the last sentence as it currently reads will open the door to regimens (drug/ duration) that have not been adequately studied. The rest of B recommendation is valid and does not need this statement to be complete.<br>II. 1491 Further to previous comment, please consider the current understanding that vanc alone is inferior pharmacologically to vanc and cefazolin, presenting a risk of inadequate coverage for common nonresistant staph species when vancomycin only is given for to patients with high risk for resistant organisms. In the absence of any data meeting the inclusion criteria, this point should be discussed in the rationale.<br>JJ. 1538-9 It is unclear why this statement is included here and while similar statements are not in other recommendations<br>KK. 1540 "Rationale B" does not lead to the conclusion that antibiotic cement decreases risk of SSI/ PJI. The opposite conclusion follows when reading this without knowing the recommendation. When the outcome of interest is infection, the conclusion is clear - no effect; Other metrics like all-cause revisions and loosening had conflicting data but that should not change the recommendation for infection prevention. |

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| | | | LL. 1561-3 While it may be academically complete to consider the possibility of increased infection rates the authors should give a basis for this counterintuitive assertion, either data or a rational mechanism, or preferably remove it. The degradation in mechanical properties of PMMA occur with higher doses than the 1-2 % loads used for prophylaxis. There are no mechanical or clinical data to support loosening with low dose antibiotic cement. The risk should be linked to loads of 4.5% or greater. Finally the resistance issue is real but clinically has not come to fruition, would favor a statement like "increase the risk for development of antimicrobial resistance from prolonged subtherapeutic release of antimicrobials that has the potential to cause resistant infections".<br>MM. 1569-70 The points here are that the antiseptic is CHX and that the decolonization application is to the extended operative site/ corpus not including nasal decolonization …. Not that it is a cloth. The recommendation should be reworded to reflect that.<br>NN. 1576, 1596-7 The recommendation does not state only for culture positive carriers of susceptible pathogens and the risk of selecting resistant organisms is high. The rationale does not support universal or indiscriminate mupirocin use; we cannot support this recommendation. The harm statement should include the risk of developing resistant pathogens<br>OO. 1602 The recommendation title should be more specific to Intraoperative Antiseptic Lavage; also there is basic science evidence that dilute chlorhexidine is effective and it is regularly used by many, so should at least be included in the rationale<br>PP. 1612 Significant difference is a mathematical condition that means the data sets are mathematically distinct and thus the clinical difference is real. It does not give any indication of clinical effect size, which is what is needed to make an informed professional judgement of whether the difference justifies the risk and resources needed to implement this recommendation. Throughout the document, the effect size should be added to every statement of statistical significance (eg study reported a statistically significant decrease of infection rate from X% to Y%). There are many instances where the rationale could be misleading if the significance for a difference is not clinically meaningful.<br>QQ. 1615-6 "No known harm" should not be stated even with conditions attached, especially when allergy and toxicity are well known. Potential harms should also include cellular injury from the betadine, albeit not likely at the concentration used and not in healthy tissue, but documented in the basic science literature none the less. |

