Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection

Chairmen:

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Foreword

“The doorstep to the temple of wisdom is a knowledge of our own ignorance.”

Benjamin Franklin

The battle against infection is as old as human civilization. During the last few centuries, great scholars such as Louis Pasteur, Ignaz Philipp Semmelweis, Alexander Fleming, and Joseph Lister have transformed the practice of medicine through their extraordinary discoveries. Despite the progress made and strides gained, our mission to prevent infection following surgery remains unaccomplished. It is not an exaggeration to claim that fear of infection lives in the hearts of every surgeon who steps into the operating room daily.

Periprosthetic joint infection (PJI), with all its disastrous consequences,, continues to pose a challenge to the orthopaedic community. Practicing orthopaedic surgeons have invested great efforts to implement strategies that may minimize surgical site infection (SSI). Although high-level evidence may support some of these practices, many are based on little to no scientific foundation. Thus, there is a remarkable variation in practices across the globe for prevention and management of PJI.

The medical community comprehends the importance of high-level evidence and engages in the generation of such whenever possible. The community also recognizes that some aspects of medicine will never lend themselves to the generation of high-level evidence nor should one attempt to do so. It is with the recognition of the latter that The International Consensus Meeting on Periprosthetic Joint Infection was organized. Delegates from various disciplines including orthopaedic surgery, infectious disease, musculoskeletal pathology, microbiology, anesthesiology, dermatology, nuclear medicine, rheumatology, musculoskeletal radiology, veterinary surgery, pharmacy, and numerous scientists with interest in orthopaedic infections came together to evaluate the available evidence, when present, or reach consensus regarding current practices for management of SSI/PJI. The process of generating the consensus has spanned over 10 months. Every stone has been turned in search of evidence for these questions, with over 3,500 related publications evaluated. The evidence, when available, has been assessed. Otherwise the cumulative wisdom of 400 delegates from 52 countries and over 160 societies has been amassed to reach consensus about practices that lack higher level of evidence. The leadership of the Musculoskeletal Infection Society (MSIS) and the European Bone and Joint Infection Society (EBJIS), the two societies whose mission is to improve care of patients with musculoskeletal infection, have in particular contributed to this initiative immensely.

The delegates have been engaged every step of the way by communicating through a “social” website generated for this purpose (www.ForMD.com), with over 25,000 communications exchanged. The consensus document has been developed using the Delphi method under the leadership of Dr. Cats-Baril, a world-renowned expert in consensus development. The design of the consensus process was to include as many stakeholders as possible, allow participation in multiple forums, and provide a comprehensive review of the literature. All relevenat topics on PJI were assigned into one of 15 different workgroups as follows: mitigation and education on comorbidities associated with increased SSI/PJI, perioperative skin preparation, perioperative antibiotics, operative environment, blood conservation, prosthesis selection, diagnosis of PJI,

wound management, spacers, irrigation and debridement, antibiotic treatment and timing of reimplantation, one-stage versus two-stage exchange arthroplasty, management of fungal or atypical PJI, oral antibiotic therapy, and prevention of late PJI. Every consensus statement has undergone extreme scrutiny, especially by those with expertise in a specific area to ensure that implementation of these practices will lead to improvement of patient care

After synthesizing the literature and assembling a preliminary draft of the consensus statement, over 300 delegates attended the face-to-face meeting in Philadelphia and were involved in active discussions and voting on the questions/consensus statements. The delegates first met on July 31 in smaller workgroups to discuss and resolve any discrepancies and finalize their statements. Then, the delegates met in the general assembly for further discussion of questions and consensus statements. After revision, the finalized consensus statement was assembled and the document was forwarded to the Audience Response System that evening for voting to begin the next day. On August 1, 2013 the delegates came into the general assembly and voted on the 207 questions/consensus statements that were presented. The voting process was conducted using electronic keypads, where one could agree with the consensus statement, disagree, or abstain from voting. The strength of the consensus was judged according to the following scale: 1) Simple Majority: No Consensus (50.1%-59% agreement), 2) Majority: Weak Consensus (60%-65% agreement), 3) Super Majority: Strong Consensus (66%-99% agreement), and 4) Unanimous: 100% agreement. Of the 207 questions, there was unanimous vote for one question (controlling OR traffic), 202 questions received super majority (strong consensus), two questions had weak consensus, and only two questions did not achieve any consensus.

The document presented here is the result of innumerable hours of work by the liaisons, leaders, and delegates dedicated to this historic initiative. The information conveyed in this document is based on evidence, whenever present, or is the result of the cumulative wisdom of over 400 of the world's experts in musculoskeletal infection from 52 countries. We are certain that the "best practice guide" set forth by this initiative will serve many of our patients for years to come. It is essential to state that the information contained in this document is merely a guide to practicing physicians who treat patients with musculoskeletal infection and should not be considered as a standard of care. Clinicians should exercise their wisdom and clinical acumen in making decisions related to each individual patient. In some circumstances this may require implementation of care that differs from what is stated in this document.

On with our fight against infection.

