Draft Guideline for the Prevention of Surgical Site Infection

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Abbreviations

AMP	Antimicrobial prophylaxis
APRP	Autologous platelet rich plasma
ASA	Acetylsalicylic acid (aspirin)
ASEPSIS	Additional treatment, the presence of Serous discharge, Erythema, Purulent exudate, and Separation of the deep tissues, the Isolation of bacteria, and the duration of inpatient Stay
BMI	Body mass index
°C	Celsius
CABG	Coronary artery bypass graft
CDC	Centers for Disease Control and Prevention
CHG	Chlorhexidine gluconate
CMA	Centers for Medicare & Medicaid Services
DHQP	Division of Healthcare Quality Promotion
DMARD	Disease Modifying Antirheumatic Drug
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HICPAC	Healthcare Infection Control Practices Advisory Committee
ICD9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
INR	International Normalized Ratio
LMWH	Low molecular weight heparin
MRSA	Methicillin-resistant *Staphylococcus aureus*
NICU	Neonatal Intensive Care Unit
NHSN	National Healthcare Safety Network
OBS	Observational study
OR	Odds ratio
P	P value
PJI	Periprosthetic joint infection
RA	Rheumatoid arthritis
RCT	Randomized control trial
RR	Relative risk
SICU	Surgical intensive care unit
SD	Standard deviation
SR	Systematic review
SSI	Surgical site infection
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
TNF	Tumor Necrosis Factor
VTE	Venous thromboembolism
WBC	White blood cell

I. Executive Summary

Surgical site infections (SSI) are infections of the incision or organ/space occurring after surgery.[1,2] Prevention of SSI is increasingly important as the number of surgical procedures performed continues to increase.[3,4] Surgical patients presenting with more complex comorbidities[5] and the emergence of antimicrobial resistant pathogens increase the cost and challenge of treating SSIs.[6-8] Public reporting of process, outcome, and other quality improvement measures is now required,[9,10] and reimbursements[11] for treating SSIs are being reduced or denied.

The *Draft Guideline for Prevention of Surgical Site Infection* addresses new and updated strategies for the prevention of SSI in healthcare settings.[12] This guideline does not provide comprehensive infection control recommendations for prevention of SSIs. The select areas of focus were informed by feedback received from clinical experts and input from the Healthcare Infection Control Practices Advisory Committee (HICPAC), a federal advisory committee to the Centers for Disease Control and Prevention (CDC). The **Core section** includes recommendations intended to be generalizable across surgical procedures. The **Prosthetic Joint Arthroplasty section** focuses on this frequently performed procedure with a high human and economic burden. This guideline does not specifically address SSI prevention issues unique to: burns, trauma, surgical incisions allowed to heal by secondary intention, transplant procedures, transmission of blood borne pathogens from healthcare personnel to the patient, pediatric surgical practice, minimally invasive procedures, procedures performed outside the operating room (e.g., endoscopic procedures), non-surgical invasive procedures (e.g., cardiac catheterization, interventional radiology), and other procedures or conditions not specifically mentioned. In general, SSI prevention measures deemed effective in adults are also indicated in the pediatric population, and those effective in the operating room can be adapted or modified for other settings. In addition, this update does not address SSI surveillance or public reporting.[1,2] Recommendations on infection control in healthcare personnel,[13] environmental infection control,[14] and disinfection and sterilization of medical devices[15] in health care settings all of which may have an impact on the incidence of SSI, are topics addressed by other guidelines.

This document is intended for use by surgeons, physician assistants, perioperative nurses and other allied perioperative assistive personnel, anesthesia providers, postoperative inpatient and clinic nurses, infection prevention staff, healthcare epidemiologists, healthcare administrators, other healthcare providers, and persons responsible for developing, implementing, delivering, and evaluating infection prevention and control programs for surgical procedures performed in an operating room (inpatient or ambulatory setting). The guideline can also be used as a resource for professional societies or organizations that wish to develop more detailed implementation guidance or to identify future research priorities where there are evidence gaps for the prevention of SSI.

Our goal was to develop a guideline based on a targeted systematic review of the best available evidence, with explicit links between the evidence and recommendations. To accomplish this

we used an adapted Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system for evaluating quality of evidence and determining strength of recommendations.[16-19] The methodology, structure, and components of this guideline were adopted by the Centers for Disease Control and Prevention (CDC) and Healthcare Infection Control Practices Advisory Committee (HICPAC) in 2009. [20,21] A more detailed description of our approach is found in the Methods section. Evidence-based recommendations were cross-checked with those from other guidelines identified in an initial systematic search.

The Key Questions, Evidence Review, and Summary of Recommendations, are each organized as follows:

CORE section

To evaluate the evidence on SSI prevention across multiple surgical specialties and procedures, published material addressing ten key questions and related subquestions were examined:

Parenteral antimicrobial prophylaxis (AMP)

Q1. What are the most effective strategies for administering parenteral AMP to reduce the risk of SSI?

A. What is the optimal timing of preoperative AMP?

B. What is the optimal timing of AMP in cesarean section: prior to skin incision or at cord clamping?

C. How safe and effective is weight-adjusted AMP dosing?

D. How safe and effective is intraoperative redosing of AMP?

E. How safe and effective is postoperative AMP and what is the optimal duration?

Non-parenteral antimicrobial prophylaxis

Q2. What are the most effective strategies for administering non-parenteral antimicrobial prophylaxis at the surgical incision to reduce the risk of SSI?

A. How safe and effective is antimicrobial irrigation?

B. How safe and effective are antimicrobial agents applied to the surgical incision?

C. How safe and effective are antimicrobial-coated sutures; when and how should they be used?

D. How safe and effective are antimicrobial dressings applied to surgical incisions following primary closure in the operating room?

Glycemic control

Q3. How do perioperative blood glucose and hemoglobin A1C levels impact the risk of SSI, and what are their optimal perioperative target levels in diabetic and non-diabetic patients?

Normothermia

Q4. How safe and effective is the maintenance of perioperative normothermia in reducing the risk of SSI?

Q5. What are the most effective strategies for achieving and maintaining perioperative normothermia?

Oxygenation

Q6. In patients with normal pulmonary function, how safe and effective is the perioperative use of increased fraction of inspired oxygen (FiO_2) in reducing the risk of SSI?

Q7. What is the optimal target FiO_2 to reduce the risk of SSI; how and when should it be administered?

Antiseptic Prophylaxis

Q8. What are the most effective strategies for preparing the patient's skin prior to surgery to reduce the risk of SSI?

A. How safe and effective is preoperative antiseptic bathing or showering?

B. How safe and effective are antiseptic skin preparation agents individually and in combination?

C. How safe and effective is the application of an antimicrobial sealant immediately following skin preparation?

D. How safe and effective are plastic adhesive drapes?

Q9. How safe and effective is antiseptic irrigation prior to closing the surgical incision?

Q10. How safe and effective is repeat application of an antiseptic skin preparation agent to the surgical site immediately prior to closing the surgical incision?

PROSTHETIC JOINT ARTHROPLASTY Section

To evaluate the evidence on SSI prevention in prosthetic joint arthroplasty procedures, published material addressing 10 key questions and related subquestions were examined:

Blood transfusion

Q11. How do perioperative blood transfusions impact the risk of SSI in prosthetic joint arthroplasty patients?

A. Are specific blood products associated with a risk of SSI?

B. If the risk of SSI is increased, can this effect be isolated from the risk associated with more complex cases?

C. How does the volume of transfused blood product impact the risk of SSI?

D. How safe and effective is withholding blood transfusion to reduce the risk of SSI?

Systemic immunosuppressive therapy

Q12. How does systemic corticosteroid or other immunosuppressive therapy impact the risk of SSI in prosthetic joint arthroplasty patients?

A. Does the type of agent impact the risk of SSI?

B. Does the preoperative duration of the therapy impact the risk of SSI?

C. Does the agent dose impact the risk of SSI?

Q13. What are the most effective strategies in managing systemic corticosteroid or other immunosuppressive therapy perioperatively to reduce the risk of SSI in prosthetic joint arthroplasty patients?

A. How safe and effective is the discontinuation of these agents preoperatively, and when should they be resumed?

B. Should the agent dose be adjusted, and if so, for how long?

Q14. What is the optimal duration of postoperative AMP to reduce the risk of SSI in prosthetic joint arthroplasty patients who are on systemic corticosteroid or other immunosuppressive therapy?

Intra-articular corticosteroid injections

Q15. How do preoperative intra-articular corticosteroid injections impact the risk of SSI in prosthetic joint arthroplasty patients?
Q16. What are the most effective strategies for managing the preoperative use of intra-articular corticosteroid injections to reduce the risk of SSI in prosthetic joint arthroplasty patients?

A. Does the length of time between intra-articular corticosteroid injection and prosthetic joint arthroplasty impact the risk of SSI?
B. Does the corticosteroid injection dose impact the risk of SSI?

Anticoagulation

Q17. What are the most effective strategies for managing perioperative venous thromboembolism (VTE) prophylaxis to reduce the risk of SSI?

A. Does the risk of SSI differ by individual VTE prophylaxis agent?
B. What is the optimal timing and duration of perioperative VTE prophylaxis that also reduces the risk of SSI?
C. How safe and effective is modifying the dose of the perioperative VTE prophylaxis agent to reduce the risk of SSI?

Orthopaedic space suit

Q18. How safe and effective are orthopaedic space suits in reducing the risk of SSI in prosthetic joint arthroplasty patients, and which healthcare personnel should wear them?

Antimicrobial prophylaxis duration with drain use

Q19. What is the optimal duration of postoperative AMP to reduce the risk of SSI in prosthetic joint arthroplasty in the presence of a drain?

Biofilm

Q20. What are the most effective strategies to reduce the risk of biofilm formation and SSI in prosthetic joint arthroplasty patients?

A. How effective are cement modifications (i.e., antimicrobial and nanoparticle loading)?
B. How effective are prosthesis surface modifications (i.e., antimicrobial coating, galvanic couples, “printing” technologies, and nanotechnology)?
C. How effective are vaccines?
D. How effective are other biofilm control agents (e.g., biofilm dispersants, quorum-sensing inhibitors, novel antimicrobial agents)?

Evidence addressing the key questions was used to formulate recommendations and explicit links between the evidence and recommendations are available in the Evidence Review in the body of the guideline and Evidence Tables and GRADE Tables in the Appendices. **Category I recommendations are ALL considered strong and should be equally implemented;** only the *quality* of the evidence underlying the recommendation that distinguishes between levels A and B. Category IC recommendations are required by state or federal regulation and without regard to level of supporting evidence. Category II recommendations are considered weak recommendations, discretionary for the individual institution, and not intended to be enforced. The categorization scheme used in this guideline is presented in Table 1: Summary of Recommendations and described further in the Methods section.

Readers who wish to examine the evidence underlying the recommendations are referred to the Evidence Review in the body of the guideline, and the Evidence Tables and GRADE Tables in the Appendices. The Evidence Review includes narrative summaries of the data presented in the Evidence Tables and GRADE Tables. The Evidence Tables include all study-level data used in the guideline, and the GRADE Tables assess the overall quality of the evidence for each question and outcome examined. The Appendices also contain a clearly delineated search strategy that can be used for periodic updates to ensure that the guideline remains a timely resource as new information becomes available.

II. Summary of Recommendations

Table 1. CDC and HICPAC Categorization Scheme for Recommendations*[20,21]	
Category IA	A strong recommendation supported by high to moderate quality[*20,21] evidence suggesting net clinical benefits or harms.
Category IB	A strong recommendation supported by low-quality evidence suggesting net clinical benefits or harms, or an accepted practice (e.g., aseptic technique) supported by low to very low-quality evidence.
Category IC	A strong recommendation required by state or federal regulation.
Category II	A weak recommendation supported by any quality evidence suggesting a tradeoff between clinical benefits and harms.
No recommendation/ unresolved issue	An unresolved issue for which there is either low to very low-quality evidence with uncertain tradeoffs between benefits and harms or no published evidence on outcomes deemed critical to weighing the risks and benefits of a given intervention.

* Please refer to Methods section and Umscheid et al., "Updating the Guideline Methodology of the Healthcare Infection Control Practices Advisory Committee" (HICPAC; http://www.cdc.gov/hicpac/pdf/guidelines/2009-10-29HICPAC_GuidelineMethodsFINAL.pdf), for the process used to grade quality of evidence and formulate recommendations.

CORE SECTION

I. PARENTERAL ANTIMICROBIAL PROPHYLAXIS

1A. Administer preoperative antimicrobial agent only when indicated, based on published clinical practice guidelines and timed such that a bactericidal concentration of the agent is established in the serum and tissues when the incision is made **(Category IB)** [12] (Key Question 1A)

- No further refinement of timing can be made for preoperative antimicrobial agent based on clinical outcomes. **(No recommendation/unresolved issue)** (Key Question 1A)

1B. Administer the appropriate parenteral prophylactic antimicrobial agent prior to skin incision in all cesarean sections. **(Category IA)** [22-25] (Key Question 1B)

1C. No recommendation can be made regarding the safety and effectiveness of weight-adjusted dosing of parenteral prophylactic antimicrobial agents for the prevention of surgical site infection. **(No recommendation/unresolved issue)** (Key Question 1C)

1D. No recommendation can be made regarding the safety and effectiveness of intraoperative redosing of parenteral prophylactic antimicrobial agents for the prevention of surgical site infection. **(No recommendation/unresolved issue)** [26] (Key Question 1D)

1E. In clean and clean-contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain. **(Category IA)** [27-65] (Key Question 1E)

II. NON-PARENTERAL ANTIMICROBIAL PROPHYLAXIS

2A.1. No recommendation can be made regarding the safety and effectiveness of intraoperative antimicrobial irrigation (e.g., intra-abdominal, deep or subcutaneous tissues) for the prevention of surgical site infection. **(No recommendation/unresolved issue)** (Key Question 2A)

2A.2. No recommendation can be made regarding the safety and effectiveness of soaking prosthetic devices in antimicrobial solutions prior to implantation for the prevention of surgical site infection. **(No recommendation/ unresolved issue)** (Key question 2A)

2B.1. Do not apply antimicrobial agents (i.e., ointments, solutions, powders) to the surgical incision for the prevention of surgical site infection **(Category IB)** [66-72] (Key Question 2B)

2B.2. Application of autologous platelet rich plasma is not necessary for the prevention of surgical site infection. **(Category II)** [73-75] (Key Question 2B)

2C. Use of antimicrobial coated sutures is not necessary for the prevention of surgical site infection. **(Category II)** [76-79] (Key Question 2C)

2D. No recommendation can be made regarding the safety and effectiveness of antimicrobial dressings applied to surgical incisions following primary closure in the operating room for the prevention of surgical site infection. **(No recommendation/ unresolved issue)** (Key Question 2D)

III. GLYCEMIC CONTROL

3A.1. Implement perioperative glycemic control and use blood glucose target levels <200mg/dL in diabetic and non-diabetic patients. **(Category IA)** [80,81] (Key Question 3)

3A.2. No recommendation can be made regarding the safety and effectiveness of lower (<200mg/dL) or narrower blood glucose target levels, nor the optimal timing, duration, or delivery method of perioperative glycemic control for the prevention of surgical site infection. **(No recommendation/unresolved issue)** (Key Question 3)

3B. No recommendation can be made regarding optimal hemoglobin A1C target levels for the prevention of surgical site infection in diabetic and non-diabetic patients. **(No recommendation/unresolved issue)** (Key Question 3)

IV. NORMOTHERMIA

4. Maintain perioperative normothermia **(Category IA)** [82-84] (Key Question 4)

5. No recommendation can be made regarding the safety and effectiveness of strategies to achieve and maintain normothermia, the lower limit of normothermia, or the optimal timing and duration of normothermia for the prevention of surgical site infection. **(No recommendation/unresolved issue)** (Key Question 5)

V. OXYGENATION

6A. For patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation, administer increased fraction of inspired oxygen (FiO_2) both intraoperatively and post-extubation in the immediate postoperative period. To optimize tissue oxygen delivery, maintain perioperative normothermia and adequate volume replacement. **(Category IA)** [85-90] (Key Question 6)

6B. No recommendation can be made regarding the safety and effectiveness of administering perioperative increased fraction of inspired oxygen (FiO_2) for the prevention of surgical site infection in patients with normal pulmonary function undergoing either general anesthesia without endotracheal intubation or neuraxial anesthesia (i.e., spinal, epidural, or local nerve blocks). **(No recommendation/unresolved issue)** [91] (Key Question 6)

6C. No recommendation can be made regarding the safety and effectiveness of administering increased fraction of inspired oxygen (FiO_2) via facemask or nasal cannula only during the postoperative period for the prevention of surgical site infection in patients with normal pulmonary function. **(No recommendation/unresolved issue)**[92,93] (Key Question 6)

7. No recommendation can be made regarding the optimal target level, duration, and delivery method of the fraction of inspired oxygen (FiO_2) for the prevention of surgical site infection. **(No recommendation/ unresolved issue)** (Key Question 7)

VI. ANTISEPTIC PROPHYLAXIS

8A. Advise patients to shower or bathe (full body) with either soap (antimicrobial or non-antimicrobial) or an antiseptic agent on at least the night before the operative day **(Category IB)** [94-102] (Key Question 8A)

8A.1. No recommendation can be made regarding the optimal timing of the preoperative shower or bath, the total number of soap or antiseptic agent applications, or the use of chlorhexidine gluconate washcloths for the prevention of surgical site infection. **(No recommendation/ unresolved issue)** (Key Question 8A)

8B. Perform intraoperative skin preparation with an alcohol-based antiseptic agent, unless contraindicated. **(Category IA)** [103-116] (Key Question 8B)

8C. Application of an antimicrobial sealant immediately following intraoperative skin preparation is not necessary for the prevention of surgical site infection. **(Category II)** [117-119] (Key Question 8C)