## Workgroup Responses to Reviewer #5

A. No response needed
B. No response needed
C. Antimicrobials were added to recommendation wording and titles where appropriate
D. This has been corrected
E. No response needed
F. The reason for the ambiguity is that that the strength of evidence is not very good, so more clinical judgement is necessary but we have worked to clarify the recommendation.
G. The grouping is based on the strength of evidence of studies supporting a recommendation, not on its importance as a risk factor. To reach a limited strength of recommendation, you need to have consistent evidence from two or more observational studies with reasonably good research methodologies. Active infection was only supported by a single observational study with sufficient research methodology for inclusion, and therefore could only be a consensus level recommendation. Institutionalization also only had sufficient evidence for a consensus recommendation. Again, the grouping is based on the strength of evidence of studies (or lack of studies) supporting the statement, and NOT on its importance as a risk factor. For example, the fact tobacco use is listed in the limited recommendation and active infection is listed under consensus DOES NOT mean that tobacco is more likely to cause PJI than active infection. It does mean that there was a sufficient number of adequate quality observational studies to support a limited recommendation for tobacco use, but not for active infection. Our rules of evidence would not allow the work group to make a stronger recommendation for active infection than for institutionalization or other consensus level of evidence risk factors, but they wanted to make it clear that they believed active infection to be more important than the other consensus level risk factors. This prompted the addition of the parenthetical comments and is why active infection says, “strongly caution against proceeding with surgery” while the others say “proceed only after careful consideration of the risks.”
H. Based on our methodology, we cannot change the wording “in the absence of reliable evidence,”. However, we agree the wording of the rest of the recommendation is not very clear, and requires one to closely read the rationale to understand the recommendation. Therefore, we added parentheses to clear this up
I. The scope of the SSI guideline was more general, in that it covered both superficial and deep/PJI and was not limited to only hip/knee replacement procedures. The PJI CPG is only of deep infections specific to hip and knee replacement procedures. Some studies in the PJI recommendation addressed ESR and CRP independently, while others addressed them in combination.
J. Agreed. Comment added in the implementation and harms section
K. Responded to comment below
L. The recommendation is not that the test must be used, it is that limited strength evidence suggests that the test might provide useful diagnostic information if the test is able to be performed in a health care setting.
M. This information can be found in the rationale and the evidence tables of the CPG
N. The titles for the antimicrobial effect on diagnosis has been changed to be more descriptive
O. The harms of implementation section now says “There may be scenarios where withholding antibiotic treatment may not be appropriate, such as in the case of sepsis. However, in a hemodynamically stable patient, there are no known associated risks or harms with this recommendation. It is important to note that there is not clear evidence as to the risk of delaying antibiotic treatment in the patient with suspected but undiagnosed periprosthetic infection which argues for expeditious evaluation to make the diagnosis.”
P. The evidence from the included studies supports the recommendation. Based on our guideline methodology, in vitro studies are excluded from AAOS CPGs. Language added to risks and harms section.
Q. Citations would need to be provided to respond to this comment
R. Citations would need to be provided to respond to this comment. All three included studies used chlorhexidine cloths.

S. The recommendation has been changed to “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 prior to hip and knee arthroplasty in patients who are MRSA carriers.”
T. We searched the literature for all types of antiseptic washes/irrigations, but the only adequate quality studies that met inclusion criteria was for dilute betadine solution. The 3 included studies evaluated a group of both primary and revision arthroplasty patients. DAIR was beyond the scope of this CPG.
U. This section is more to address scope of this guideline, in that it was looking specifically at prevention and diagnosis deep infection/PJI and not at superficial infections, and also does not evaluate treatment strategies after PJI is diagnosed (PJI treatment strategies will be addressed in a separate guideline). When appraising the studies, MSIS criteria was considered the best reference standard, however this wasn’t used in all of the studies, especially older ones. We did not exclude studies with other reference standards, but the validity of the reference standard was part of quality appraisal.
V. References are provided in the burden of disease section
W. This sentence, and the one after, are meant to say that the recommendations are made using a balance of benefits and harms of implementation. To clarify this point, it was changed to “This guideline comprehensively evaluates the available evidence regarding recommendations for prevention and diagnosis of PJI. Effort has also been made to identify potential harms that may be associated with implementing each individual recommendation.”
X. Thank you for pointing that out. It was supposed to link to eAppendix 1. This has now been corrected.
Y. The first table describes how we arrive at final strength of evidence. Strength of evidence is based on the number, quality, and consistency of results of the included studies for a recommendation. The second table indicates that recommendations with weaker strength of evidence are more likely to change in the future if higher quality studies are published that contradict the lower quality evidence from the studies included in this guideline. It also indicates that clinical judgement and shared decision making with patients are more important in lower strength recommendations that are not based on high quality evidence.
Z. Correct. This has been changed to “current diagnostic and prevention strategies”
AA. Updated
BB. True, but the rationale makes it clear that risk may be higher if injections are given closer to arthroplasty
CC. A statement was added to the harms of implementation section about this issue.
DD. The recommendation is worded that the tests can be used to aid in the diagnosis of PJI, which already implies that they shouldn’t be used alone as the sole test. Also, the limitations of these tests are described in the harms of implementation section of the rationale, and there is a statement in the future research section that says “No test should be used alone.”.
EE. The quantity and quality of evidence was insufficient for MRI, since only one low quality study met inclusion criteria. Since two or more low quality studies are required for a limited strength recommendation, MRI could not be listed in the recommendation.
FF. Comment has been added to clarify
GG. There was a sentence in the rationale that states that those with a known pathogen would benefit from antibiotics. It was implied that the known pathogen would be from a preop aspiration. To clear up confusion the sentence was changed to “Additionally, patients with an established diagnosis of PJI and a known pathogen from preoperative synovial aspirate who are undergoing surgery would also benefit from preoperative antibiotic prophylaxis.
HH. The sentence was needed to say that we did find studies for the comparisons list at the end of the rationale that showed no difference, but the strength of evidence was very low due to a combination of the low number of moderate or high quality RCTs and low statistical power.
II. There was low quality data regarding the comparison of vanco and cefazolin for PJI, so this statement would contradict the evidence from the studies that were included. Language added to risks and harms section.
JJ. This was mainly for consistency with our antibiotic cement recommendation in the surgical management of osteoarthritis of the knee (SMOAK) guideline, which included many of the same studies. It was also necessary to explain why the evidence from these RCT studies did not result in a recommendation for antibiotic cement in the general TKA population. The RCT evidence came from studies with special populations, like revision and diabetic patients, and therefore didn’t warrant a recommendation for antibiotic cement in the general primary TKA population.
KK. Thanks for pointing out that the data appeared conflicting. The wording of the rationale does send a mixed message, due to an incorrect reporting of the Dale 2012 study in the rationale. In regards to that study, the rationale incorrectly stated they found “increased infection rates with the use of antibiotic cement

(Dale, 2012).” The Dale 2012 study actually showed revision for infection was reduced with antibiotic cement compared to cement with antibiotics. This error has been fixed.

LL. Wording in the risks and harms section has been updated to “Indiscrimate use of antibiotic laden cement may have unintended consequences that were not specifically evaluated with this recommendation. Although the studies did not show increased risk of implant loosening, it is possible that cement with higher doses of antibiotics could increase risk of loosening by changing the mechanical properties of the cement fixation. Similarly, there is the potential for other effects such as antimicrobial resistance or increased costs to the healthcare system that should be considered.”

MM. The included studies only looked at CHX cloths

NN. The recommendation has been changed to “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 prior to hip and knee arthroplasty in patients who are MRSA carriers.”

OO. Citations need to be provided to respond to this comment

PP. Effect sizes are provided in the evidence tables in the appendices

QQ. Allergy is already discussed in the harms section

## Peer Reviewer Detailed Responses

Reviewer #6

| Reviewer Number | First Name | Society you are representing | Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: |
|---|---|---|---|
| 6 | Robert Sautter, PhD, HCLD (ABB) CC | American Society of Microbiology (ASM) | Thank you for the opportunity to review and comment on the AAOS Draft Clinical Practice Guideline on the Diagnosis and Prevention of Periprosthetic Joint Infections. The guideline was reviewed by two members of the American Society for Microbiology's (ASM) Evidence-based Laboratory Medicine Practice Guideline Subcommittee, and ASM is pleased to endorse the guideline. We find it to be in substantial compliance with previous IDSA guidelines for management of PJI and with IDSA/ASM guidelines for utilization of the microbiology laboratory. In particular we are in support of areas related to clinical microbiology with the following comments:<br>A. Synovial fluid tests (211-225): We are in full support of the recommendation for aerobic and anaerobic cultures. Further, we support the recommendation for use of blood culture bottles (1213-1214) and suggest that be included in the summary statement (216). It is important that the guideline acknowledge the lack of FDA-cleared or approved assays for several recommended tests, particularly those based on NAAT, eg PCR (1220-1230) and we applaud the acknowledgement of this issue.<br>B. Intraoperative tests: We support the recommendation for use of multiple samples for aerobic and anaerobic cultures (235-240). While it is acknowledged that the scope of this guidelines does not include an assessment of the optimal number of samples (1235-1236) or methods of sonication and significance of cutoff levels (1237-1241), these details are critically important to clinical microbiology, and it is hoped these issues may be addressed in future iterations of this guideline. Similarly, holding time (ie incubation beyond the usual 2-3 days and up to 2-3 weeks) for cultures is an important issue addressed in microbiology literature that is not addressed in this guideline, and should be considered in future versions.<br>C. Note that the 2018 IDSA/ASM Guide to Utilization of the Microbiology Laboratory for the Diagnosis of Infectious Diseases provides a recent summary of current expert consensus guidelines for microbiologic handling of samples for PJI (https://www.idsociety.org/globalassets/idsa/practice-guidelines/a-guide-to-utilization-of-the- |