8D. Use of plastic adhesive drapes with or without antimicrobial properties, is not necessary for the prevention of surgical site infection. **(Category II)** [104,120-124] (Key Question 8D)

9A. Consider intraoperative irrigation of deep or subcutaneous tissues with aqueous iodophor solution for the prevention of surgical site infection. Intra-peritoneal lavage with aqueous iodophor solution in contaminated or dirty abdominal procedures is not necessary. **(Category II)** [125-131] (Key Question 9)

9B. No recommendation can be made regarding the safety and effectiveness of soaking prosthetic devices in antiseptic solutions prior to implantation for the prevention of surgical site infection. **(No recommendation/unresolved issue)** (Key Question 9)

10. No recommendation can be made regarding the safety and effectiveness of repeat application of antiseptic agents to the patient's skin immediately prior to closing the surgical incision for the prevention of surgical site infection. **(No recommendation/unresolved issue)** [132] (Key Question 10)

PROSTHETIC JOINT ARTHROPLASTY SECTION

I. BLOOD TRANSFUSION

11A. No recommendation can be made regarding the perioperative management of blood transfusions for the prevention of surgical site infection in prosthetic joint arthroplasty. **(No recommendation/unresolved issue)**[133-141] (Key Question 11A-C)

11B. Do not withhold transfusion of necessary blood products from surgical patients as a means to prevent surgical site infection **(Category IB)**[12] (Key Question 11D)

II. SYSTEMIC IMMUNOSUPPRESSIVE THERAPY

12 and 13. No recommendation can be made regarding the perioperative management of systemic corticosteroid or other immunosuppressive therapy for the prevention of surgical site infection in prosthetic joint arthroplasty. **(No recommendation/ unresolved issue)** [142-148] (Key Questions 12 and 13)

14. For prosthetic joint arthroplasty patients on systemic corticosteroid or other immunosuppressive therapy, Recommendation 1E applies: In clean and clean-contaminated

procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain. **(Category IA)**[27-65] (Key Question 14)

III. INTRA-ARTICULAR CORTICOSTEROID INJECTION

15 and 16. No recommendation can be made regarding the management of preoperative intra-articular corticosteroid injection for the prevention of surgical site infection in prosthetic joint arthroplasty. **(No recommendation/ unresolved issue)** [149-153] (Key Questions 15 and 16)

IV. ANTICOAGULATION

17. No recommendation can be made regarding the perioperative management of venous thromboembolism prophylaxis for the prevention of surgical site infection in prosthetic joint arthroplasty. **(No recommendation/unresolved issue)**[154-167] (Key Question 17)

V. ORTHOPAEDIC SPACE SUIT

18. No recommendation can be made regarding the safety and effectiveness of orthopaedic space suits or the health care personnel who should wear them for the prevention of surgical site infection in prosthetic joint arthroplasty. **(No recommendation/unresolved issue)** [168-170] (Key Question 18)

VI. POSTOPERATIVE AMP DURATION WITH DRAIN USE

19. In prosthetic joint arthroplasty, Recommendation 1E applies: In clean and clean-contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain. **(Category IA)** [27-65] (Key Question 19)

VII. BIOFILM

20A. No recommendation can be made regarding the safety and effectiveness of cement modifications and the prevention of biofilm formation or surgical site infection in prosthetic joint arthroplasty. **(No recommendation/ unresolved issue**) [171,172] (Key Question 20A)

20B. No recommendation can be made regarding the safety and effectiveness of prosthesis modifications for the prevention of biofilm formation or surgical site infection in prosthetic joint arthroplasty. **(No recommendation/unresolved issue)** (Key Question 20B)

20C. No recommendation can be made regarding the safety and effectiveness of vaccines for the prevention of biofilm formation or surgical site infection in prosthetic joint arthroplasty. **(No recommendation/unresolved issue)** (Key Question 20C)

20D. No recommendation can be made regarding the safety and effectiveness of biofilm control agents such as biofilm dispersants, quorum-sensing inhibitors, or novel antimicrobial agents for the prevention of biofilm formation or surgical site infection in prosthetic joint arthroplasty. **(No recommendation/unresolved issue)** (Key Question 20D)

III. Background

In 2006, approximately 80 million surgical procedures were performed in United States (U.S.) inpatient hospital (46 million)[4] and ambulatory hospital-affiliated or free-standing (32million) settings.[3] Between 2006 and 2009, SSIs complicated approximately 1.9% of surgical procedures in the United States.[173] However, the number of SSIs is likely to be underestimated given that approximately 50% become evident after discharge.[2] From January 2009 through December 2010, SSIs accounted for 23% of 69,475 healthcare-associated infections (HAIs) reported to the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) surveillance system by 2,039 hospitals.[174] An attempt to establish a national surveillance definition for SSI[175] has not been widely adopted in the scientific literature, which in combination with inconsistencies in coding and a lack of standardization of post-discharge surveillance, has made it challenging to evaluate or compare interventions and track SSIs over time.[5]

Multiple patient co-morbidities and risk factors, in addition to procedure-related risk factors, can impact the risk of SSI.[5] SSIs result in increased morbidity, mortality, and direct and indirect costs including increased hospital length of stay, readmissions for treatment including repeat surgical procedures, outpatient and emergency care visits, use of ancillary services, additional medications (including prolonged antimicrobial therapy), lost productivity, and temporary or permanent disability.[176] Actual attributable costs of SSIs are difficult to determine. Cost estimates are commonly restricted to hospital charges and vary according to surgical procedure, depth of infection, facility, region, country, publication year, study design, and accounting method.[176-178] Estimated average attributable costs of SSIs range from $10,443 to $25,546 per infection (2005 and 2002 dollars, respectively).[6-8,179] *Staphylococcus aureus* and coagulase negative staphylococci are the organisms most commonly associated with SSIs, but pathogens can vary by procedure.[174] Costs can exceed $90,000 per infection when the SSI involves a prosthetic joint implant[180,181] or antimicrobial resistant organism.[182]

In 2002 CDC and Centers for Medicare & Medicaid Services (CMS) instituted the Surgical Infection Prevention (SIP) project with the goal of reducing SSIs. [183] In 2006, SIP became the Surgical Care Improvement Program (SCIP) and expanded to include patient hair removal at the surgical site, glycemic control, and normothermia process measures.[184] With the Deficit Reduction Act of 2005, the U.S. Congress set forth a mandate for hospital reporting of process, outcome, and other quality improvement measures and for making this information available to the public and CMS.[11] In addition, this act required CMS to adjust payments downward for HAIs that could have been prevented through the application of evidence-based strategies. In 2009, the U.S. Department of Health and Human Services' *National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination* set a 5-year target goal of a 25% reduction in SSIs detected on admission and readmission or a 0.75 Standardized Infection Ratio (SIR).[9] Since January of 2012, CMS's Hospital Inpatient Quality Reporting Program has required facilities to report SSI outcome data through CDC's NHSN.[10] Between 2009 and 2010 improved prevention of deep incisional and organ/space SSIs detected on admission and readmission was documented for coronary artery bypass graft (CABG), total knee arthroplasty (TKA), and colon

surgical procedures (18%, 11%, and 9% relative risk reduction of SSIs, respectively).[185] Approximately 55% of SSIs are deemed preventable by application of evidence-based strategies.[179]

Prosthetic joint arthroplasty

Prevention efforts should target all surgical procedures, but especially those where both human and financial burden is greatest. In 2011, primary TKAs accounted for over half of the 1.2 million prosthetic joint arthroplasty procedures (primary and revision) performed in the United States, followed by total hip arthroplasty (THA), and hip hemi-arthroplasties.[186] Primary shoulder, elbow, and ankle arthroplasties are much less common. By 2030, prosthetic joint arthroplasties are projected to increase to 3.8 million procedures per year.[187-189]

Infection is the most common indication for revision in TKA[190] and the third most common indication in THA,[190] following instability/dislocation and mechanical loosening. *S. aureus* and coagulase negative staphylococci are the most common pathogens associated with orthopaedic SSI.[174] Between 2001 and 2009, there was a significant increase in the risk of infection following hip and knee arthroplasties (from 1.99% to 2.18% and from 2.05% to 2.18%, respectively).[181] By 2030 the infection burden for hip and knee arthroplasty is expected to increase to 6.5% and 6.8%, respectively.[191] Owing to both increasing risk and the number of individuals undergoing prosthetic joint arthroplasty procedures, between 2010 and 2020, the total number of hip and knee prosthetic joint infection (PJI) cases is projected to increase from 25,000 to 70,000 and up to 221,500 cases per year by 2030.[181,191] Treatment of PJI commonly involves a 2-stage procedure, with 4 to 8 weeks of parenteral antimicrobial therapy between stages. When eradication of the infection is not possible, treatment can include arthrodesis or even amputation.[192] In 2009 the average hospital cost for the revision of an infected hip or knee arthroplasty was $93,600 and $24,200, respectively.[181] Between 2001 and 2009, estimated total hospital costs for treating PJI increased from $320 million to $566 million, and is projected to reach $1 billion by 2014 and $1.62 billion by 2020.[181]

Any indwelling medical device or prosthetic implant has the potential to become colonized by organisms embedded in biofilm.[193,194] In the United States, as many as 13 million people experience a biofilm-related infection every year.[195] Biofilm is defined as "a microbially derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are embedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription".[194] Biofilm organisms exhibit significant resistance to antimicrobial agents (10 to 1000 times the minimum inhibitory concentration [MIC]) as compared to their free floating, planktonic counterparts.[194] Mechanisms involved in this increased antimicrobial resistance may include: "…delayed penetration of the antimicrobial agent through the biofilm matrix, altered growth rate of the biofilm organisms, and other physiologic changes due to the biofilm mode of growth".[194] Between 7% and 39% of PJIs are culture negative,[196,197] which is often attributed to

previous antimicrobial therapy[198] or the presence of difficult to culture biofilm organisms, making diagnosis, treatment, and the identification of prevention measures critical.

Evidence-based guidelines have provided recommendations for the diagnosis of PJI using conventional testing techniques including serologic and synovial fluid markers, tissue histopathology, traditional culture-based techniques, and imaging studies.[199] Recently published studies further support or add to these recommendations.[197,198,200-202] Potential future strategies for the diagnosis of PJI include the use of novel serologic[203-207] and synovial fluid[208] markers. In addition, novel strategies to improve the recovery of biofilm organisms may enhance detection of organisms present in lower numbers or species present as a minority.[193] Sonication of the explanted prosthesis[197,209-212] or cement spacer[211] produces a diluent of released biofilm sonicate. Culture of sonicate effluent may have improved culture sensitivity as compared to standard synovial fluid or tissue culture techniques. Different growth media[197,213] and microscopic[197,213-217] techniques to better grow and characterize biofilm and the embedded organisms are also being explored. Adjunct molecular techniques hold the potential to improve the sensitivity and specificity of traditional culture-based techniques.[213-215,217-223] However, only culture-based techniques provide information on antimicrobial susceptibility, which drives PJI treatment, therefore exploring ways to enhance culturing techniques continues to be important.[224] Multidisciplinary work to standardize the clinical diagnosis of PJI is ongoing. [225]

IV. Scope and Purpose

This guideline provides updated and new recommendations for the prevention of SSI. This guideline does not provide comprehensive infection control recommendations for prevention of SSIs. The select areas of focus were informed by feedback received from clinical experts and input from the Healthcare Infection Control Practices Advisory Committee (HICPAC), a federal advisory committee to the Centers for Disease Control and Prevention (CDC). As in the Guideline for Prevention of Surgical Site Infection, 1999 this guideline does not specifically address SSI prevention issues unique to: burns, trauma, surgical incisions allowed to heal by secondary intention, transplant procedures, transmission of blood borne pathogens from healthcare personnel to the patient, pediatric surgical practice, minimally invasive procedures, procedures performed outside of the operating room (e.g., endoscopic procedures), non-surgical invasive procedures (e.g., cardiac catheterization, interventional radiology) and other procedures or conditions not specifically mentioned.[12] In general, SSI prevention measures deemed effective in adults are also indicated in the pediatric surgical population, and those effective in the operating room can be adapted or modified for other settings. In addition, this update does not address SSI surveillance or public reporting.[1,2] Recommendations on infection control in healthcare personnel,[13] environmental infection control,[14] and disinfection and sterilization of medical devices[15] in health care settings are topics addressed by other guidelines.

To evaluate the evidence on SSI prevention, key questions addressing 13 intervention categories were examined. Six topics evaluated the literature across **all surgical procedures** and comprise the ***Core section*** of the guideline: Parenteral antimicrobial prophylaxis, Non-parenteral antimicrobial prophylaxis, Glycemic control, Normothermia, Oxygenation, and Antiseptic prophylaxis. Seven other topics evaluated the literature specific to ***Prosthetic Joint Arthroplasty*** and comprise the second section: Blood transfusions, Systemic immunosuppressive therapy, Intra-articular corticosteroid injections, Anticoagulation, Orthopaedic space suit, Postoperative antimicrobial prophylaxis duration with drain use, and Biofilm. The specific key questions were:

CORE SECTION

Parenteral antimicrobial prophylaxis (AMP)

Q1. What are the most effective strategies for administering parenteral AMP to reduce the risk of SSI?

Non-parenteral Antimicrobial prophylaxis

Q2. What are the most effective strategies for administering non-parenteral antimicrobial prophylaxis at the surgical incision to reduce the risk of SSI?

Glycemic control

Q3. How do perioperative blood glucose and hemoglobin A1C levels impact the risk of SSI, and what are their optimal perioperative target levels in diabetic and non-diabetic patients?

Normothermia

Q4. How safe and effective is the maintenance of perioperative normothermia in reducing the risk of SSI?

Q5. What are the most effective strategies for achieving and maintaining perioperative normothermia?

Oxygenation

Q6. In patients with normal pulmonary function, how safe and effective is the perioperative use of increased fraction of inspired oxygen (FiO_2) in reducing the risk of SSI?

Q7. What is the optimal target FiO_2 to reduce the risk of SSI; how and when should it be administered?

Antiseptic prophylaxis

Q8. What are the most effective strategies for preparing the patient's skin prior to surgery to reduce the risk of SSI?

Q9. How safe and effective is antiseptic irrigation prior to closing the surgical incision?

Q10. How safe and effective is repeat application of antiseptic skin preparation agent to the surgical site immediately prior to closing the surgical incision?

PROSTHETIC JOINT ARTHROPLASTY SECTION

Blood transfusion

Q11. How do perioperative blood transfusions impact the risk of SSI in prosthetic joint arthroplasty patients?

Systemic immunosuppressive therapy

Q12. How does systemic corticosteroid or other immunosuppressive therapy impact the risk of SSI in prosthetic joint arthroplasty patients?

Q13. What are the most effective strategies in managing systemic corticosteroid or other immunosuppressive therapy perioperatively to reduce the risk of SSI in prosthetic joint arthroplasty patients?

Q14. What is the optimal duration of postoperative AMP to reduce the risk of SSI in prosthetic joint arthroplasty patients on systemic corticosteroid or other immunosuppressive therapy?

Intra-articular corticosteroid injections

Q15. How do preoperative intra-articular corticosteroid injections impact the risk of SSI in prosthetic joint arthroplasty patients?

Q16. What are the most effective strategies for managing the preoperative use of intra-articular corticosteroid injections to reduce the risk of SSI in prosthetic joint arthroplasty patients?

Anticoagulation

Q17. What are the most effective strategies for managing perioperative venous thromboembolism (VTE) prophylaxis to reduce the risk of SSI?

Orthopaedic space suit

Q18. How safe and effective are orthopaedic space suits in reducing the risk of SSI in prosthetic joint arthroplasty patients, and which healthcare personnel should wear them?

Postoperative antimicrobial prophylaxis duration with drain use

Q19. What is the optimal duration of postoperative AMP to reduce the risk of SSI in prosthetic joint arthroplasty in the presence of a drain??

Biofilm

Q20. What are the most effective strategies to reduce the risk of biofilm formation and SSI in prosthetic joint arthroplasty?

Evidence-based recommendations were cross-checked with those from other guidelines identified in an initial systematic search.

This document is intended for use by surgeons, physician assistants, perioperative nurses and other allied perioperative assistive personnel, anesthesia providers, postoperative inpatient and clinic nurses, infection prevention staff, healthcare epidemiologists, healthcare administrators, other healthcare providers, and persons responsible for developing, implementing, delivering, and evaluating infection prevention and control programs for surgical procedures performed in an operating room (inpatient or ambulatory setting). The guideline can also be used as a resource for professional societies or organizations that wish to develop more detailed implementation guidance or to identify future research priorities where there are evidence gaps for the prevention of SSI.

V. Methods

This guideline was based on a systematic review of the best available evidence on SSI prevention. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of the available evidence, the strength of resulting the recommendations, and to provide explicit links between thems.[16-19] The guideline development process has been previously described.[21] Methods and details that were unique to this guideline are included below.

Development of Key Questions

A preliminary list of key questions was developed from a review of the 1999 CDC SSI guideline.[12] Content experts were surveyed to provide feedback on the questions and identify additional topics of interest. Key questions were put in final form after vetting them with a panel of content experts and HICPAC members.

Literature Search

Following the development of the key questions, search terms were developed for identifying literature most relevant to those questions. For the purposes of quality assurance, these terms were compared to those used in relevant seminal studies and guidelines. These search terms were then incorporated into search strategies for the relevant databases. Searches were performed in MEDLINE, EMBASE, CINAHL, and the Cochrane Library. All databases were searched from 1998, when the previous guideline searches ended, through June 2011 for the Core section and December 2011 for the Prosthetic Joint Arthroplasty Section. References were imported into a reference manager where duplicates were resolved. The detailed search strategy and results for the **Core section** can be found in *Appendix 1* and for the **Prosthetic Joint Arthroplasty section** in *Appendix 2*.