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| | | | microbiology-laboratory-for-diagnosis-of-infectious-diseases-2018-update-by-the-infectious-diseases-society-of-america-and-the-american-society-for-microbiology.pdf). Selected references to support the relevance of these issues are listed here:<br>1. Schäfer P, Fink B, Sandow D, Margull A, Berger I, Frommelt L; Prolonged Bacterial Culture to Identify Late Periprosthetic Joint Infection: A Promising Strategy; *Clinical Infectious Diseases*, 47(11): 1403–1409 (2008) https://academic.oup.com/cid/article/47/11/1403/281649<br>2. Larsen LH, Lange J, Xu Y and Schønheyder HC; Optimizing culture methods for diagnosis of prosthetic joint infections: a summary of modifications and improvements reported since 1995; *Journal of Medical Microbiology* 61: 309-316 (2012) https://www.microbiologyresearch.org/docserver/fulltext/jmm/61/3/309_jmm035303.pdf?expires=1547572196&id=id&accname=guest&checksum=94BBDA69FAF7ED5C98D8F95D2CA45E9C<br>3. Font-Vizcarra L, Garcia S, Martinez-Pastor JC, Sierra JM, and Soriano A; Blood Culture Flasks for Culturing Synovial Fluid in Prosthetic Joint Infections; *Clin Orthop Relat Res* 468(8): 2238-2243 (2010) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2895826/<br>4. Shen H, Tang J, wang Q, Jiang Y, and Zhang X; Sonication of Explanted Prosthesis Combined with Incubation in BD Bactec Bottles for Pathogen-Based Diagnosis of Prosthetic Joint Infection , *J Clin Microbiol* 53(3): 777-781 (2015) https://jcm.asm.org/content/jcm/53/3/777.full.pdf<br>D. Gram stain (285-288): While we agree that the "practitioner avoid the use of intraoperative gram stain to rule-out periprosthetic joint infection", Gram stains are generally routinely performed on samples from normally sterile sites (ie synovial fluid and intraoperative periprosthetic samples) and may suggest a potential infecting agent that may guide subsequent culture methods and immediate therapeutic approaches. We would suggest that the rationale for this recommendation (1362) emphasize the potential utility of a positive Gram stain result<br>E. Preoperative screening and decolonization (404-406): Regarding the "absence of reliable evidence for screening and nasal decolonization", we would recommend a clarification on what constitutes "screening". It is assumed that "screening for MRSA by molecular and/or culture-based methods" is the issue, but a point of clarification in the rationale (1584) and future research (1601) is suggested.<br>F. Although suggestions to be included in future revisions of the important guideline are listed above, it is our recommendation to include these as possible in the current document. |

## Workgroup Responses to Reviewer #6

A. Thank you for you feedback.
B. Agreed. These are important issues that hopefully be addressed when this CPG is updated.
C. Articles addressed as follows:
    1. Included article
    2. Our methodology does not allow us to include other systematic reviews in our CPGs, although we do screen their bibliographies for relevant primary studies
    3. Included article
    4. Unfortunately, this article did not come up in our literature search, but would have been excluded as not best available evidence, since sonication formed part of the reference standard, leading to incorporation bias. Also, the study would have been downgraded due to lack of blinded interpretation of the reference standard.
D. Agreed. Thank you for pointing that out. The evidence from the included studies did find that a positive gram stain result was good at ruling in infection, in that a positive test produced a large increase in probability of infection (all studies had positive likelihood ratios over 10). The purpose of the recommendation was to emphasize that the test is very poor as a rule out test, in that a negative test should not be taken as proof that a patient isn't infected, but it is worth mentioning the good rule in results from the evidence as well. Therefore, we added the caveat that the test was good at ruling in infection. The second sentence of the rationale was changed to "Although these studies found a positive gram stain to be a strong rule-in test, all had negative likelihood ratios over 0.5, indicating a negative Gram stain is not a strong indicator of absence of periprosthetic joint infection whether performed on synovial fluid, tissue, or sonicate fluid."
E. The recommendation has been changed to "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 prior to hip and knee arthroplasty in patients who are MRSA carriers."
F. Thank you for your input.