Study Selection

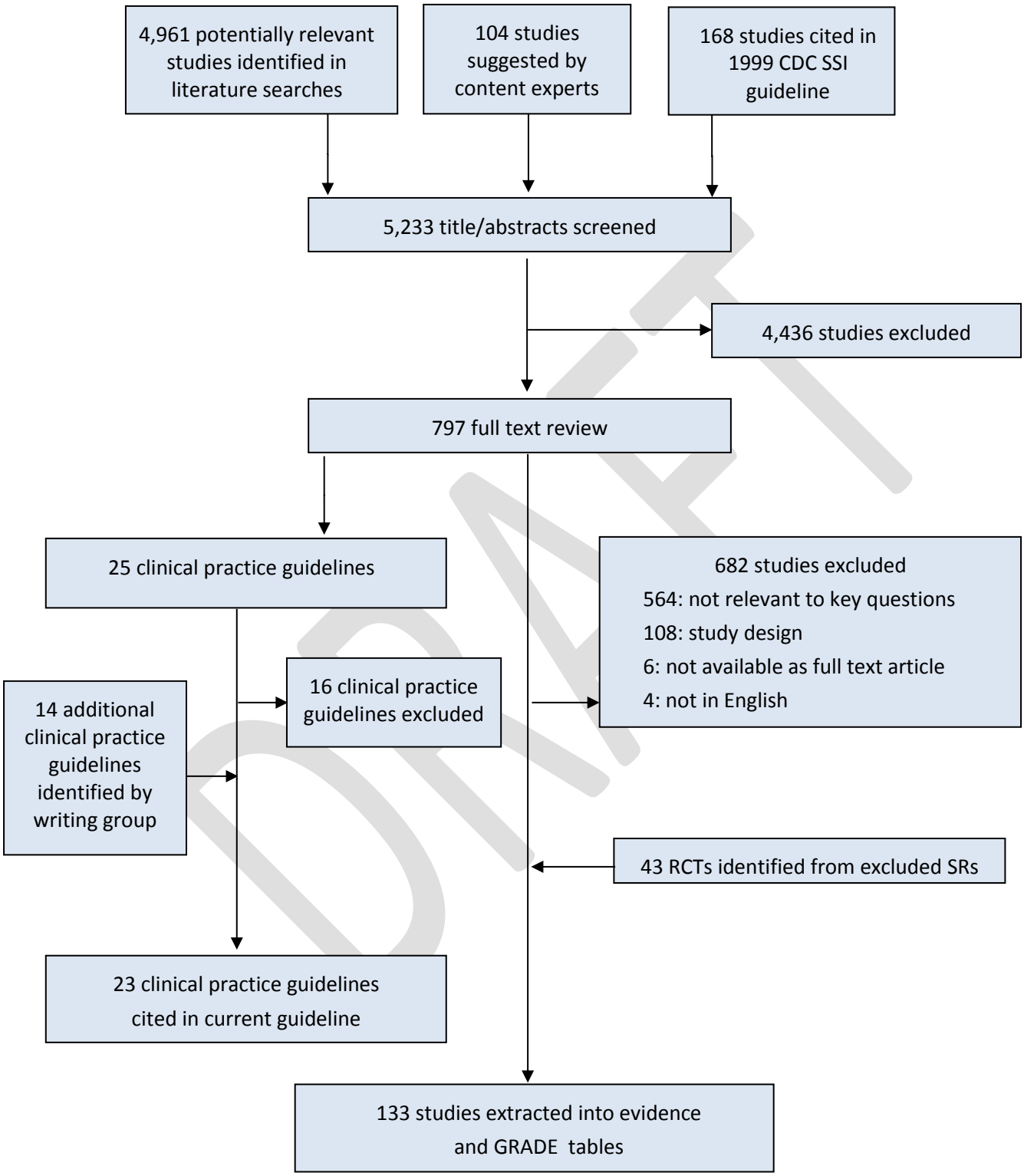
Titles and abstracts were screened by one independent reviewer (S.I.B.T., R.K., or C.R.). A random sample of 10% of titles and abstracts had a second independent review to ensure consistency in screening. Kappa scores, used to measure agreement between the two independent reviewers beyond chance, ranged from 0.4 – 0.5, indicating "moderate agreement" between reviewers.[226] Full text articles were retrieved if they were: 1) relevant to one or more key questions; 2) clinical practice guidelines, systematic review (SRs) or primary study designs meeting the inclusion criteria (randomized control trial [RCTs] for the Core and Prosthetic Joint Arthroplasty sections and observational [OBS] studies for the Prosthetic Joint Arthroplasty section because none of that section's key questions were adequately addressed by results from the initial search); 3) written in English; and 4) available as full text studies (meeting abstracts were excluded). Animal studies and in vitro basic science studies were excluded from all topics except Biofilm. Pediatric patient studies were included. Although the literature databases were searched from 1998 to 2011, studies published earlier than 1998

were eligible for inclusion (e.g., studies suggested by the expert panel, included in the previous guideline or in published SRs).

Full-text articles were screened by two independent reviewers (S.I.B.T and R.K. or S.I.B.T. and C.R.) and disagreements were resolved by discussion. Full-text articles were excluded if: 1) SSI was not reported as an outcome; 2) all patients included had "dirty" surgical procedures (except for Q2 addressing the use of aqueous iodophor irrigation); 3) the study only included oral medicine or dental health procedures; 4) the surgical procedures did not include primary closure of the incision in the operating room (e.g. orthopedic pin sites, thoracotomies, or percutaneous endoscopic gastrostomy (PEG) procedures, or wounds healing by secondary intention); or 5) the study evaluated wound protectors used post incision. For the Core section, Q1 Parenteral antimicrobial prophylaxis, studies comparing the efficacy of antimicrobial prophylaxis to no prophylaxis (placebo-controlled studies) and studies comparing the efficacy of different prophylactic antimicrobial agents were excluded. Also for Q2 Non-parenteral antimicrobial prophylaxis, use of gentamycin collagen sponge studies (not approved by the Food and Drug Administration [FDA])were excluded. For Q8-10 Antiseptic prophylaxis, studies evaluating vaginal antisepsis in combination with abdominal antisepsis were excluded. In addition, studies using electrolyzed ionized solution (not approved by the Food and Drug Administration [FDA] for intraoperative irrigation of the surgical site) and dry povidone iodine powder spray studies were excluded. For the Prosthetic Joint Arthroplasty section, studies were excluded if they did not specifically examine prosthetic joint arthroplasties. Questions from four topics in the Prosthetic Joint Arthroplasty section were excluded from a targeted search when both: 1) the initial broad search identified very few or no RCTs or SRs that fit the inclusion criteria and 2) the content experts excluded them as priority topics and/or key questions (i.e., Surgical attire- gloves, Surgical techniques, Anesthesia, and Environmental factors). Also, questions and related studies addressing diagnosis of PJI or biofilm were excluded because they did not address SSI prevention. Special inclusion criteria for the Core section were: for Q1, studies on the optimal timing of AMP in cesarean sections; for Q2 autologous platelet rich plasma gel; for Q9 and Q10 aqueous iodophor solution irrigation or repeat application to skin prior to closing the surgical incision. Special inclusion criteria for the Prosthetic Joint Arthroplasty section included: for Q11 Blood transfusion- studies that evaluated the administration of epoetin alpha in combination with blood transfusion.

A draft bibliography was shared with a panel of content experts and additional suggested references then progressed through title/abstract and full text review as above. Results of the entire study selection process are depicted in *Figure 1.*

Figure 1. Results of the Study Selection Process



Data Extraction and Synthesis

For studies meeting the inclusion criteria, data on the study author, year, design, risk of bias, objective, population, setting, sample size, interventions, and results of clinically relevant outcomes were extracted into standardized evidence tables. From these, evidence tables were developed for each clinical topic represented by the key questions. Studies were extracted into the most relevant evidence table. Studies were organized by individual key questions and subquestions. Data were extracted by a single author (S.I.B.T., E.C.S., B.L., or R.A.) and cross-checked by another author (S.I.B.T.). Disagreements were resolved by the remaining authors. Data and analyses were extracted as originally presented in the included studies. Meta-analyses were performed only where their use was deemed critical to a recommendation and only in circumstances in which multiple studies with sufficiently homogenous populations, interventions, and outcomes could be analyzed. The risk of bias associated with each study was assessed using scales developed by the Penn Medicine Center for Evidence-based Practice, and scores were recorded in the evidence tables. *Appendices 1 and 2* include the questions used to assess the risk of bias of the included SRs, RCTs, and OBS for the **Core** and **Prosthetic Joint Arthroplasty Sections**, respectively.

Systematic reviews were included in this review if the individual studies in the review fit our inclusion criteria. To avoid duplication of data, primary studies identified by our search were excluded if they were also included in a systematic review captured in our search. The exception to this was 1) if the primary study also addressed a relevant question that was outside the scope of the included systematic review or 2) if it was one of a select number of studies in the systematic review that fit our inclusion criteria and was used to perform a new meta-analysis. Systematic reviews that analyzed primary studies that were fully captured in a more recent systematic review were excluded. The only exception to this was if the older systematic review also addressed a relevant question that was outside the scope of the newer systematic review.[227]

To ensure that all relevant studies were captured in the search, the bibliography was vetted by a panel of content experts. Statistical analyses were performed using Review Manager 5.1. For the purposes of our review, statistical significance was defined as $p \leq 0.05$.

For all other methods (i.e., Grading of Evidence, Formulation of Recommendations, and Finalizing of the Guideline) please refer to the Guideline Methods supplement.[21]

Reviewing and Finalizing the Guideline

The writing group completed a draft of the guideline, including evidence reviews, recommendations, evidence tables, and GRADE tables, and shared it with the expert panel for in depth review. Based on the expert panel's feedback, the writing group revised the guideline documents and presented draft recommendations to HICPAC at public meetings for their review and input. Following further revisions, CDC then submitted the guideline for an initial

clearance at CDC and is posting it in the Federal Register for a period of public comment. After this period of public comment, the comments will be reviewed at a HICPAC meeting, revised accordingly, and the final guideline will be submitted to CDC for final clearance. Once cleared, the guideline will be posted to CDC's website and published.

Updating the Guideline

Revisions to this guideline will be guided by new research and technological advancements for preventing SSIs.

VI. Evidence Review: Core section

PARENTERAL ANTIMICROBIAL PROPHYLAXIS (AMP)

Q1. What are the most effective strategies for administering parenteral AMP to reduce the risk of SSI?

To answer this question, we focused on five subquestions: A) What is the optimal timing of preoperative AMP? B) What is the optimal timing of AMP in cesarean section: prior to skin incision or at cord clamping? C) How safe and effective is weight-adjusted AMP dosing? D) How safe and effective is intraoperative redosing of AMP? and E) How safe and effective is postoperative AMP and what is the optimal duration?

Q1A. What is the optimal timing of preoperative AMP?

Our search did not identify RCTs or SRs that evaluated different timings of preoperative AMP administration and its impact on the risk of SSI.

Other Guidelines

The 1999 CDC Guideline for Prevention of Surgical Site Infection and other clinical practice guidelines, based on a review of the evidence and expert opinion, recommend administering by the intravenous route a single dose of prophylactic antimicrobial agent only when indicated. For most prophylactic agents, the 1999 CDC guideline recommended preoperative administration be timed such that a bactericidal concentration of the drug is established in the serum and tissues when the incision is made and now other clinical practice guidelines recommend that administration should be within 60 minutes prior to incision (vancomycin and fluoroquinolones within 60-120 minutes prior to incision).[12,183,228-232] None of the recommendations address whether it is necessary to administer a complete or a partial infusion of the parenteral AMP dose prior to surgical incision.

Q1B. What is the optimal timing of AMP in cesarean section: prior to skin incision or at cord clamping?

The available data on optimal timing of antimicrobial prophylactic agent administration in cesarean section examined AMP administered prior to skin incision versus at cord clamping.

For this comparison we considered post-partum endometritis as the critical outcome. Incisional SSI, neonatal sepsis, neonatal sepsis workup, and neonatal intensive care unit (NICU) admission outcomes were also evaluated. In general, endometritis was defined as fever > 100.4°F on two occasions with uterine tenderness, purulent lochia, tachycardia or leukocytosis. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 1B.

High-quality evidence suggested a benefit of AMP administration prior to skin incision as compared to administration immediately after the umbilical cord is clamped in cesarean sections. This was based on a SR[22] (low risk of bias) with a meta-analysis (N=749) of 3 RCTs[23-25] suggesting a 53% reduction in post-partum endometritis and no difference in proven neonatal sepsis or neonatal sepsis workups. High-quality evidence from a meta-analysis (N=681 neonates) of 2 studies suggested no difference in NICU admissions.[23,24] One study suggested significantly shorter NICU stays and no difference in neonatal sepsis causative organisms with administration of AMP prior to skin incision.[23]

Other Guidelines

Clinical practice guidelines based on a review of the evidence and expert opinion recommend administration of a single preoperative prophylactic antimicrobial agent by the intravenous route, based on the agent pharmacokinetics, commonly beginning within 60 minutes prior to skin incision in both elective and emergency cesarean section.[228-230,232] Administration of AMP after cord clamping is no longer recommended.[12]

Q1C. How safe and effective is weight-adjusted AMP dosing?

Our search did not identify RCTs or SRs that evaluated weight-adjusted AMP dosing and its impact on the risk of SSI.

Other Guidelines

Clinical practice guidelines based on a review of the evidence and expert opinion recommend increasing the single preoperative prophylactic antimicrobial agent dose for select prophylactic antimicrobial agents in obese and morbidly obese patients.[228-232] For cefazolin, recommendations are to administer 2g[229-231] for patients weighing >60-80kg and 3g[230] if >120kg. For aminoglycosides, dosing is calculated using the patient's ideal body weight plus 40% of the difference between the actual and ideal body weight.[230,233] Vancomycin should be dosed at 15mg/kg.[229-231]

Q1D. How safe and effective is intraoperative redosing of AMP?

The available data examining intraoperative redosing of AMP compared one preoperative dose versus one preoperative dose plus an additional dose at 2 hours intraoperatively.

For this comparison we considered abdominal and perineal wound SSI and intra-abdominal abscess as the outcomes of interest. Antimicrobial resistance outcome was also evaluated. The evidence for this question consists of 1 RCT at moderate risk of bias in elective colorectal surgery.[26] The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 1D.

Moderate-quality evidence suggested no benefit of intraoperative AMP redosing. This was based on no difference in abdominal or perineal wound infection, intra-abdominal abscess, or

antimicrobial resistance in 1 elective colorectal surgery study from 1991.[26] However, procedures with durations >3 hours had a significantly higher risk of SSI and 22% of patients with procedure durations ≥2 hours were not redosed. Fecal contamination almost doubled the SSI rate at every level of contamination (of note, patients underwent mechanical bowel prep alone). Procedure duration and fecal contamination were not reported by study group. Limited power of the study could result in a false negative finding.

Other Guidelines

Clinical practice guidelines based on a review of the evidence and expert opinion recommend prophylactic antimicrobial agent redosing in cases of prolonged procedures (when the procedure exceeds the half-life of the prophylactic antimicrobial agent or is longer than 3-4 hours) and in patients with major blood loss (>1500 ml) or extensive burns.[229-232,234] Redosing should also be performed at intervals of 1-2 times the prophylactic antimicrobial agent half-life, starting at the beginning of the preoperative dose.[229-232,234] No recommendations are provided for optimal prophylactic antimicrobial agent dosing in obese and morbidly obese patients when redosing.

Q1E. How safe and effective is postoperative AMP and what is the optimal duration?

To answer this question, we focused on studies that used the same prophylactic antimicrobial agent in both arms. We evaluated administration of postoperative AMP both with all surgical procedures combined and by select surgical specialties. Studies that compared different prophylactic antimicrobial agents or those administering only oral AMP were excluded. We defined postoperative AMP as any parenteral prophylactic antimicrobial agent administered after intraoperative closure of the surgical incision. Therefore, postoperative AMP (in hours or days), does not include any AMP administered as a single preoperative dose, and/or any intraoperative redosing.

The available data examined the following comparisons for different postoperative AMP durations:

1. All surgeries - None vs. ≤24 hours
2. Cardiac
    a. None vs. ≤24 hours
    b. None vs. 72-96 hours
3. Thoracic - None vs. 2 days
4. Vascular
    a. None vs. ≤24 hours
    b. <24 hours vs. 3-5 days
    c. None vs. 5 days
5. Ear, nose, and throat - ≤24 hours vs. 3-5 days
6. Gynecologic

a. None vs. ≤24 hours
b. <24 hours vs. <2.5 days

7. Orthopaedic
    a. Fracture - None vs. ≤24 hours
    b. Prosthetic Joint Arthroplasty - None vs. ≤24 hours
8. Colorectal: Bowel preparation with oral antimicrobials
    a. None vs. 3 days
    b. ≤24 hours vs. 5 days
9. Colorectal: Bowel preparation only
    a. None vs. ≤24 hours
    b. None vs. <2-3 days
10. Colorectal: Bowel preparation not reported
    a. None vs. ≤24 hours
    b. ≤24 hours vs. 2-3 days
11. Colorectal: No bowel preparation
    a. None vs. ≤24 hours
    b. None vs. <2-3 days
12. Appendectomy
    a. None vs. ≤24 hours
    b. None vs. 2 days
13. Rectal surgery- None vs. ≤24 hours
14. Gastric surgery
    a. None vs. ≤24 hours
    b. None vs. 4 days
15. Hepatectomy – 2 days vs. 5 days

For all comparisons, we considered SSI (superficial, deep incisional, and organ/space) and trocar wound infection as the critical outcomes. Antimicrobial resistance, adverse events, length of stay, mortality, and pharyngocutaneous fistula outcomes were also evaluated. The evidence for this question consists of 39 RCTs in cardiac,[27-30] thoracic,[31] vascular,[32-34] ear, nose and throat,[35,36] gynecologic,[37-41] orthopaedic,[42-47] and general surgical[48-65] procedures. Twenty-eight (72%) studies were published between 1972 and 1998; 11 (28%) studies were published between 2003 and 2011. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 1E.

Q1E.1. All surgeries - None vs. ≤24 hours

High-quality evidence suggested no benefit of continuing AMP after intraoperative closure of the surgical incisions. This was based on no difference in SSI in 1 large meta-analysis (N=13,408) of 19 RCTs in cardiac, thoracic, vascular, ear, nose and throat, gynecologic, orthopaedic, and general surgical procedures.[27,32,37-40,42-47,50-53,57,62,63] Fourteen (74%) studies were published between 1984 and 1995; 5 were published between 2005 and 2008. Results by

select surgical specialties or procedures and individual comparators are available in the GRADE table.

Q1. Recommendations

1A. Administer preoperative antimicrobial agent only when indicated, based on published clinical practice guidelines and timed such that a bactericidal concentration of the agent is established in the serum and tissues when the incision is made **(Category IB)** [12] (Key Question 1A)

- No further refinement of timing can be made for preoperative antimicrobial agent based on clinical outcomes. **(No recommendation/unresolved issue)** (Key Question 1A)

1B. Administer the appropriate parenteral prophylactic antimicrobial agent prior to skin incision in all cesarean sections. **(Category IA)** [22-25] (Key Question 1B)

1C. No recommendation can be made regarding the safety and effectiveness of weight-adjusted dosing of parenteral prophylactic antimicrobial agents for the prevention of surgical site infection. **(No recommendation/unresolved issue)** (Key Question 1C)

1D. No recommendation can be made regarding the safety and effectiveness of intraoperative redosing of parenteral prophylactic antimicrobial agents for the prevention of surgical site infection. **(No recommendation/unresolved issue)** [26] (Key Question 1D)

1E. In clean and clean-contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain. **(Category IA)** [27-65] (Key Question 1E)

NON-PARENTERAL ANTIMICROBIALPROPHYLAXIS

Q2. What are the most effective strategies for administering non-parenteral antimicrobial prophylaxis at the surgical incision to reduce the risk of SSI?

To answer this question we focused on four subquestions: A) How safe and effective is antimicrobial irrigation? B) How safe and effective are antimicrobial agents applied to the surgical incision? C) How safe and effective are antimicrobial-coated sutures, when and how should they be used? and D) How safe and effective are antimicrobial dressings applied to the surgical incision following primary closure in the operating room?

2A. How safe and effective is antimicrobial irrigation?

Our search did not identify RCTs or SRs that evaluated the safety and effectiveness of antimicrobial irrigation or the soaking of surgical implants (e.g., meshes, neurosurgical ventricular shunts) in antimicrobial solution prior to insertion (in combination with parenteral AMP) and its impact on SSI.

Other Guidelines

One clinical practice guideline, based on a review of the evidence, recommends against antimicrobial wound irrigation or intra-cavity lavage to reduce the risk of SSI.[234]

Q2B. How safe and effective are antimicrobial agents applied to the surgical incision?

The available data examined the following comparisons:

1. Ampicillin vs. No topical antimicrobial agent
2. Chloramphenicol vs. No topical antimicrobial agent
3. Rifampin vs. No topical antimicrobial agent
4. Autologous platelet rich plasma (APRP) (spray or gel) vs. No APRP

For all comparisons, we considered SSI the critical outcome. Wound dehiscence and wound closure outcomes were also evaluated. The evidence for the pharmacologic antimicrobial prophylactic agent comparators consists of 1 SR[66] and 2 RCTs[67,68] and for the APRP comparator 3 RCTs[73-75]. APRP provides a platelet concentrate commonly used to enhance both, wound hemostasis (formation of a fibrin clot) and wound healing (clot provides a matrix for the migration of tissue-forming cells and endothelial cells involved in angiogenesis and remodeling of the clot into repair tissue).[235,236] These characteristics have led to a significant increase in the use of APRP therapies for the treatment of chronic wounds and multiple orthopaedic conditions including bone repair, tendon, and soft tissue injuries.[237,238] In addition, in vitro studies have demonstrated that APRP holds strong bactericidal activity, and suggested its potential value as an adjunct topical antimicrobial prophylactic agent for use at the time of surgical incision closure.[239,240]In all studies, both groups received parenteral AMP. Our search did not identify RCTs or SRs that evaluated the safety and effectiveness of vancomycin powder for the prevention of SSI. The findings of the evidence review and grades for all important outcomes are shown in Evidence Review Table 2B.

Q2B.1. Ampicillin vs. no topical antimicrobial agent

High-quality evidence suggested no benefit of topical ampicillin solution or powder in combination with parenteral AMP. This was based on no difference in SSI in one SR's[66] meta-analysis (N=699) of 4 older (1985-1994) RCTs in clean-contaminated colorectal[70,71] and appendectomy[69,72] procedures.

Q2B.2. Chloramphenicol vs. no topical antimicrobial agent

Moderate-quality suggested no benefit of topical chloramphenicol ointment in combination with parenteral AMP. This was based on no difference in SSI in one small study at low risk of bias, in 92 hemi-arthroplasty or dynamic hip screw fixation procedures for hip fractures.[67]

Q2B.3. Rifampin vs. no topical antimicrobial agent

Low-quality evidence suggested a benefit of topical rifampin in combination with parenteral AMP. This was based on a reduced risk of wound leakage, fewer local signs of inflammation, and reduced risk of wound dehiscence at the umbilical port site in one very small (N=48) laparoscopic cholecystectomy study at moderate risk of bias.[68] Umbilical port-site infection was defined as "purulent wound leakage". Based on results reported in a histogram, 12 hours postoperatively, 71% of patients had purulent wound leakage including almost half of the rifampin and all of the control groups. By 24 hours the entire control group remained infected; a week later, only 2 infections remained. It is not clear if any of these were true infections.

Other Guidelines

Clinical practice guidelines based on a review of the evidence and expert opinion have recommendations both for[231] and against[234] the use of non-parenteral antimicrobials in the prevention of SSI. There are also strong recommendations against the use of antimicrobial ointments or creams on umbilical catheter insertion sites and other insertion sites, except for dialysis catheters, because of their potential to promote fungal infections and antimicrobial resistance.[241]

Q2B.4. Autologous platelet rich plasma (spray or gel) vs. nothing

Moderate-quality evidence suggested no benefit of APRP spray or gel in combination with parenteral AMP. This was based on no difference in SSI in a meta-analysis (N=257) of 3 small RCTs: 2 studies in cardiac procedures (low[73] and moderate[74] risk of bias) and 1 study in TKA procedures[75] (low risk of bias). Each individual study found no difference. The cardiac studies applied APRP spray[73] or gel[74] (produced using the same type of commercial platelet concentrate system) to the saphenous vein harvest site[73,74] and/or the sternum[74]. The TKA study applied APRP spray (produced using a different platelet concentrate system than the cardiac studies) to the femoral and tibial cut bone surfaces and joint capsule followed by platelet poor plasma sprayed on the subcutaneous tissue. Moderate-quality evidence from this latter study suggested significantly increased risk of delayed total wound closure at 2 weeks postoperatively.

Q2C. How safe and effective are antimicrobial-coated sutures, when and how should they be used?

The available data examined antimicrobial-coated sutures (absorbable) versus non-antimicrobial-coated sutures (absorbable and non-absorbable) for the prevention of SSI.

For this comparison we considered SSI the critical outcome. ASEPSIS score[242], where points are given for "Additional treatment, the presence of Serous discharge, Erythema, Purulent exudate, and Separation of the deep tissues, the Isolation of bacteria, and the duration of inpatient Stay", and product related adverse event outcomes were also evaluated.

The evidence for this question consists of 4 RCTs.[76-79] The findings of the evidence review and grades for all important outcomes are shown in Evidence Review Table 2C.

High-quality evidence suggested no benefit of using antimicrobial coated sutures. This was based on no difference in SSI in a meta-analysis (N=420) of 4 RCTs and no product-related adverse events.[76-79] There was no difference in SSI among three small studies evaluating triclosan-coated suture in modified radical mastectomy (triclosan-coated suture subcuticular skin closure vs. Chinese silk suture interrupted transcutaneous skin closure)[76] appendectomy for acute and ruptured appendicitis (abdominal sheath closure),[77] and pediatric general surgery (level of closure not specified)[79] procedures. One study[79] at low risk for bias was designed to evaluate the surgeon's assessment of intraoperative handling characteristics of the suture and another,[76] the cosmetic outcome, but not SSI as a primary outcome. Only one very small study (N=86) in predominantly pediatric patients undergoing cerebrospinal fluid shunt implantation or revision procedures suggested a reduction in risk of shunt infections with triclosan-coated suture closure of the galea and fascia.[78] This study also used plastic iodine-impregnated adhesive drapes, antimicrobial irrigation, and soaked the silicone shunt component in aqueous iodophor solution prior to implantation in both groups. Use of parenteral AMP was only reported for the appendicitis and cerebrospinal fluid shunt implantation studies.

Q2D. How safe and effective are antimicrobial dressings applied to surgical incisions following primary closure in the operating room?

Our research did not identify RCTs or SRs that evaluated the safety and effectiveness of antimicrobial dressings (i.e., iodine, silver, or other antimicrobial ointment impregnated dressing) applied to surgical incisions closed primarily in the operating room (i.e., the skin edges are re-approximated at the end of the operation) and their impact on the risk of SSI.[12] Our search identified a SR of 16 RCTs evaluating various non-antimicrobial dressings.[243] This SR found no evidence to suggest that either covering the wound was effective or that any one non-antimicrobial dressing was more effective than another in reducing the risk of SSI in surgical incisions that were closed primarily in the operating room. This guideline does not address prevention of SSI in trauma-related procedures, in surgical incisions left open to heal by secondary intention (i.e., left open in the operating room to be closed later, left open to heal by granulation, or which break open postoperatively) or burns.

Q2. Recommendations

2A.1. No recommendation can be made regarding the safety and effectiveness of intraoperative antimicrobial irrigation (e.g., intra-abdominal, deep, or subcutaneous tissues) for the prevention of surgical site infection. **(No recommendation/unresolved issue)** (Key Question 2A)

2A.2. No recommendation can be made regarding the safety and effectiveness of soaking prosthetic devices in antimicrobial solutions prior to implantation for the prevention of surgical site infection. **(No recommendation/ unresolved issue)** (Key Question 2A)

2B.1. Do not apply antimicrobial agents (i.e., ointments, solutions, powders) to the surgical incision for the prevention of surgical site infection **(Category IB)** [66-72] (Key Question 2B)

2B.2. Application of autologous platelet rich plasma is not necessary for the prevention of surgical site infection. **(Category II)** [73-75] (Key Question 2B)

2C. Use of antimicrobial coated sutures is not necessary for the prevention of surgical site infection. **(Category II)** [76-79] (Key Question 2C)

2D. No recommendation can be made regarding the safety and effectiveness of antimicrobial dressings applied to surgical incisions following primary closure in the operating room for the prevention of surgical site infection. **(No recommendation/ unresolved issue)** (Key Question 2D)

GLYCEMIC CONTROL

Q3.How do perioperative blood glucose and hemoglobin A1C levels impact the risk of SSI, and what are their optimal perioperative target levels in diabetic and non-diabetic patients?

To answer this question we focused on two subtopics: A) Blood glucose and B) Hemoglobin A1C, their optimal perioperative target levels and the risk of SSI.

Q3A. Blood glucose and optimal perioperative target levels

The available data examined strict versus standard blood glucose control in the prevention of SSI.

For this comparison we considered SSI and hypoglycemia as the critical outcomes. Each study reported a primary composite outcome variable that included SSI. Mortality and length of hospital stay, and surgical intensive care unit (SICU) stays were also evaluated in weighing the risks and benefits of perioperative glycemic control. The evidence for this question consists of 2 RCTs in cardiac surgery patients with glycemic control protocols (intravenous, intensive insulin

therapy) instituted intraoperatively and continued in the SICU for 24-36 hours.[80,81] Seventy to 80% of patients in both of these studies are non-diabetics, highlighting the importance of glycemic control in both diabetic and non-diabetic surgical populations. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 3.

Moderate-quality evidence suggested no benefit of strict (80-100mg/dL[80] or 80-130mm/dL[81]) as compared to standard blood glucose target levels (<200mg/dL[80] or 160-200mg/dL[81]) in diabetic and non-diabetic cardiac patients. This was based on no differences between groups for both a composite outcome variable and SSI in both studies. In Ghandi et al.,[80] (N=371) the composite outcome variable included: death, sternal wound infections, prolonged pulmonary ventilation, cardiac arrhythmias, heart block requiring pacemaker or cardiac arrest, stroke or acute renal failure within 30 days postoperatively. In Chan et al.,[81] (N=109) the composite outcome variable of infection included pneumonia, urinary tract infection, sepsis, septic shock, wound infection, bloodstream infection, and "catheter" infection (did not specify if venous or urinary).

High-quality evidence suggested no increased risk of hypoglycemia with strict blood glucose target levels. This was based on no differences between groups for number of hypoglycemic episodes in the SICU[80] or ratio of hypoglycemic episodes per number of glucose measurements.[81] Hypoglycemia definitions differed between studies: <60mg/dL in Ghandi and <50mg/dL in Chan. In Chan et al., while there was no difference between groups for the number of hypoglycemic episodes in the SICU, both groups reported a higher proportion of them there as compared to intraoperatively, suggesting the importance of continued close monitoring of glucose levels and the risk of hypoglycemic episodes in the postoperative period, even with standard glycemic control. No clinical complications resulting from hypoglycemia were reported at 30 days of follow up.

<u>Other guidelines</u>

While previous CDC guideline recommendations did not specify a perioperative blood glucose target level, they reported that in diabetics "increased glucose levels (>200mg/dL) in the immediate postoperative period (≤48 hours) were associated with increased risk of SSI".[12] Blood glucose target level of <200mg/dL became standard clinical practice. Both studies reviewed in this guideline used <200mg/dL as the upper blood glucose target level.[80,81] Recently published professional society guidelines have recommended a slightly lower absolute serum blood glucose target level of <180mg/dL in diabetic[244,245] and non-diabetic,[244] non-critically ill patients. In critically ill patients blood glucose target levels <150-180mg/dL[246] and 140-200mg/dL[247] have been recommended. For terminally ill patients, those with limited life expectancy, or those at high risk for hypoglycemia, a blood glucose target level of 200mg/dL has been recommended.[245] Intensive insulin therapy (blood glucose target levels of 80-110mg/dl) to normalize blood glucose in the intensive care unit setting (surgical and medical) is not recommended in either diabetic or non-diabetic patients.[247]

Q3B. Perioperative hemoglobin A1C and optimal target levels

Our search did not identify RCTs or SRs examining the association between hemoglobin A1C levels and risk of SSI.

Q3. Recommendations

3A.1. Implement perioperative glycemic control and use blood glucose target levels <200mg/dL in diabetic and non-diabetic patients. **(Category IA)** [80,81] (Key Question 3)

3A.2. No recommendation can be made regarding the safety and effectiveness of lower (<200mg/dL) or narrower blood glucose target levels, nor the optimal timing, duration, or delivery method of perioperative glycemic control for the prevention of surgical site infection. **(No recommendation/unresolved issue)** (Key Question 3)

3B. No recommendation can be made regarding optimal hemoglobin A1C target levels for the prevention of surgical site infection in diabetic and non-diabetic patients. **(No recommendation/unresolved issue)** (Key Question 3)

NORMOTHERMIA

Q4. How safe and effective is the maintenance of perioperative normothermia in reducing the risk of SSI?

The available data examined the following comparisons:

1. Warming vs. no warming
2. Warming: perioperative vs. intraoperative only

For all comparisons, we considered SSI the critical outcome. ASEPSIS score, mortality, blood loss, core temperature, length of hospital stay and duration of surgery outcomes were also evaluated. The evidence for this question consists of 3 RCTs.[82-84] The lower limit of normothermia has been inconsistently defined, ranging from a core temperature of 35.5°C to 36°C. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 4.

Q4A.1. Warming vs. no warming

High-quality evidence suggested a benefit of patient warming over no warming. This was based on a reduced risk of SSI in a meta-analysis (N=616) of 2 RCTs and reduced risk of ASEPSIS scores >20 with warming and maintenance of normothermia using various warming techniques in patients undergoing elective hernia repair, varicose vein surgery, and breast surgery

(preoperative warming)[82] and elective colorectal surgery (intraoperative warming).[83] Normothermia was also associated with lower mean units of blood transfused per patient, fewer patients transfused, and reduced hospital length of stay.[83] No difference in mortality was observed.[83]

Q4A.2. Warming: perioperative vs. intraoperative only

Moderate-quality evidence suggested a benefit of perioperative warming. This was based on reduced incidence of SSI with perioperative warming in 1 RCT of 103 patients undergoing elective major abdominal surgery.[84]

Q4. Recommendation

4. Maintain perioperative normothermia **(Category IA)** [82-84] (Key Question 4)

Q5. What are the most effective strategies for achieving and maintaining perioperative normothermia?

Our search did not identify RCTs or SRs that evaluated the most effective strategies for achieving and maintaining perioperative normothermia and their impact on the risk of SSI.

Other Guidelines

Evidence-based clinical practice guidelines provide recommendations on perioperative management of normothermia including risk factor assessment, temperature monitoring tools, and the safety and effectiveness of warming devices.[248-250]

Q5. Recommendation

5. No recommendation can be made regarding the safety and effectiveness of strategies to achieve and maintain normothermia, the lower limit of normothermia, or the optimal timing and duration of normothermia for the prevention of surgical site infection. **(No recommendation/unresolved issue)** (Key Question 5)

OXYGENATION

Q6. In patients with normal pulmonary function, how safe and effective is the perioperative use of increased fraction of inspired oxygen (FiO2) in reducing the risk of SSI?