## Public Commenter Demographics

| **Name of Reviewer (Required)** | **Lisa Fatheree, BS, SCT(ASCP), CA-AM** | **Adolph Yates, MD** | **Ann MacIntyre, DO, MHS, FIDSA** | **Stephen Liang, MD** | **Paul Auwaerter, MD** |
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| Please list your primary specialty (Required): | Pathology, Laboratory Medicine | Total Joint | Infectious Diseases | Infectious Diseases | |
| Please list your work setting (Required): | Non-profit medical society | Academic Practice | | Academic Practice | Academic Practice |
| Are you reviewing this guideline as a representative of a professional society? | Yes | No | Yes | Yes | Yes |
| May we list your society as a reviewer of this guideline? | Yes | | Yes | Yes | Yes |
| If reviewing on behalf of a professional society, please list the name of the society that you are representing | College of American Pathologists | | Infectious Diseases Society of America | Infectious Diseases Society of America | IDSA |
| Have you declared your conflicts of interest in the AAOS Disclosure database? | No | Yes | No | No | No |
| A) Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? | No | | No | No | No |
| B) Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? | No | | No | No | No |
| C) Are you or a member of your immediate family a | No | | No | No | No |

| **Name of Reviewer (Required)** | **Lisa Fatheree, BS, SCT(ASCP), CA-AM** | **Adolph Yates, MD** | **Ann MacIntyre, DO, MHS, FIDSA** | **Stephen Liang, MD** | **Paul Auwaerter, MD** |
|---|---|---|---|---|---|
| PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier?No | | | | | |
| D) Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? | No | | No | No | No |
| E) Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? | No | | No | No | No |
| F) Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) | No | | No | No | Yes; Johnson & Johnson (equity) Collodion (stock options) |
| G) Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or | No | | No | Yes; ContraFect, Allergan | |

| Name of Reviewer (Required) | Lisa Fatheree, BS, SCT(ASCP), CA-AM | Adolph Yates, MD | Ann MacIntyre, DO, MHS, FIDSA | Stephen Liang, MD | Paul Auwaerter, MD |
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| equipment company, or supplier? | | | | | |
| H) Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? | No | | No | No | No |
| I) Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? | No | | No | No | No |
| J) Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? | No | | No | No | No |
| What CPG topic are you reviewing? | Pathology | Periprosthetic Infection | PJI | Diagnosis and prevention of prosthetic joint infection | |

## Public Comment Responses to Structured Public Comment Form Questions

| **Name of Reviewer (Required)** | **Lisa Fatheree, BS, SCT(ASCP), CA-AM** | **Adolph Yates, MD** | **Ann MacIntyre, DO, MHS, FIDSA** | **Stephen Liang, MD** | **Paul Auwaerter, MD** |
|---|---|---|---|---|---|
| 1. The overall objective(s) of the guideline is (are) specifically described. | Strongly Agree | Agree | Agree | Strongly Agree | Agree |
| 2. The health question(s) covered by the guideline is (are) specifically described. | Strongly Agree | Agree | Agree | Strongly Agree | Agree |
| 3. The guideline's target audience is clearly described. | Strongly Agree | Agree | Agree | Strongly Agree | Agree |
| 4. There is an explicit link between the recommendations and the supporting evidence. | Strongly Agree | Neutral | Agree | Strongly Agree | Agree |
| 5. Given the nature of the topic and the data, all clinically important outcomes are considered. | Neutral | Disagree | Neutral | Agree | Neutral |
| 6. The patients to whom this guideline is meant to apply are specifically described. | Strongly Agree | Neutral | Agree | Strongly Agree | Agree |
| 7. The criteria used to select articles for inclusion are appropriate. | Strongly Agree | Neutral | Agree | Strongly Agree | Agree |
| 8. The reasons why some studies were excluded are clearly described. | Strongly Agree | Neutral | Agree | Strongly Agree | Agree |
| 9. All important studies that met the article inclusion criteria are included. | Neutral | Neutral | Agree | Strongly Agree | Neutral |
| 10. The validity of the studies is appropriately appraised. | Strongly Agree | Neutral | Agree | Strongly Agree | Neutral |
| 11. The methods are described in such a way as to be reproducible. | Strongly Agree | Neutral | Agree | Strongly Agree | Agree |
| 12. The statistical methods are appropriate to the material and the objectives of this guideline. | Neutral | Neutral | Agree | Strongly Agree | Agree |
| 13. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed. | Neutral | Neutral | Agree | Strongly Agree | Agree |
| 14. Health benefits, side effects, and risks are adequately addressed. | Neutral | Disagree | Agree | Strongly Agree | Agree |
| 15. The writing style is appropriate for health care professionals. | Agree | Agree | Agree | Strongly Agree | Agree |

| Name of Reviewer (Required) | Lisa Fatheree, BS, SCT(ASCP), CA-AM | Adolph Yates, MD | Ann MacIntyre, DO, MHS, FIDSA | Stephen Liang, MD | Paul Auwaerter, MD |
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| 16. The grades assigned to each recommendation are appropriate. | Neutral | Neutral | Neutral | Strongly Agree | Agree |
| Would you recommend these guidelines for use in clinical practice? | Recommend | | Recommend | Strongly Recommend | Neutral |

## Public Comment Open Responses

| Name of Reviewer (Required) | Lisa Fatheree, BS, SCT(ASCP), CA-AM | Adolph Yates, MD | Ann MacIntyre, DO, MHS, FIDSA |
|---|---|---|---|
| Public Comment Open Responses | Christina Wojewoda, MD, and Romney Humphries, PhD, D(ABMM), M(ASCP)cm, MT(ASCP) reviewed the draft guideline on behalf of the Microbiology Committee of the College of American Pathologists.<br><br>All previous peer review comments were incorporated and no additional edits are needed at this time.<br><br>Sincerely,<br>Lisa Fatheree<br>Director, Pathology and Laboratory Quality Center for Evidence-based Guidelines | It is difficult to use the given form in that it is asking for approval/disapproval of the overall product when there might be specific recommendations that could be improved. It forces the reviewer to remain neutral.<br><br>Observations:<br><br>1.) It would have been valuable to have treated obesity by the tiers of obesity, morbid obesity, and super-obesity.<br><br>2.) The literature strongly suggests that the presence of Hepatitis C is a significant risk factor; given that there is now effective treatment that can eliminate the virus in three months in most patients, separate treatment of this element would be valuable.<br><br>3.) Given the multitude of new adjuvant methods to obtain an organism, including sonication, and also given the literature that shows little effect from a pre-operative antibiotic in establishing an organism, it is arguable that it might be appropriate to use one. This is an example of the possible utility of a number needed to treat analysis. It is known that preoperative infection is greatly reduced with prophylaxis; the few cases where it interferes with obtaining an organism might be outweighed by the avoidance of infection de novo in many other patients. Being dogmatic about holding antibiotics in questionable cases might be hurting more people than helping.<br><br>4.) The title of the "Intra-operative" | |

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| | | section is misleading; one could interpret the word intra-operative" to mean a set of tools that help the surgeon to determine the likelihood of infection while still in the OR (e.g., frozen sections, leukoestarase, etc.). Cultures and other tests that require time might be obtained intra-operatively, but do not add additional information during the case. | |
| Additional Comments regarding this clinical practice guideline? | | | |

| **Name of Reviewer (Required)** | **Stephen Liang, MD** | **Paul Auwaerter, MD** |
|---|---|---|
| Public Comment Open Responses | The guideline is well-written and based on a systematic review of the current literature. The questions addressed are clinically important and recommendations feasible. I have added comments to the DropBox version of the guideline for your consideration.<br><br>Line 1667 - betadine misspelled<br><br>Line 1618 - would also worry about systemic toxicity from antibiotic laden cement (gentamicin, vancomycin).<br><br>Line 1476 - future research could look at whether a time window exists in which antibiotics administered do not significantly impact culture yield (e.g., within 4 hours, etc.)<br><br>Line 1274 - no evidence supports routine fungal and mycobacterial cultures - maybe add a caveat that fungal and mycobacterial cultures should however be obtained based if there is heightened clinical suspicion?<br><br>Line 981 - please clarify what is meant by "asymptomatic urinary tract infection" - do you mean asymptomatic bacteriuria? Generally, if a patient is symptomatic and has bacteriuria or | I have some reservations about consensus, expert recommendations that could be construed as more evidence-based than they are, especially as the document says they will be outlined in a separate commentary.<br><br>L 871: suggest Bongratz 2008 study be qualified as rheumatoid arthritis, otherwise readers would conclude all types of inflammatory arthritis. RA is special in increased risk of bacterial infection whether in native joints, prosthetic joints or on/off immunosuppressives.<br><br>L1124: IL-6 remains a non-FDA approved test (at least through Quest Labs). I'd indicate as these kits and normal value ranges have not been sufficiently clinically validated (which may give pause to including this at the same breath as ESR and CRP as an aid in the diagnosis of PJI). Also unclear given the reservations expressed on L1128-1130, why IL-6 is placed at a high level with ESR and CRP.<br><br>1146 and forward: I remain concerned about lumping tests that are not FDA-approved such as alpha-defensin, synovial CRP at the same "moderate level of evidence" as synovial fluid leukocytes which is well established as a testing method. Also, clinicians will need to focus |