To answer this question we focused on three settings of oxygen delivery: A) General anesthesia: Intraoperative endotracheal intubation and postoperative non-rebreathing mask, B) Neuraxial anesthesia: Intraoperative and postoperative non-rebreathing mask and C) Postoperative only: Facemask and/or nasal cannula.

Q6A. General anesthesia: Intraoperative endotracheal intubation and postoperative non-rebreathing mask

The available data examined the following comparisons:

1. 80% oxygen vs. 30% oxygen - both without nitrous oxide
2. 80% oxygen/20% nitrous oxide vs. 35% oxygen/65% nitrous oxide - both with nitrous oxide started 30 minutes after surgical incision

For all comparisons, we considered SSI the critical outcome. ASEPSIS scores, mortality, respiratory failure, atelectasis, tissue oxygenation, and length of stay outcomes were also evaluated. The evidence for this question consists of 6 RCTs.[85-90] One study[89] represents a subanalysis of a larger study;[88] therefore results in the GRADE table reflect solely those of the larger study. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 6.

Q6A.1. 80% oxygen vs. 30% oxygen - both without nitrous oxide

Moderate-quality evidence suggested a benefit of supplemental 80% FiO_2 administered via endotracheal intubation intraoperatively and non-rebreathing mask for 2-6 hours postoperatively in patients under general anesthesia. This was based on a 40% reduction in SSI reported in 3 studies at low risk of bias (2 in 800 elective colorectal[85,87] and 1 in 210 elective open appendectomy[86] procedures), no difference in 1 multicenter, mixed surgical population[88,89] study at low risk of bias, and no significant difference in adverse events.

The three studies reporting a significant SSI reduction all optimized perioperative tissue oxygen delivery by maintaining normothermia and avoiding hypo or hypervolemia.[85-87] Greif et al.,[87] the larger colorectal study (N=500) actually confirmed optimized tissue oxygen delivery, measuring significantly higher intraoperative and postoperative subcutaneous tissue oxygen tension and higher muscle oxygen tension using 80% oxygen.

Meyhoff et al., [88,89] the large (N=1400), multicenter, mixed population study of emergency or elective laparotomy for a variety of general and gynecologic surgical conditions, found no difference in overall, organ/space, deep, or superficial SSI. However, due to a number of factors, the study failed to optimize tissue oxygen delivery. While the target core temperatures were 36°C -37°C, the minimum reported temperatures were 35.0°C and 35.1 in each group, respectively. Most potentially limiting to the optimization of oxygen delivery was the intentional restriction of fluid replacement, limiting postoperative weight gain to less than 1kg.

Mortality at 14-30 days was rare, there was no difference between groups, and it was not associated with use of increased oxygenation.[85,87] In a recent follow-up study (median 2.3 years, range 1.3-3.4), administration of 80% oxygen was associated with significantly increased long-term mortality only in patients undergoing cancer surgery. The only gynecologic patients included in this study were those with ovarian cancer.[251] It is not clear what other cancer patients were included.

Q6A.2. 80% oxygen/20% nitrous oxide vs. 35% oxygen/65% nitrous oxide – both groups nitrous oxide started 30 minutes after incision

Moderate-quality evidence suggested no benefit of supplemental 80% FiO_2 (20% nitrous oxide added 30 minutes after incision) administered via endotracheal intubation intraoperatively and non-rebreathing mask for 2-6 hours postoperatively in patients under general anesthesia. This was based on increased risk of SSI (all combined) in one small (N=160), mixed surgical population study.[90] Several factors may account for the increased incidence of total SSIs in the intervention group. Patients in the 80% FiO_2 group had significantly increased body mass index (BMI), higher blood loss, and more crystalloid infused. On multivariate logistic regression analysis, 80% oxygen and remaining intubated postoperatively remained predictive of SSI. Mortality was rare in either group and unrelated to increased supplemental oxygenation.

Q6B. Neuraxial anesthesia: Intraoperative and postoperative non-rebreathing mask

The available data on the impact of different levels of supplemental increased fraction of inspired oxygen on SSI in patients under regional anesthesia examined 80% oxygen versus 30% oxygen.

For this comparison we considered SSI the critical outcome. Length of stay outcome was also evaluated. The evidence for this question consists of 1 RCT.[91] The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 6.

Moderate quality evidence suggested no benefit of supplemental 80% FiO_2 administered via non-rebreathing mask intra and postoperatively in patients under neuraxial anesthesia. This was based on no difference in risk of SSI in study (N=143) in cesarean sections, at low risk of bias.[91] Despite no difference in blood loss between groups, it was the only factor predictive of SSI in an associated regression analysis. The study did not note any protocol used during the study to optimize tissue oxygenation.

Q6C. Postoperative only: Facemask and/or nasal cannula

The data available on the impact of different levels of supplemental increased fraction of inspired oxygen used in the postoperative period only examined 28-30% oxygen versus room air.

For this comparison we considered SSI as the critical outcome. SSI type (organ/space, superficial and deep SSI), ASEPSIS scores, mortality, adverse events, tissue oxygenation, and length of stay outcomes were also evaluated. The evidence for this question consists of 2 RCTs. [92,93] The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 6.

High-quality evidence suggested no benefit of supplemental 28-30% FiO_2 administered via facemask and/or nasal cannula solely in the postoperative period. This was based on no difference in SSIs from two studies.[92,93] Turtiainen et al., [92] a lower limb vascular surgery study (N=143) at low risk of bias used 30% oxygen via facemask in the recovery room and on the first postoperative day on the ward (~36 hours), followed by constant oxygen flow of 5L/min via nasal cannula during the second postoperative day. A significant reduction in SSI was seen only in isolated groin incisions. Subcutaneous tissue oxygen tension (measured hourly for the first four hours, then at 18 and 36 hours) was significantly higher in the supplemental oxygenation group. Whitney et al.,[93] a second, smaller, study at high risk of bias, in 24 cervical spine procedures, reported no wound complications in either group with supplemental 28% oxygen administered at 2L/min via nasal cannula for 36 hours after discharge from the post-anesthesia care unit as compared to the room air group. Mortality[92] and adverse events[92,93] were rare, did not differ between groups, and were unrelated to use of supplemental oxygenation.

Q6. Recommendations

6A. For patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation, administer increased fraction of inspired oxygen (FiO_2) both intraoperatively and post-extubation in the immediate postoperative period. To optimize tissue oxygen delivery, maintain perioperative normothermia and adequate volume replacement. **(Category IA)** [85-90] (Key Question 6)

6B. No recommendation can be made regarding the safety and effectiveness of administering perioperative increased fraction of inspired oxygen (FiO_2) for the prevention of surgical site infection in patients with normal pulmonary function undergoing either general anesthesia without endotracheal intubation or neuraxial anesthesia (i.e., spinal, epidural, or local nerve blocks). **(No recommendation/unresolved issue)** [91] (Key Question 6)

6C. No recommendation can be made regarding the safety and effectiveness of administering increased fraction of inspired oxygen (FiO_2) via facemask or nasal cannula only during the postoperative period for the prevention of surgical site infection in patients with normal pulmonary function. **(No recommendation/unresolved issue)** [92,93] (Key Question 6)

Q7. What is the optimal target FiO_2 to reduce the risk of SSI; how and when should it be administered?

Our search did not identify RCTs or SRs that both evaluated the optimal fraction of inspired oxygen, how and when it should be administered, and included SSI as an outcome. All studies evaluating the use of supplemental increased oxygenation both intraoperative and postoperatively used 80% FiO_2 as the target level.

Other Guidelines

Evidence-based clinical practice guidelines recommend maintaining patient homeostasis, by optimizing oxygenation during major surgery and in the recovery period (maintaining a >95% hemoglobin saturation), in concert with maintaining both patient temperature to avoid hypothermia and adequate perfusion during surgery.[234]

Q7. Recommendation

7. No recommendation can be made regarding the optimal target level, duration, and delivery method of the fraction of inspired oxygen (FiO_2) for the prevention of surgical site infection. **(No recommendation/ unresolved issue)** (Key Question 7)

ANTISEPTIC PROPHYLAXIS

Q8. What are the most effective strategies for preparing the patient's skin prior to surgery to reduce the risk of SSI?

To answer this question we focused on four subquestions: A) How safe and effective is preoperative antiseptic bathing or showering? B) How safe and effective are antiseptic skin preparation agents individually and in combination? C) How safe and effective is the application of an antimicrobial sealant immediately following intraoperative skin preparation? and D) How safe and effective are plastic adhesive drapes?

Q8A. How safe and effective is preoperative antiseptic bathing or showering?

The available data examined the following comparisons:

1. Chlorhexidine gluconate (CHG) solution vs. placebo solution
2. CHG solution vs. un-medicated bar soap
3. CHG solution vs. no wash
4. CHG whole body wash vs. partial body wash
5. Aqueous iodophor solution vs. control ("routine personal hygiene")

For all comparisons we considered SSI as the critical outcome. Product-related adverse reaction outcomes were also evaluated. The evidence for this question consists of 1 SR[94] (7

RCTs[95-101]) evaluating CHG solution and 1 RCT[102] evaluating povidone iodine solution. The RCTs span a 26 year period with 6 published between 1983 and 1992 and 2 between 2008[102] and 2009.[100] Our search did not identify RCTs or SRs that evaluated optimal preoperative timing, number of showers/baths, number of product applications at each shower/bathing episode, or CHG-washcloths, and their impact on the risk of SSI. The findings of the evidence review and grades for all important outcomes are shown in Evidence Review Table 8A.

Q8A.1. CHG solution vs. placebo solution

High-quality evidence suggested no benefit of preoperative bathing or showering with 4% CHG solution as compared to placebo. This was based no difference in SSI in both a meta-analysis (N=7791) of 4 RCTs[94,95,97,99,100] and a meta-analysis (N=6302) restricted to only the 2 higher quality studies.[94,95,99] Each individual trial found no difference. Five months into 1 large study, the placebo solution was found to have antimicrobial properties and was changed; however, the study did not stratify by or exclude that data.[97] Procedures included in the studies were elective or potentially contaminated surgery,[95] elective inpatient surgery,[97] elective clean mixed surgical procedures including thyroidectomy, inguinal herniorrhaphy, hip and knee surgery, laminectomy, mastectomy, vascular surgery,[99] and elective plastic surgery of the trunk.[100] Number of preoperative showers/baths, amount of antiseptic used per bath, bathing instructions to each group, intraoperative antiseptic skin preparation agent, use of AMP, and follow up varied between studies. Three studies instructed patients to shower[95,99,100] and one instructed them to shower or bathe.[97] Product-related adverse reactions (irritation, itching, reddening of the skin) were rare and did not differ between groups.[94,95,99,100]

Q8A.2. CHG solution vs. un-medicated bar soap

High-quality evidence suggested no benefit of preoperative bathing or showering with 4% CHG solution as compared to un-medicated bar soap. This was based on no difference in SSI in a meta-analysis (N=1443) of 3 RCTs. [94,96-98] Heterogeneity for this comparison was high. Only the largest study (N=1315) reported a reduction in SSI with 4% CHG; however, no special showering/bathing instructions were given to the un-medicated bar soap group whereas "great care was taken to ensure that the patients using [CHG]…complied with the instructions."[97] For the two smaller, lesser quality studies, one study[96] suggested a higher rate of SSI with CHG while the other[98] suggested no difference. Number of preoperative baths, bathing instructions, intraoperative antiseptic skin preparation agent, AMP use, procedures, and follow up varied between studies. One study instructed patients to bathe,[96] one to shower,[98] and one to shower or bathe.[97]

Q8A.3. CHG solution vs. no wash

Moderate-quality evidence suggested no benefit of preoperative showering with 4% CHG solution as compared to no wash. This was based on no difference in a meta-analysis (N=1142) of 3 RCTs. [94,98,100,101] Despite instructions not to shower, it is unclear if the "no wash" groups

showered. The largest study[101] favored 4% CHG, while the other two[98,100] suggested no difference. Heterogeneity for this comparison was significant. Studies included outpatient and inpatient procedures, patients undergoing vasectomy,[98] plastic surgery of the trunk,[100] and elective, clean biliary tract, inguinal hernia or breast cancer[101] procedures. There were also differences in SSI definitions between studies.

Q8A.4. CHG whole body vs. partial body wash

Moderate-quality evidence suggested a benefit of a CHG shower (i.e., a whole body wash including the scalp) as compared to a partial body wash (restricted to the proposed surgical site). This was based on reduced risk of SSI with whole body washing (1 time, 2 applications on the afternoon before surgery) in one large RCT (N=1093) of elective clean biliary tract, inguinal hernia, and breast cancer procedures.[94,101]

Q8A.5. Aqueous iodophor solution vs. control ("routine personal hygiene")

Very low-quality evidence suggested no benefit of preoperative shower with 10% aqueous iodophor solution as compared to routine personal hygiene. This was based on no infections reported in either group in 1 small RCT (N=114) in elective, clean plastic surgical procedures (thorax or abdomen) designed to evaluate the product's efficacy in reducing skin contamination, not SSI.[102]

<u>Other Guidelines</u>

Clinical practice guidelines recommend that patients shower or bathe with an antiseptic agent or soap on at least the night before surgery.[12,234] They do not favor the use of one antiseptic agent in preference of another. There may be contraindications for specific antiseptic-agent use in some patients or surgical procedures.

Q8B. How safe and effective are antiseptic skin preparation agents individually and in combination?

The available data examined the following comparisons:

1. Aqueous iodophor: 1-step vs. 2-step
2. Aqueous iodophor (1 or 2-step) vs. iodophor in alcohol (1-step with or without adhesive drape)
3. CHG-alcohol (1 or 2-step) vs. aqueous iodophor (1 or 2-step)
4. CHG-alcohol (1 or 2-step) vs. iodophor-alcohol (1 or 2-step)
    a. CHG-alcohol (2-step) vs. iodophor-alcohol (2-step)
    b. CHG-alcohol (1-step) vs. iodophor-alcohol (1-step)

For all comparisons, we considered SSI the critical outcome. Product-related adverse event outcomes were also evaluated. The evidence for this question consists of 14 RCTs.[103-116] The

findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 8B.

Q8B.1. Aqueous iodophor: 1-step vs. 2-step

High-quality evidence suggested no benefit of using 2-step as compared to 1-step aqueous iodophor for skin preparation of the surgical site. This was based on no difference in SSI in 2 RCTs at moderate risk of bias.[103,104] One study in 234 clean (30%) and clean-contaminated (70%) oncologic, non-laparoscopic abdominal procedures compared povidone iodine paint (1% iodine) to a 5 minute povidone iodine scrub (0.75% iodine) followed by povidone iodine paint (1% iodine).[103] Another study in 108 CABG procedures did not report the product concentration or scrub duration.[104] In the latter study, patients were also instructed to take antimicrobial showers (unspecified product) the evening before and the morning of surgery.

Q8B.2. Aqueous iodophor (1 or 2-step) vs. iodophor in alcohol (1-step with or without adhesive drape)

Moderate-quality evidence suggested no benefit of iodophor in alcohol as compared to aqueous iodophor. This was based on no difference in SSI in a meta-analysis (N=626) of 5 RCTs including 4 RCTs at moderate risk[104-107] and 1 at low risk[108] of bias. Only one study at moderate risk of bias in CABG procedures showed a reduced risk of sternal SSI with iodophor in alcohol (with or without plastic adhesive drape).[104] A second study (low risk of bias) in CABG procedures using iodophor impregnated plastic adhesive drape at the sternal site showed no difference between groups.[108] The three remaining studies (moderate risk of bias) in THA and TKA,[106] shoulder,[107] and foot and ankle[105] procedures reported no infections, however, each was designed to evaluate the products' efficacy in reducing skin contamination, not SSI.

Q8B.3. CHG-alcohol (1 or 2-step) vs. aqueous iodophor (1 or 2-step)

High-quality evidence suggested a benefit of CHG-alcohol as compared to aqueous iodophor. This was based on a reduced risk of SSI in a meta-analysis (N=1976) of 5 RCTs (two low risk,[109,110] one moderate risk,[107] and two high risk[111,112] of bias) and no difference in product-related adverse events. Only one large study showed a reduced risk of SSI in multiple mixed clean-contaminated abdominal and non-abdominal (thoracic, gynecologic, and urologic) procedures.[110] CHG-alcohol was specifically associated with reduced risk of superficial and deep incisional SSI, but not organ space SSI or sepsis. The study in clean hernia repairs (herniotomy, herniorraphy, or hernioplasty) showed no difference between groups.[109] In both of these studies, authors reported receiving funds from and/or being employed by the manufacturer of the CHG-alcohol product. Of the three studies at moderate or high risk of bias, one in clean, clean-contaminated or contaminated general surgery[112] procedures showed no difference, and the studies in clean elective shoulder[107] and foot and ankle[111] procedures reported no infections; however, each was designed to evaluate the products' efficacy in reducing skin contamination, not SSI.

High-quality evidence from 2 studies suggested no difference in product-related adverse events including skin irritation or pruritis or erythema around the wound.[110,112]

Q8B.4. CHG-alcohol (1 or 2-step) vs. iodophor-alcohol (1 or 2-step)

High-quality evidence suggested no benefit of CHG-alcohol (1 or 2-step) as compared to iodophor alcohol (1-or 2 step). This was based on no difference in SSI in a meta-analysis (N=1223) of 5 RCTs.[107,113-116] Three studies (one low risk,[115] one moderate risk,[113] and one high risk[114] of bias) compared 2-step application, and two studies[107,116] (moderate risk of bias) compared 1 step product application. There was no difference in SSI in individual meta-analyses of "2-step" or "1-step" product application. Details are available under the individual comparators below.