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| | leukoycturia, they are diagnosed as UTI. If they don't have symptoms, they don't have an infection (UTI) per many ID specialists.<br><br>Line 980 - delete second "the" at end of line<br><br>Line 484 - consider changing "emergency medicine providers" to "emergency physicians" | closely on the supporting text to understand that 5-10 WBC/HPF are the minimum values that are used to help rule-in PJI on histopathology. Moving such information support by meta-analysis to the high level would be very helpful. Also strange that synovial leukocyte counts are not given an established range in the evidence synthesis.<br><br>1525: although studies cited are of limited power to distinguish impact on low-frequency event such as PJI for hips/knees, other studies have suggested increased rates of MSSA if vancomycin is used, and if cefazolin is used, higher rates of MRSA for other surgeries but no clear superiority. That said, I agree with your statement and deferral to institutional antibiotic stewardship, infection control groups.<br><br>1560: Although tagged by limited evidence, I felt the two red recommendations should be labeled as for primary TKA and THR?<br><br>1657: One observational, single-surgeon study is interesting to be incorporated as a consensus, expert opinion that is likely to increase this practice without more careful study? Retrospective design and other changes besides dilute betadine could account for the changes seen. |
| Additional Comments regarding this clinical practice guideline? | | |

## Appendix A – Structured Peer Review/Public Comment Form

### Review Questions (REQUIRED)

| | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|
| 1. The overall objective(s) of the guideline is (are) specifically described. | ○ | ○ | ○ | ○ | ○ |
| 2. The health question(s) covered by the guideline is (are) specifically described. | ○ | ○ | ○ | ○ | ○ |
| 3. The guideline's target audience is clearly described. | ○ | ○ | ○ | ○ | ○ |
| 4. There is an explicit link between the recommendations and the supporting evidence. | ○ | ○ | ○ | ○ | ○ |
| 5. Given the nature of the topic and the data, all clinically important outcomes are considered. | ○ | ○ | ○ | ○ | ○ |
| 6. The patients to whom this guideline is meant to apply are specifically described. | ○ | ○ | ○ | ○ | ○ |
| 7. The criteria used to select articles for inclusion are appropriate. | ○ | ○ | ○ | ○ | ○ |
| 8. The reasons why some studies were excluded are clearly described. | ○ | ○ | ○ | ○ | ○ |
| 9. All important studies that met the article inclusion criteria are included. | ○ | ○ | ○ | ○ | ○ |
| 10. The validity of the studies is appropriately appraised. | ○ | ○ | ○ | ○ | ○ |
| 11. The methods are described in such a way as to be reproducible. | ○ | ○ | ○ | ○ | ○ |
| 12. The statistical methods are appropriate to the material and the objectives of this guideline. | ○ | ○ | ○ | ○ | ○ |
| 13. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed. | ○ | ○ | ○ | ○ | ○ |
| 14. Health benefits, side effects, and risks are adequately addressed. | ○ | ○ | ○ | ○ | ○ |
| 15. The writing style is appropriate for health care professionals. | ○ | ○ | ○ | ○ | ○ |
| 16. The grades assigned to each recommendation are appropriate. | ○ | ○ | ○ | ○ | ○ |

**Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline:**

**Would you recommend these guidelines for use in clinical practice? (REQUIRED)**

- ○ Strongly Recommend
- ○ Recommend
- ○ Would Not Recommend
- ○ Unsure

**Additional Comments regarding this clinical practice guideline?**