Q8B.4.a. CHG-alcohol (2-step) vs. iodophor-alcohol (2-step)

High-quality evidence suggested no benefit of 2-step CHG-alcohol as compared to 2-step iodophor-alcohol. This was based on no difference in SSI in 3 studies comparing 0.5% chlorhexidine gluconate and alcohol with 10% povidone-iodine (1% available iodine) and 23% isopropyl alcohol.[113-115] No preoperative antiseptic shower protocol was reported in the studies. The large, moderate risk of bias study in a mixed general surgery population reported no difference.[115] CHG-alcohol was associated with a significant reduction in SSI in biliary and "other clean procedures". One study (high risk of bias) in elective, clean, plastic surgery breast procedures reported no difference between groups.[114] The smallest study (moderate risk of bias) in foot procedures reported no infections in either group.[113] However, the study was designed to evaluate the products' efficacy in reducing skin contamination, not SSI.

Q8B.4.b. CHG-alcohol (1-step) vs. iodophor-alcohol (1-step)

High-quality evidence suggested no benefit of 1-step CHG-alcohol as compared to 1 step iodophor-alcohol. This was based on no difference in SSI in two studies at moderate risk of bias comparing 2% chlorhexidine gluconate with 70% alcohol (water insoluble film) to 0.7% iodine with 74% alcohol (water insoluble film).[107,116] One study in shoulder procedures (96 arthroscopies and 4 arthroplasties) reported no infections in either group.[107] Patients were instructed to shower the evening prior to surgery (product not reported). Iodophor-impregnated plastic adhesive drapes were applied to the shoulder arthroplasties' operative site. The second study reported only one wound infection following 80 foot and ankle procedures.[116] Patients were not instructed to take an antiseptic shower prior to surgery. Both studies were designed to evaluate the products' efficacy in reducing skin contamination, not SSI, and both received funding by one or both product manufacturers.

<u>Other Guidelines</u>

Clinical practice guidelines recommend skin preparation with an antiseptic agent, but do not favor one antiseptic agent over another.[12,234] There may be contraindications to use of specific antiseptic skin preparation agents.

Q8C. How safe and effective is the application of an antimicrobial sealant immediately following intraoperative skin preparation?

The available data examined the application of a cyanoacrylate-based anti-microbial skin sealant immediately after skin preparation as compared to no sealant.

For this comparison we considered SSI as the critical outcome. Product-related adverse event outcomes were also evaluated. The evidence for this question consists of 3 RCTs.[117-119] The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 8C.

High-quality evidence suggested no benefit of cyanoacrylate-based antimicrobial skin sealant applied immediately following skin preparation. This was based on no difference in SSI in a meta-analysis (N=553) of 3 RCTs evaluating surgical site skin preparation with povidone iodine-alcohol[117,118] or aqueous povidone iodine [118,119] solution followed by application of cyanoacrylate-based skin sealant before skin incision (1 CABG sternal and/or venous harvest site,[118] 1 CABG leg saphenous vein harvest site,[117] 1 open inguinal hernia repair[119]). The two CABG studies also followed skin sealant application with plastic adhesive drape application. Two studies at low risk of bias suggested no difference between groups.[118,119] However, due to the low number of events in the latter study, superiority of the antimicrobial sealant could not be established and study enrollment ceased once the cyanoacrylate sealant was granted regulatory approval by the FDA (based on porcine data on skin contamination.[119] Both studies were funded by and/or authors had a financial relationship with the skin sealant manufacturer. Only one small study[117] (low risk of bias) suggested a reduced risk of SSI; however, authors acknowledged that the apparent increased risk of SSI in the control legs could be explained by their use of a grading system[252] whose stringent criteria included minimal erythema or discharge as SSI. High-quality evidence suggested no significant product-related sensitivity or other adverse events.[117-119] In the inguinal hernia repair study surgeons reported difficulty incising through the clear film (4/166 patients) and one reported visible “flaking” of the film at the time of procedure (no report of plastic adhesive drape use).[119]

Q8D. How safe and effective are plastic adhesive drapes?

The available data examined the following comparisons:

1. Non-iodophor impregnated adhesive drape vs. no drape
2. Iodophor-impregnated adhesive drape vs. no drape

For all comparisons, we considered SSI as the critical outcome. The evidence for this question consists of 6 RCTs. [104,120-124] The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 8D.

Q8D.1. Non-iodophor impregnated drape vs. no drape

High-quality evidence suggested no benefit of non-iodophor impregnated plastic adhesive drapes in addition to skin preparation as compared to skin preparation alone. This was based on no difference in SSI in a meta-analysis (N=1742) of 4 RCTs spanning a 30 year period (1971-2001), each reporting no difference.[120-123] The two most recent studies[120,121] used polyurethane adhesive drapes; drape material information was not reported in the older[122,123] studies. The surgical skin preparation agent applied prior to the application of the adhesive drapes varied between studies and may have impacted drape adhesion. Studies included general surgery,[122,123] cesarean section,[120] and hip fracture[121] surgery.

Q8D.2. Iodophor-impregnated drape vs. no drape

High-quality evidence suggested no benefit of iodophor-impregnated plastic adhesive drapes in addition to skin preparation as compared to skin preparation alone. This was based on no difference in SSI in a meta-analysis (N=1113) of 2 RCTs, spanning a 15 year period (1987-2002) each reporting no difference.[104,124] Both studies used povidone iodine –alcohol skin preparation (2-step application in the study at low risk of bias in abdominal procedures[124] and one-step application in the study at moderate risk of bias in CABG[104] procedures).

<u>Other guidelines</u>
One evidence-based clinical practice guideline recommends against the routine use of non-iodophor impregnated plastic adhesive drapes and recommends that if a plastic adhesive drape is required, then an iodophor-impregnated one should be used (unless the patient has an iodine allergy).[234]

Q8. Recommendations

8A. Advise patients to shower or bathe (full body) with either soap (antimicrobial or non-antimicrobial) or an antiseptic agent on at least the night before the operative day **(Category IB)** [94-102] (Key Question 8A)

8A.1. No recommendation can be made regarding the optimal timing of the preoperative shower or bath, the total number of soap or antiseptic agent applications, or the use of chlorhexidine gluconate washcloths for the prevention of surgical site infection. **(No recommendation/ unresolved issue)** (Key Question 8A)

8B. Perform intraoperative skin preparation with an alcohol-based antiseptic agent, unless

contraindicated. **(Category IA)** [103-116] (Key Question 8B)

8C. Application of an antimicrobial sealant immediately following intraoperative skin preparation is not necessary for the prevention of surgical site infection. **(Category IA)** [117-119] (Key Question 8C)

8D. Use of plastic adhesive drapes with or without antimicrobial properties, is not necessary for the prevention of surgical site infection. **(Category II)** [104,120-124] (Key Question 8D)

Q9. How safe and effective is antiseptic irrigation prior to closing the surgical incision?

Our search did not identify RCTs or SRs that evaluated the safety and effectiveness of soaking surgical implants (e.g., meshes, neurosurgical ventricular shunts) in antiseptic solution prior to insertion (in combination with parenteral AMP) and its impact on SSI.

The available data examined aqueous iodophor irrigation versus normal saline for the prevention of surgical site infection.

For this comparison, we considered superficial and deep SSIs and organ/space abscess as the critical outcomes. Product related adverse events including wound healing and iodine toxicity outcomes were also evaluated. The evidence for this question consists of 7 RCTs.[125-131] In all studies, both groups received parenteral AMP, but the specific protocol was not necessarily described in all. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 9.

Moderate-quality evidence suggested a benefit of intraoperative aqueous iodophor irrigation of the deep incision, in combination with parenteral AMP, for clean spine procedures. This was based on moderate-quality evidence from a meta-analysis (N=660) of 2 RCTs suggesting a reduced risk of deep SSI when the deep tissues were irrigated and allowed to soak for 3 minutes with 0.35% povidone iodine solution, then irrigated with an additional 2L of normal saline prior to bone grafting and spinal instrumentation.[125,126] All procedures in both studies were performed by the same surgeon. Perioperative AMP included preoperative parenteral dose, postoperative parenteral dosing for 2 days followed by oral prophylaxis for an additional 3 days. Over 80% of the SSIs were MRSA SSIs.

High-quality evidence suggested a benefit of aqueous iodophor irrigation of the subcutaneous tissue, in combination with parenteral AMP, for clean-contaminated, contaminated, and dirty open abdominal procedures. This was based on reduced risk of superficial SSI on meta-analysis (N=329) of 2 RCTS that performed 60 seconds of subcutaneous tissue irrigation with 10% aqueous iodophor solution prior to wound closure.[127,128] The larger [127] study administered parenteral AMP preoperatively and for 48 hours postoperatively, while the smaller[128] study

only reports administering perioperative parenteral AMP. Individual meta-analyses of clean-contaminated (N=149) and dirty (N=90) procedures both showed reduced risk of superficial SSI.

Moderate-quality evidence suggested no benefit of aqueous iodophor peritoneal lavage in contaminated and dirty general surgical abdominal cases. This was based on no difference in organ/space abscess formation in meta-analysis (N=268) of 3 RCTs.[129-131] Aqueous iodophor solution amount, concentration, application, and perioperative AMP regimen varied between studies.

High-quality evidence from 3 studies suggested no increased risk of product-related adverse events[126,128,129] or iodine toxicity.[128,129,131] Moderate-quality evidence from 2 studies suggested no wound healing problems.[125,128]

Q9. Recommendation

9A. Consider intraoperative irrigation of deep or subcutaneous tissues with aqueous iodophor solution for the prevention of surgical site infection. Intra-peritoneal lavage with aqueous iodophor solution in contaminated or dirty abdominal procedures is not necessary. **(Category II)** [125-131] (Key Question 9)

9B. No recommendation can be made regarding the safety and effectiveness of soaking prosthetic devices in antiseptic solutions prior to implantation for the prevention of surgical site infection. **(No recommendation/ unresolved issue)** (Key Question 9)

Q10. How safe and effective is repeat application of an antiseptic skin preparation agent to the surgical site immediately prior to closing the surgical incision?

The available data examined the repeat application of aqueous iodophor solution to the patient's skin immediately prior to closing the surgical incision versus no additional application of topical antiseptic agent for the prevention of surgical site infection. Our search did not identify RCTs or SRs that evaluated repeat application of chlorhexidine, chlorhexidine-alcohol, iodophor alcohol or other topical antiseptic agent The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 10.

Low-quality evidence suggested no benefit of application of aqueous iodophor solution to the patient's skin immediately prior to closing the surgical incision, in combination with parenteral AMP. This was based on no difference in SSI (combined or individual incisional or organ/space SSI) in a small study at high risk of bias, in 107 gastric and colorectal procedures.[132]

Q10. Recommendation

10. No recommendation can be made regarding the safety and effectiveness of repeat application of antiseptic agents to the patient's skin immediately prior to closing the surgical incision for the prevention of surgical site infection. **(No recommendation/unresolved issue)** [132] (Key question 10)

VII. Evidence Review- Prosthetic Joint Arthroplasty section

BLOOD TRANSFUSION

Q11. How do perioperative blood transfusions impact the risk of SSI in prosthetic joint arthroplasty patients?

To answer this question we first addressed the general question of any blood transfusion and its impact on the risk of SSI. We then focused on four subquestions: A) Are specific blood products associated with a risk of SSI? B) If the risk of SSI in increased, can this effect be isolated from the risk associated with more complex cases? C) How does the volume of transfused blood product impact the risk of SSI? and D) How safe and effective is withholding blood transfusion to reduce the risk of SSI?

For the general question of risk of any blood transfusion on SSI, we considered SSI as the critical outcome. The evidence for this question consists of 2 RCTs[133,134] and 4 OBS[135-138] studies. All of the studies reflect European transfusion practices between 1999 and 2007. Studies were published between 2001 and 2008; however, only 2 report the study periods (1998-2000).[137,138] All studies were at low risk of bias. When reported, hemoglobin thresholds for blood transfusion ranged between 8 and 11g/dL. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 11.

High-quality evidence suggested blood transfusions increased the risk of SSI. This was based on increased risk of SSI in a meta-analysis (N=8493) of 6 studies, 2 RCTs[133,134] and 4 OBS studies,[135-138] and a separate meta-analysis (N=7484) of the 4 OBS studies. Analysis combined allogeneic, autologous, and autologous plus allogeneic blood transfusion data. Data in both of these meta-analyses may be driven by 2 OBS studies with a large number of patients who received allogeneic only blood transfusion and the possibility of selection bias inherent in observational studies.[136,138] In contrast, meta-analysis (N=1009) of the 2 RCTs (N=1009) does not suggest an increased risk of SSI with autologous and autologous plus additional allogeneic blood transfusions.

Q11A. Are specific blood products associated with a risk of SSI?

The available data examined the following comparisons:

1. Allogeneic blood (any) vs. no transfusion
    a. Allogeneic not WBC depleted vs. no transfusion
    b. Allogeneic WBC depleted vs. no transfusion
    c. Allogeneic “buffy coat depleted” vs. no Transfusion
    d. Allogeneic WBC filtered vs. no transfusion
    e. Allogeneic “lower WBC content” vs. allogeneic “higher WBC content”
2. Autologous blood (any) vs. no transfusion
    a. Autologous ±WBC filtration vs. no transfusion

b. Autologous whole blood vs. no transfusion
c. Autologous "not WBC depleted" vs. no transfusion
d. Autologous buffy coat depleted vs. no transfusion
e. Autologous "lower WBC content" vs. autologous "higher WBC content"
f. Post-operative salvage only vs. autologous donated blood

3. Allogeneic blood (any) vs. autologous blood (any)
    a. Allogeneic WBC± WBC depleted vs. autologous not WBC depleted
    b. Allogeneic WBC filtered vs. autologous buffy coat depleted.
4. Combined autologous and allogeneic (any) vs. no transfusion
    a. Combined autologous and allogeneic vs. autologous only

For all comparisons, we considered SSI, PJI, or reoperation due to wound infection as the critical outcomes. Wound disturbance outcome was also evaluated. The evidence for this question consists of 2 RCTs[133,134] and 7 OBS[135-141] studies. There were differences between studies including: surgical procedures, definition of SSI, blood product WBC content, length of blood product storage, hemoglobin transfusion trigger levels and other criteria for transfusion, as well as follow up. In several studies, missing data resulted in discrepancies in the numbers. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review and GRADE Table 11A.

1. Allogeneic blood transfusions

Q11A.1. Allogeneic blood (any) vs. no transfusion

Low-quality evidence suggested that allogeneic blood transfusions increased the risk of SSI. This was based on increased risk of SSI in a meta-analysis (N=5737) of 4 OBS[135-138] studies in primary and revision THA and TKA and no difference in reoperation due to wound infection in another OBS[139] study. See individual comparators in GRADE table 9A for specific study findings.

2. Autologous blood transfusions

Q11A.2 Autologous blood (any) vs. no transfusion

Moderate-quality evidence suggested that autologous blood transfusions did not increase the risk of SSI. This was based on no difference in a meta-analysis (N=970) of 2 RCTs. [133,134] One large RCT in THA suggested no difference at 90 days of follow up.[133] The second small RCT in THA reported no infections in either group; however, this study was designed to evaluate transfusion induced immunomodulation, not SSI, and follow up was limited to 7 days.[134] In contrast, 1 large[136] (N=912) prospective OBS study in primary and revision THA and TKA suggested reduced risk of SSI and a smaller[135] study in primary THA and TKA reported only 1 infection in the transfused group. See individual comparators in GRADE table 11A for specific study findings.

3. Allogeneic vs. Autologous blood transfusions

Q11A.3. Allogeneic blood (any) vs. autologous blood (any)

Moderate-quality evidence suggested that allogeneic blood transfusions increased the risk of SSI. This was based on a greater than 4 fold increase in risk in a meta-analysis (N=2592) of 3 OBS studies.[135,136,140] Allogeneic blood products included whole blood, WBC depleted, WBC filtered and not filtered; autologous included whole blood, buffy coat depleted, and perioperative cell salvage-washed blood. See individual comparators in GRADE table 11A for specific study findings.

4. Combined Autologous and Allogeneic blood transfusions

Q11A.4. Combined autologous and allogeneic blood (any) vs. no transfusion

Moderate-quality evidence suggested that combined autologous and additional allogeneic blood transfusions did not increase the risk of SSI. This was based on no difference in subanalysis in 1 RCT[133] (N=470) and 2 OBS[135,136] studies (N=1632). In each study, patients received allogeneic blood transfusion only after all (2-3 units) of the autologous donated blood (with or without additional salvage blood) had been transfused. Autologous blood products included autologous blood donation whole blood, packed red blood cells, salvage blood,[136] "buffy coat depleted",[135] or "WBC filtered"[133]. Allogeneic blood products included "WBC depleted or not depleted",[136] or "WBC filtered (WBCF)".[135,138] Transfusion triggers included: hemoglobin levels of 8-9g/dL,[133,136] <11g/dL for autologous transfusions and <6g/dL for allogeneic transfusions or <10g/dL in patients with cardiovascular or cerebrovascular disease, or symptomatic anemia in another[141] study. See individual comparators in GRADE table 11A for specific study findings.

<u>Other Guidelines</u>

Recent blood transfusion practice guidelines recommend more restrictive transfusion strategies than those used in these studies.[253] In hemodynamically stable postoperative surgical patients, transfusion is recommended for hemoglobin levels of 8g/dL or less for symptoms (e.g., chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure). In adult and pediatric intensive care unit patients, the recommended hemoglobin level for transfusion is 7g/dL or less.

Q11B. If the risk of SSI is increased, can this effect be isolated from the risk associated with more complex cases?

Our search did not identify data that directly evaluated the association between increasing blood transfusion requirements, more complex cases, and the risk of SSI in prosthetic joint arthroplasty patients. However, data from 3 OBS[136,138,141] studies stratified blood transfusion

requirements and 1 OBS[136] study reported blood loss, both by procedure type. See individual comparators in GRADE table 11B for specific study findings.

Q11C. How does the volume of transfused blood product impact the risk of SSI?

Our search did not identify data that evaluated differences in the volume of transfused blood product and their impact on the risk of SSI in prosthetic joint arthroplasty patients.

Q11D. How safe and effective is withholding blood transfusions to reduce the risk of SSI?

Our search did not identify data that both evaluated the safety and effectiveness of withholding blood transfusions and its impact on the risk of SSI in prosthetic joint arthroplasty patients.

Other Guidelines

Clinical practice guidelines recommend against withholding transfusion of necessary blood products from surgical patients as a means to prevent SSI.[12]

Q11. Recommendation

11A. No recommendation can be made regarding the perioperative management of blood transfusions for the prevention of surgical site infection in prosthetic joint arthroplasty. **(No recommendation/unresolved issue)**[133-141] (Key Question 11A-C)

11B. Do not withhold transfusion of necessary blood products from surgical patients as a means to prevent surgical site infection. **(Category IB)** [12] (Key Question 11D)

SYSTEMIC IMMUNOSUPPRESSIVE THERAPY

Q12. How does systemic corticosteroid or other immunosuppressive therapy impact the risk of SSI in prosthetic joint arthroplasty patients?

Immunosuppressive therapy agents used to treat rheumatoid arthritis (RA) are divided into disease modifying antirheumatic drugs (DMARDs) and biologic agents. The most common DMARD is methotrexate, but can also include hydroxychloriquine, leflunomide, minocycline, sulfasazaline, azathioprine, cyclosporine and gold. DMARD combination therapy includes 2 or 3 drugs, most of which are methotrexate based. Biologic agents are commonly divided into "non-tumor necrosis factor (TNF)" agents (e.g., anakinra, abatacept, rituximab, and tocilizumab) and "anti-TNF" agents (e.g., adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab). In the treatment of both early (<6 months) and established (>6 months) RA, progression from DMARD monotherapy, to DMARD double or triple therapy, to use of biologic agents is indicative of progression from low to high disease activity with or without poor

prognostic features (e.g., functional limitation, extra-articular disease, positive rheumatoid factor or anti-cyclic citrullinated peptide antibodies, and bony erosion by radiographs).[254] Systemic corticosteroids most commonly refer to oral prednisone use.

To answer this question, we focused on two subquestions: A) Does the type of agent impact the risk of SSI? B) Does the preoperative duration of therapy impact the risk of SSI? and C) Does the agent dose impact the risk of SSI?

Q12A. Does the type of agent impact the risk of SSI?

The available data examined the following comparisons:

1. Biologic agents (non-TNF and anti-TNF) vs. disease modifying antirheumatic drugs (DMARDs)
2. DMARDs: methotrexate vs. no DMARD therapy

For all comparisons we considered SSI, PJI, superficial SSI, deep wound abscess, and infected hematoma as the critical outcomes. Drug-related adverse events, as well as adverse events of the surgical wound necrotic eschar, and serous drainage outcomes were also evaluated. "Adverse events of surgical wound" was a composite variable that included: wound dehiscence (not completely healed 14 days after surgery or needs secondary closure), continued discharge, and culture-positive infection. The evidence for this question consists of 4 OBS studies in RA patients.[142-145] All studies were at low risk of bias. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 12A.

Q12.1. Biologic agents (non-TNF and anti-TNF) vs. DMARDs

Very low-quality evidence suggested biologic agent therapy (non-TNF and anti-TNF) increased the risk of SSI. This was based on greater than 5-fold increase in risk of SSI and superficial SSI, but no difference in PJI in 3 separate meta-analyses (N=528) of 2 OBS studies.[142,143] Multivariate logistic regression analyses in both studies identified biologic agents as a significant risk factor for infection, and in one study[142] they were also a risk factor for deep venous thrombosis (DVT). Very-low quality evidence also suggested no difference in other adverse events of the surgical wound.[144] For superficial SSI, the large[143] study in primary or revision THA or TKA RA patients (superficial SSI rate 18.8%) reported a significantly increased risk with biologic agents while the smaller[142] study (superficial SSI rate of 7.4%) reported no difference. The large and small studies each reported no difference in PJI, however the number of events in both groups (n=3 and 1, respectively) and the number of patients in the smaller one (N=108) limited the power of the analyses.

Biologic agents included anti-TNFs (etanercept, infliximab, adalimumab) and non-TNFs (anakinra, abatacept and rituximab). In each study patients had established RA (on average > 10 years). All patients on biologic agent therapy also received prednisone 3-5mg/day, and the majority also received methotrexate (88%[142] to 92%[144]) and/or another DMARD[142] (13%).

DMARD patients in all three studies were on single or multiple DMARD therapy in addition to daily prednisone (average, 3mg/day). The most common DMARD was methotrexate but none of the studies reported average weekly doses and only one reported the DMARD perioperative administration protocol (it was administered continuously).[143]

Q12.2. DMARDs: methotrexate vs. no DMARD therapy

Very low-quality evidence suggested methotrexate therapy did not increase the risk of SSI. This was based on no difference in PJI, deep wound abscess, infected hematoma, necrotic eschar, or serous drainage at 6 months of follow up in 1 OBS study.[145] Both the study size and the total number of events for each outcome were limited. This 1991 study utilized data collected between 1978 and 1987 with patients on a mean weekly methotrexate dose of 8.7mg (range: 7.5-12.5mg) and could be considered sub-therapeutic in current clinical practice.[255] The methotrexate group included both patients who had continued and patients who had stopped methotrexate within 4 weeks of surgery. While patients in the no therapy group had never taken methotrexate, some were on daily prednisone (study does not report how many).

Q12B. Does the preoperative duration of the therapy impact the risk of SSI?

Our search did not identify data that directly evaluated length of time that immunosuppressive therapy was used preoperatively and its impact on the risk of SSI in prosthetic joint arthroplasty patients. Thus, we evaluated disease duration as a proxy. We considered SSI as the critical outcome. The evidence for this question consists of 2 OBS studies.[142,143] Our search did not reveal data that evaluated patients with early RA (<6 months). The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 12B.

Low-quality evidence suggested that in patients with established RA (>6 months), years of disease duration was a risk factor for SSI. This was based on increased risk in 2 OBS studies that performed multivariate logistic regression analyses comparing infected to non-infected patients on biologic (anti-TNF) agents and DMARDs.[142,143]

Q12C. Does the agent dose impact the risk of SSI?

Our search did not identify data that directly evaluated different doses of biologic agents or DMARDs and their impact on the risk of SSI in arthroplasty patients. The available data examined doses of prednisone and risk of SSI in patients on biologic agents (anti-TNF) as compared to those on DMARDs.

For this comparison, we considered SSI as the critical outcome. The evidence for this question consists of 2 OBS studies in RA patients.[142,143] The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 12C.

Very low-quality evidence suggested higher prednisone dose increased the risk of SSI. This was based on increased risk of SSI on multivariate logistic regression analyses comparing infected and non-infected patients in 2 OBS studies.[142,143] The small study, with the majority of patients on combination biologic/DMARD or dual DMARD therapy, suggested that increasing prednisone dose was a risk factor for SSI.[142] Patients in the biologic agent group were on significantly higher daily prednisone doses (5mg/day; range 2-7) than those in the DMARD group (3mg/day; range 0-5). The larger study, where none of the patients were on combination biologic and DMARD therapy, suggested prednisone dose was not a risk factor for SSI. Patient in both groups were on an average prednisone dose of 3mg/day (range, 0-5).[143] Results were not stratified by immunosuppressive therapy agent.

Q13. What are the most effective strategies in managing systemic corticosteroids or other immunosuppressive therapy perioperatively to reduce the risk of SSI in prosthetic joint arthroplasty patients?

To answer this question we focused on two subquestions: A) How safe and effective is the discontinuation of these agents preoperatively and when should they be resumed? and B) Should the agent dose be adjusted, and if so, for how long?

Q13A. How safe and effective is the discontinuation of these agents preoperatively and when should they be resumed?

The available data examined the following comparisons:

1. DMARDs: methotrexate stopped vs. continued perioperatively
2. Biologic agents: anti-TNF stopped vs. continued perioperatively

The evidence for this question consists of 4 OBS studies examining DMARDs[145-148] and 1 OBS study examining biologic agents[148] in RA patients. All studies were at low risk of bias. For all comparisons we considered PJI the critical outcome. RA flares, infected hematomas, necrotic eschar, and non-communicating serous drainage outcomes were also evaluated. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 13A.

Q13A.1. DMARDs: methotrexate stopped vs. continued perioperatively

Low-quality evidence suggested no increased risk of PJI with methotrexate continued throughout the perioperative period. This was based on no difference in PJI in a meta-analysis of 3 small[145-147] OBS studies and a separate [148] OBS study. In the meta-analysis, both the number of patients (N=135) and events (n=6) were small. The studies were performed between 1991 and 1996 and the methotrexate doses could be considered subtherapeutic in current practice.[255] Procedures followed and length of time during which therapy was stopped

varied. In a larger study, stopping DMARD therapy at the time of surgery (not defined) reduced the incidence of subsequent PJI.[148]

Q13A.2. Biologic agents: anti-TNF stopped vs. continued perioperatively

Very low-quality evidence suggested no difference in risk of PJI with continuation of biologic (anti-TNF) therapy perioperatively. This was based on no difference in risk of PJI in a small subanalysis in 1 OBS study in THA and TKA patients. [148] Both the number of patients (N=50) and events (n=3), all in the group continuing biologic agent therapy perioperatively, were very small.

Q13B. Should the agent dose be adjusted, and if so, for how long?

Our search did not identify data that evaluated perioperative immunosuppressive therapy dose adjustment and its impact on the risk of SSI in prosthetic joint arthroplasty patients.

Other Guidelines

Clinical practice guidelines provide conflicting recommendations regarding the perioperative management of immunosuppressive therapy. In 2008 the American College of Rheumatology provided no recommendation for the perioperative management of DMARDs due to the "absence of consistent evidence".[256] The following year, a multinational guideline suggested that methotrexate could be safely continued in the perioperative period in RA patients undergoing elective orthopaedic surgery.[255] Their recommendation was based on studies with low methotrexate dosing (4-13mg/week). For biologic agents, the British Society for Rheumatology recommended in 2005 that treatment with anti-TNF agents be withheld for 2-4 weeks prior to major surgical procedures and restarted postoperatively if there was no evidence of infection and wound healing was satisfactory.[257] Recommendations were based solely on information provided by pharmaceutical companies. In 2008, the American College of Rheumatology (ACR) recommended that biologic agents not be used for at least one week prior to and one week following surgery (based on the pharmacokinetic properties of a given agent).[256] The 2012 ACR update does not address perioperative management of immunosuppressive therapy.[254]

Q12 and Q13. Recommendation

12 and 13. No recommendation can be made regarding the perioperative management of systemic corticosteroid or other immunosuppressive therapy for the prevention of surgical site infection in prosthetic joint arthroplasty. **(No recommendation/ unresolved issue)** [142-148] (Key Questions 12 and 13)

Q14. What is the optimal duration of postoperative AMP to reduce the risk of SSI in prosthetic joint arthroplasty patients who are on systemic corticosteroid or other immunosuppressive therapy?

Our search did not identify data that specifically evaluated differences in duration of postoperative AMP in prosthetic joint arthroplasty patients who were on systemic corticosteroids or other immunosuppressive agents and its impact on the risk of SSI. However, multiple procedures examined in the Core section, Q1.E: Postoperative AMP duration that included patients on immunosuppressive therapy showed no benefit of continuing AMP after closing the surgical incision in the operating room. Therefore, the broader recommendation for duration of postoperative AMP should be applied to prosthetic joint arthroplasty procedures irrespective of use if systemic corticosteroid or other immunosuppressive therapy.

Q14. Recommendation

14. For prosthetic joint arthroplasty patients on systemic corticosteroid or other immunosuppressive therapy, Recommendation 1E applies: In clean and clean-contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain. **(Category IA)**[27-65] (Key question 14)

INTRA-ARTICULAR CORTICOSTEROID INJECTIONS

Q15. How do preoperative intra-articular corticosteroid injections impact the risk of SSI in prosthetic joint arthroplasty patients?

The available data examined the following comparisons:

1. History of corticosteroid injection vs. no injection
    a. TKA: Injection vs. no injection
    b. THA: Injection vs. no injection

For all comparisons we considered any SSI, PJI, and superficial SSI as the critical outcomes. The evidence for this question consists of 2 OBS studies in TKA[149,150] and 3 OBS studies in THA[151-153] patients. All studies were at low risk of bias. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 15.

Low-quality evidence suggested that preoperative intra-articular corticosteroid injection did not increase the risk of SSI following total joint arthroplasty. This was based on no difference in a

meta-analysis (N=1146) of 5 OBS studies in TKA[149,150] and THA.[151-153] See individual comparators below and in the GRADE table for individual TKA and THA findings.

Q15.1.a. TKA: Injection vs. no injection

Very low-quality evidence suggested that preoperative intra-articular corticosteroid injection did not increase the risk of SSI following TKA. This was based on no difference in SSI, PJI, or superficial SSI in meta-analyses (N=414) of 2 OBS studies.[149,150] Both the total number of patients and events was small. One study in 144 patients[149] suggested that a history of preoperative intra-articular injection was significantly associated with PJI after TKA (3 infections, all in the injection group) while another study in 270 TKAs[150] reported no PJIs in either group. Both studies had 1 year of follow up. The majority of infections were superficial SSIs and no difference was reported at 30 days of follow up. In the smaller study, patients received injections in the orthopaedic clinic, rheumatology clinic, or general practice setting, while those in the larger study all received their injections in the operating room using strict aseptic technique. Patients had been injected within 11[149] and 12[150] months of surgery.

Q15.1.b. THA: Injection vs. no Injection

Very low-quality evidence suggested that a preoperative intra-articular corticosteroid injection did not increase the risk of infection following THA. This was based on no difference in SSI, PJI, or superficial SSI on separate meta-analyses of 3 OBS studies.[151-153] No difference in PJI or superficial SSI was reported in each individual study. In 2 studies, both the number of patients and events was small.[151,153] Corticosteroid doses and follow up periods varied. In each study, corticosteroid injection was administered in a radiology suite using standard protocols for aseptic technique and one study also indicated that the radiologists wore sterile masks and gowns.[153]

Q16. What are the most effective strategies for managing the preoperative use of intra-articular corticosteroid injections to reduce the risk of SSI in prosthetic joint arthroplasty patients?

Our search did not identify data that evaluated different intra-articular corticosteroid injection agents and their impact on risk of SSI.
To answer this question we focused on 2 subquestions: A) Does the length of time between corticosteroid injection and prosthetic joint arthroplasty impact the risk of SSI? and B) Does the corticosteroid injection dose impact the risk of SSI?

Q16A. Does the length of time between intra-articular corticosteroid injection and prosthetic joint arthroplasty impact the risk of SSI?

The available data evaluated different lengths of time between preoperative intra-articular corticosteroid injection and prosthetic joint arthroplasty and the impact on the risk of SSI in THA only, not TKA.

For all comparisons we considered SSI as the critical outcome. The evidence for this question consists of 2 OBS studies.[152,153] The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 16.

Low-quality evidence suggested no association between the length of time between intra-articular corticosteroid injection and THA and the development of SSI. This was based on no difference in the length of time between injection and surgery and the development of SSI in 2 OBS studies.[152,153] The smaller, underpowered study, also reported no association between the number of injections and SSI.[153] In the larger study, while there was no difference in PJI or superficial SSI (mean time between injection and THA was 112 days), the mean time from injection to surgery for those diagnosed with PJI was less than half as long those diagnosed with superficial SSI (44 vs. 112 days).[152]

Q16B. Does the corticosteroid injection dose impact the risk of SSI?

Our search did not identify data that evaluated different doses of preoperative intra-articular corticosteroid injections and their impact on the risk of SSI.

Other Guidelines

While clinical practice guidelines include intra-articular corticosteroid injections among their pharmacologic recommendations for the initial management of knee and hip osteoarthritis, they do not provide recommendations on management strategies with regard to SSI prevention.[258] Safe injection practices apply to the administration of intra-articular corticosteroid injections.[259]

Q15 and Q16. Recommendation

15 and 16. No recommendation can be made regarding the management of preoperative intra-articular corticosteroid injections for the prevention of surgical site infection in prosthetic joint arthroplasty. **(No recommendation/ unresolved issue)**[149-153] (Key questions 15 and 16)

ANTICOAGULATION

Q17. What are the most effective strategies for managing perioperative venous thromboembolism (VTE) prophylaxis to reduce the risk of SSI in prosthetic joint arthroplasty patients?

To answer this question we focused on two subquestions: A) Does the risk of SSI differ by individual VTE prophylaxis agent? B) What is the optimal timing and duration of perioperative VTE prophylaxis that also reduces the risk of SSI in prosthetic joint arthroplasty patients? and C) How safe and effective is modifying the dose of the perioperative VTE prophylaxis agent to reduce the risk of SSI?

Q17A. Does the risk of SSI differ by individual VTE prophylaxis agent?

The available data examined the following comparisons between different anticoagulation agents:

1. Enoxaparin vs. fondaparinux
2. Enoxaparin vs. rivaroxaban
3. Enoxaparin vs. aspirin (ASA) and mechanical prophylaxis
4. Enoxaparin vs. bemiparin vs. fraxiparin vs. fondaparinux
5. LMWHs or fondaparinux vs. ASA
6. Warfarin vs. no pharmacologic or mechanical prophylaxis
7. Warfarin vs. ASA ± mechanical prophylaxis
8. Higher vs. lower mean INR

For all comparisons we considered SSI and PJI as the critical outcomes. Hemorrhagic wound complications, time until wound was dry or persistent wound drainage, drug related adverse events, and wound hematoma outcomes were also evaluated. The evidence for this question consists of 1 SR,[154] 4 RCTs,[159-162] and 5 OBS[163-167] studies in primary and revision, unilateral, THA, TKA, and hip fracture procedures. Injectable agents included LMWHs (Factor Xa and some thrombin inhibition), most commonly enoxaparin or the indirect Factor Xa inhibitor fondaparinux. Oral agents included rivaroxaban (direct Factor Xa inhibitor), warfarin (Vitamin K antagonist, Factor II, VII, IX, X inhibitor) and ASA (cyclooxygenase inhibitor). No reversing agents currently exist for fondaparinux or rivaroxaban. Our search did not identify studies that evaluated warfarin as compared to enoxaparin or the impact of unfractionated heparin, or clopidogrel on the risk of SSI. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 17A.

Q17A.1. Enoxaparin vs. fondaparinux

Low-quality evidence suggested no difference between perioperative injectable VTE prophylaxis with enoxaparin or fondaparinux and risk of SSI. This was based on no difference in SSI and no drug related adverse events at the end of VTE prophylaxis (11 days) in a large meta-analysis (N=7237) of 4 RCTs (in primary and revision THA, TKA, and hip fracture procedures (osteosynthesis and hemi-arthroplasties).[154-158] The studies were large, international, multi-center studies evaluating the safety and effectiveness of these agents in reducing the risk of postoperative VTE, not SSI. While fondaparinux administration was standardized (2.5mg once a

day starting postoperatively, except in hip fractures where it was started preoperatively if the case was delayed for >24 hours), enoxaparin dose and timing of administration varied between studies (30mg twice a day starting postoperatively[155,158] or 40 mg once a day starting preoperatively[156,157]). In all four studies, prophylaxis was scheduled to last 5-9 days postoperatively. SSI was a secondary outcome and follow up was limited (up to 11 days postoperatively). The 4 individual RCTs and the SR meta-analysis were all sponsored by the manufacturer of fondaparinux and authored by the same investigators, in which the lead, senior, and multiple co-authors reported serving as scientific consultants to the manufacturers of both agents evaluated in the studies. Turpie et al., indicated that the sponsor was responsible for data collection and final statistical analysis.[158]

Q17A.2. Enoxaparin vs. rivaroxaban

High-quality evidence suggested no difference between injectable enoxaparin and oral rivaroxaban, and risk of SSI. This was based on no difference in SSI in a large meta-analysis (N=12,383) of 4 RCTs in elective primary or revision THA or TKA, and no difference in hemorrhagic wound complications or drug related adverse events.[159-162] These studies were large, international, multi-center studies at low risk of bias, evaluating the safety and effectiveness of once daily dosing with enoxaparin or rivaroxaban in reducing the risk of postoperative VTE, not SSI. Eriksson et al.,[159] and Kakkar et al.,[160] compared enoxaparin 40mg once a day started preoperatively to rivaroxaban 10mg once a day started postoperatively in elective unilateral primary (95%) or revision THA. Rivaroxaban was administered for 35 days in both studies; enoxaparin was administered for 35 days in one[159] and 10-14 days in the other[160]. Follow up was approximately 2 months. Two other studies evaluated these agents in elective unilateral primary (97%) or revision TKA, administered over 10-14 days.[161,162] While rivaroxaban administration was standardized (10mg once a day, started preoperatively), enoxaparin dose and timing varied between studies (40mg once a day, started preoperatively[161] or30mg twice a day started postoperatively SSI was a secondary outcome and follow up was approximately 6 weeks. All studies were sponsored by the manufacturer of rivaroxaban and authored by investigators who were employees of the manufacturer or who served as scientific consultants to the manufacturers of both agents evaluated in the studies.

Q17A.3 Enoxaparin vs. ASA and mechanical prophylaxis

Very low-quality evidence suggested no difference between injectable enoxaparin and combined oral ASA and mechanical prophylaxis, and risk of SSI. This was based on no increased risk of SSI on logistic regression analysis in one large study in primary THA or TKA.[163] Enoxaparin was associated with a longer time until wound was dry in THA, but not TKA. Enoxaparin was started 12-24 hours postoperatively. ASA 325mg along with pneumatic compression devices was started on the morning after surgery. Analysis was limited to patients with a closed suction drain and normal coagulation profile. Duration of VTE prophylaxis and follow up period were not reported.

Q17A.4. *Enoxaparin vs. bemiparin vs. fraxiparin vs. fondaparinux*

Very low-quality evidence suggested no difference between perioperative injectable LMWH, ultra LMWH and fondaparinux and risk of SSI. This was based on no difference in PJI at 6 months of follow up in a small nested, case control study within a larger European multicenter prospective study investigating the independent effects of VTE prophylaxis timing on the risk of PJI in TKA (low risk of bias).[164] Logistic regression analysis suggested that hematoma formation increased the risk of PJI four fold.

Q17A.5. Enoxaparin, dalterparin, tinzaparin or fondaparinux vs. ASA ± mechanical prophylaxis

Very low-quality evidence suggested no difference between perioperative injectable LMWH, fondaparinux, and combined oral ASA (with or without mechanical VTE prophylaxis), and risk of SSI. This was based on no difference in SSI in a subanalysis (n=41,917) of a very large retrospective OBS study (low risk of bias) using administrative data from a national sample of primary TKAs.[165] Data were collected from 307 facilities over a 2 year period and compared the risk of VTE, bleeding, SSI, and mortality in primary TKA patients 4719 (5.0%) of whom were on ASA, 51,923 (55.3%) on oral warfarin, and 37,198 (39.6%) on injectable agents (LMWHs and fondaparinux were combined in the analysis). Pneumatic compression devices were used on the day of surgery or on the first postoperative day in 1795 (38%), 28,757 (55%), and 17,756 (48%) of the populations, respectively. Patients on ASA had fewer baseline comorbidities, lower baseline risk of venous thromboembolism, and received care in hospitals with shorter average length of stay that more commonly discharged to the patient's home after surgery. The study included SSIs detected at the time of admission or upon readmission to the hospital within 30 days of the index procedure using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) wound infection codes. Authors indicated that subtherapeutic dosing and/or inappropriate dose timing of the LMWHs or synthetic Factor Xa inhibitor may have impacted the results.

Q17A.6. Warfarin vs. no pharmacologic or mechanical prophylaxis

Very low-quality evidence suggested no difference between oral warfarin VTE prophylaxis and no pharmacologic or mechanical prophylaxis, and risk of SSI. This was based on no difference in SSI (deep or superficial) in one large retrospective OBS study in primary unilateral TKA at 3 months of follow up (low risk of bias).[166] History of anticoagulation prophylaxis for cardiac (arrhythmia or prosthetic valve) or thromboembolic event was not associated with increased risk of SSI or gastrointestinal bleed in patients on 6 weeks of postoperative warfarin VTE prophylaxis. INR levels (target INR: 1.6-2.2) were monitored and medication adjusted twice weekly. Standardized postoperative protocols in both groups included continuous passive motion, physical therapy, weight bearing, and similar pain and nausea medications.

Q17A.7. Warfarin vs. ASA ± mechanical prophylaxis

Low-quality evidence suggested no difference between perioperative oral warfarin and ASA (with or without mechanical VTE prophylaxis), and risk of SSI. This was based on no difference in SSI in two large retrospective studies at low risk of bias.[163,165] In one large single institution study, logistic regression analysis suggested that in THA and TKA, warfarin (target INR=2) started on the day of surgery was not associated with an increased risk of SSI or longer time until wound was dry, as compared to ASA 325mg with pneumatic compression devices started on the morning after surgery.[163] Duration of VTE prophylaxis and follow up period were not reported. Analysis was limited to patients with a closed suction drain and normal coagulation profile. A second, large study using administrative data collected from 307 facilities over a 2 year period suggested no difference in SSI in primary TKAs.[165] Target INR was not reported. Pneumatic compression devices were used on the day of surgery or on the first postoperative day in 55% of patients on warfarin and 38% of patients on ASA. SSIs were detected on admission or readmission to the hospital within 30 days of the index procedure using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) wound infection codes. Authors indicated that subtherapeutic dosing or inappropriate timing may have impacted results.

Q17A.8. Higher vs. lower INR

Very low-quality evidence suggested no difference between higher and lower oral warfarin INRs, and risk of SSI. This was based on no difference in PJI in a small (N=154) 1:2 case control study in primary and revision THA and TKAs (low risk of bias).[167] Low dose warfarin (target INR=1.5) was administered on the day of surgery and continued for 6 weeks. Thirteen patients on anticoagulation therapy preoperatively for a chronic condition, were heparinized postoperatively until fully anticoagulated on warfarin with a higher target INR=2-3. All of these patients were in the infected cohort. The INR was also significantly higher in patients with wound-related problems who later developed infection. In addition, infected patients and those with wound complications were more likely to have INR > 1.5 at the time of hospital discharge. Infected patients also had a significantly higher incidence of wound hematomas. On multivariate logistic regression analysis, wound hematomas and persistent wound drainage were significant risk factors for PJI. Nine (69%) of the heparinized patients developed wound complications including: hematomas, persistent wound drainage, or delayed wound healing.

Q17B. What is the optimal timing and duration of perioperative VTE prophylaxis that also reduces the risk of SSI?

The available data examined VTE prophylaxis started preoperatively as compared to postoperatively in patients receiving injectable LMWHs (enoxaparin, bemiparin, or fraxiparin) or fondaparinux.

For this comparison we considered PJI as the critical outcome. The evidence for this question consists of 1 OBS study in TKA, at low risk of bias.[164] Our search did not identify data that evaluated optimal timing in THA or in patients taking oral agents. Our search did not identify

data that evaluated optimal duration of perioperative anticoagulation prophylaxis and its impact on SSI. The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review and GRADE table 17B.

Very low-quality evidence suggested that close perioperative administration of injectable LMWHs or fondaparinux VTE prophylaxis agents did not increase the risk of PJI. This was based on no difference in PJI at 6 months of follow up, in a small, nested, multicenter, case control study in TKAs.[164]

Other Guidelines

Clinical practice guidelines, on prevention of VTE in patients undergoing THA, TKA, or hip fracture procedures provide recommendations on choice, timing, and duration of VTE prophylaxis.[260,261]

Q17C.How safe and effective is modifying the dose of perioperative VTE prophylaxis agent to reduce the risk of SSI?

Our search did not identify data that evaluated the safety and effectiveness of modifying the dose of perioperative VTE prophylaxis agent and its impact on the risk of SSI.

Q17. Recommendation

17. No recommendation can be made regarding perioperative management of venous thromboembolism prophylaxis for the prevention of surgical site infection in prosthetic joint arthroplasty. **(No recommendation/unresolved issue)** [154-167] (Key Question 17)

ORTHOPAEDIC SPACE SUIT

Q18. How safe and effective are orthopaedic space suits in reducing the risk of SSI in prosthetic joint arthroplasty patients, and which healthcare personnel should wear them?

The available data evaluated the use of a space suit as compared to no space suit.

For this comparison we considered deep SSI requiring reoperation, deep SSI requiring revision, and deep SSI as the critical outcomes. Superficial SSI outcome was also evaluated. The evidence for this question consists of 3 OBS studies at low risk of bias.[168-170] The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 18.

Very-low quality evidence suggested no benefit to using an orthopaedic space suit to reduce the risk of SSI. This was based on no difference in deep SSI requiring reoperation,[168] deep SSI requiring revision surgery,[169] or deep or superficial SSI[170] in 3 OBS studies. The number of events for each of these studies was low. The largest national joint registry study with multiple subgroup analyses suggested that use of a space suit was associated with an increased number of deep SSIs requiring revision surgery within 6 months of THA or TKA, but this evidence was limited in size.[169] Results did not differ based on the presence or absence of laminar flow. A large multicenter study using administrative data from patients undergoing TKA suggested no difference in deep SSIs requiring reoperation within 90 days.[168] Reoperations included incision and drainage and implant removal. The definition of deep SSI in this study may have included PJI. Space suit and laminar flow use varied between groups. A third small study in THA and hip hemiarthroplasties reported only 1 deep SSI in the space suit group and 1 superficial SSI in each group at 24 months of follow up.[170] High-efficiency particulate air (HEPA)/mixed turbulent filtration was used in both groups.

Our search did not identify data that quantified potential complications associated with the use of space suits. In one large national joint registry study (N=88,311) comments by surgeons completing a questionnaire (n=35) included "limited spatial awareness and ease of contamination due to an apparent false sense of security" with the use of a space suit.[169] We did not evaluate the efficacy of the space suit as personal protective equipment.

Also, our search did not identify data that evaluated the association between specific health care personnel wearing a space suit and SSI. One retrospective controlled study included a surgeon questionnaire reporting that the surgeon, assistant, and scrub nurse were the team members wearing a full space suit.[169] One prospective controlled study reported those same team members wearing the space suit in the intervention group.[170]

Q18. Recommendation

18. No recommendation can be made regarding the safety and effectiveness of orthopaedic space suits or the health care personnel who should wear them for the prevention of surgical site infection in prosthetic joint arthroplasty. **(No recommendation/unresolved issue)**[168-170] (Key question 18)

POSTOPERATIVE AMP DURATION IN PROSTHETIC JOINT ARTHROPLASTY WITH THE USE OF A DRAIN

Q19. What is the optimal duration of postoperative AMP to reduce the risk of SSI in prosthetic joint arthroplasty in the presence of a drain?

Our search did not identify data that directly evaluated optimal postoperative AMP duration in the presence of a drain and its impact on the risk of SSI in prosthetic joint arthroplasty patients. However, multiple procedures examined in the Core section, Q1.E: Postoperative AMP duration that included use of a drain (including prosthetic joint arthroplasty procedures) showed no benefit of continuing AMP after closing the incision in the operating room. Therefore, the broader recommendation for postoperative AMP duration should be applied to prosthetic joint arthroplasty procedures irrespective of drain use.

Q19. Recommendation

19. In prosthetic joint arthroplasty, Recommendation 1E applies: In clean and clean-contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after the surgical incision is closed in the operating room, even in the presence of a drain. **(Category IA)**[27-65] (Key question 19)

BIOFILM

Q20. What are the most effective strategies to reduce the risk of biofilm formation and SSI in prosthetic joint arthroplasty patients?

To answer this question we focused on four subquestions: A) How effective are cement modifications (i.e., antimicrobial and nanoparticle loading)? B) How effective are prosthesis modifications (i.e., antimicrobial coating, galvanic couples, "printing" technologies, and nanotechnology)? C) How effective are vaccines? and D) How effective are other biofilm control agents (e.g., biofilm dispersants, quorum-sensing inhibitors, novel antimicrobial agents)?

Q20A. How effective are cement modifications (i.e., antimicrobial and nanoparticle loading)?

Our search did not identify data that evaluated the safety and effectiveness of cement modifications in THA and the risk of SSI. In vitro studies and studies that evaluated antimicrobial loaded cement in the absence of perioperative parenteral antimicrobial prophylaxis were excluded from our analysis. The available data examined cefuroxime loaded cement vs. plain cement in primary TKA patient receiving perioperative AMP.

For this comparison we considered deep SSI as the critical outcome. In these studies, deep SSI likely refers to or includes PJI. The evidence for this question consists of 2 RCTs. [171,172] The findings of the evidence review and the grades for all important outcomes are shown in Evidence Review Table 20A.

Moderate-quality evidence suggested a benefit of cefuroxime loaded cement. This was based on a reduced risk of deep SSI in a meta-analysis (N=428) of 2 RCTs: 1 large study in non-diabetic[171] patients and 1 small study (N=78) in diabetic [172] patients. Both studies were at moderate risk of bias. There were no deep SSIs in the cefuroxime loaded cement groups at an average 49 months of follow up. A single surgeon performed all TKAs in an operating room without ultraviolet lights, laminar flow, or use of an orthopaedic space suit. Only the tibial and patellar components were cemented. Cefuroxime 2g in 40g polymethylmethacrylate cement was used in the study groups. AMP included parenteral cefazolin and gentamycin preoperatively then every 6 and 12 hours, respectively, postoperatively for 36 hours followed by cefazolin orally for 7 more days. Data on organisms isolated from the SSIs and antimicrobial resistance were not reported.

Q20B. How effective are prosthesis surface modifications (i.e., antimicrobial coating, galvanic couples, "printing" technologies, and nanotechnology)?

Our search did not identify in vivo studies that evaluated the safety and effectiveness of prosthesis modifications and their impact on biofilm formation and the risk of SSI.

Q20C. How effective are vaccines?

Our search did not identify in vivo studies that evaluated the safety and effectiveness of vaccines and their impact on biofilm formation and the risk of SSI.

Q20D. How effective are other biofilm control agents (e.g., biofilm dispersants, quorum-sensing inhibitors, novel antimicrobial agents)?

Our search did not identify in vivo studies that evaluated the safety and effectiveness of biofilm control agents and their impact on biofilm formation and the risk of SSI.

Q20. Recommendations

20A. No recommendation can be made regarding the safety and effectiveness of cement modifications and the prevention of biofilm formation or surgical site infection in prosthetic joint arthroplasty. **(No recommendation/ unresolved issue**)[171,172] (Key Question 20A)

20B. No recommendation can be made regarding the safety and effectiveness of prosthesis modifications for the prevention of biofilm formation or surgical site infection in prosthetic joint arthroplasty. **(No recommendation/unresolved issue)** (Key Question 20B)

20C. No recommendation can be made regarding the safety and effectiveness of vaccines for the prevention of biofilm formation or surgical site infection in prosthetic joint arthroplasty.

(No recommendation/unresolved issue) (Key Question 20C)

20D. No recommendation can be made regarding the safety and effectiveness of biofilm control agents such as biofilm dispersants, quorum-sensing inhibitors, or novel antimicrobial agents for the prevention of biofilm formation or surgical site infection in prosthetic joint arthroplasty.
(No recommendation/unresolved issue) (Key Question 20D)

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