Javad Parvizi MD, FRCS

Acknowledgements:

A project of this magnitude is not possible without the assistance and leadership of many. We would like to thank Mitchell Maltenfort PhD, manager of Biostatistics and Bioethics at the Rothman Institute, who has been a critical player in orchestrating literature review, document development, and the numerous edits that have followed. Tiffany Morrison MS and her team should single-handedly be given most of the credit for their leadership in organization of the meeting, which was no small task. Tiffany and her team worked long hours in the months preceding the meeting to ensure every detail was covered and should be credited for the success of this meeting.

Special thanks to Katherine Huff BA from the Rothman Institute for her invaluable editorial skills and detail-oriented mind that could see the trees in the massive forest and ensured the accuracy of every statement made in this document.

We need to thank Greg Chang and his team from ForMD that provided the “social” platform for communication. The numerous interactions and invaluable discussions that took place between delegates would not have been possible without the ForMD. The team should be congratulated for their hard work and extremely responsive attitude that allowed efficient and timely communication between members of the consensus.

Dr. Sandra Berríos-Torres, from the Centers for Disease Control and Prevention, needs a special mention as she has provided us with her expertise and leadership throughout the consensus process and specifically worked with liaisons of some workgroups. She was also kind to attend the meeting in person. As a technical expert representing a United States federal agency, Dr. Berríos-Torres did not vote on any of the consensus statements. While we are unable to include her as a delegate in the document, her contributions to this initiative are greatly appreciated.

With Immense Gratitude to our Sponsors

A meeting of this magnitude could not take place without the generous support of industry partners whose mission parallels ours in providing better care for patients. We are indebted to every one of our industry partners for their financial support and more critically for their scholarly input throughout the process. We appreciate their input during the literature review and refinement of questions and their agreement not to be part of the voting delegates.

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EXECUTIVE SUMMARY

Periprosthetic joint infection (PJI), with its disastrous implications, continues to challenge the orthopaedic community. Practicing orthopaedic surgeons continue to invest efforts to minimize surgical site infection (SSI). Although high-level evidence may support some of these practices, many are based on little to no scientific foundation. This results in wide variation across the globe for prevention and management of PJI. To address this, The International Consensus Meeting on Periprosthetic Joint Infection was organized. Delegates from disciplines including orthopaedic surgery, infectious disease, and many others participated. The process of generating the consensus has spanned 10 months. Over 3,500 relevant publications were evaluated by 400 delegates from 52 countries and numerous societies.

This consensus document has been developed using the Delphi method under the leadership of Dr. Cats-Baril. The consensus process was designed to include many participants, allow participation in multiple forums, and provide a comprehensive review of the literature. Covered topics included the following: mitigation and education on comorbidities associated with increased SSI/PJI, perioperative skin preparation, perioperative antibiotics, operative environment, blood conservation, prosthesis selection, diagnosis of PJI, wound management, spacers, irrigation and debridement, antibiotic treatment and timing of reimplantation, one-stage versus two-stage exchange arthroplasty, management of fungal or atypical PJI, oral antibiotic therapy, and prevention of late PJI. Every consensus statement has undergone careful scrutiny by both subject matter experts and generalists to ensure that its implementation will indeed lead to improvement of care for patients. Based on this process, the following consensus statements were developed.

TABLE OF CONTENTS

William Arnold MD, PhD, Goran Bicanic MD, PhD, Stefano Bini MD, Fabio Catani MD, Jiying Chen MD, PhD, Mohammad Ghazavi MD, FRCSC, Karine M. Godefroy MD, Paul Holham MD, Hamid Hosseinzadeh MD, Kang Il Kim MD, PhD, Klaus Kirketerp-Møller MD, Lars Lidgren MD PhD, Jian Hao Lin MD, Jess H Lonner MD, Christopher C Moore MD, Panayiotis Papagelopoulos MD, Lazaros Poultsides MD MSc PhD, R Lor Randall MD, Brian Roslund PharmD, Khalid Saleh MD MSC FRCSC MHCM, Julia V Salmon MD, Edward Schwarz PhD, Jose Stuyck MD, Annette W Dahl MD, Koji Yamada MD

Workgroup 4: Operative Environment

Liaisons:

Pouya Alijanipour MD, Joseph Karam MD

Leaders:

Adolfo Llinás MD (International), Kelly G Vince MD (International), Charalampos Zalavras MD (US) 114

Delegates:

Matthew Austin MD, Grant Garrigues MD, Snir Heller MD, James Huddleston MD, Brian Klatt MD, Viktor Krebs MD, Christoph Lohmann MD, Edward J McPherson MD, Robert Molloy MD, Ali Oliashirazi MD, Mitchell Schwaber MD, Eoin Sheehan MD, Eric Smith MD, Robert Sterling MD, Gregory Stocks MD, Shrinand Vaidya MD

Workgroup 5: Blood Conservation

Liaison:

Mohammad R Rasouli MD

Leaders:

Luiz Sérgio Marcelino Gomes MD, PhD (International), Brian Parsley MD (US) 163

Delegates:

Wael Barsoum MD, Hari Bezwada MD, James Cashman MD, Julio Garcia MD, William Hamilton MD, Eric Hume MD, Rajesh Malhotra MD, Stavros Memtsoudis MD, PhD, Alvin Ong MD, Fabio Orozco MD, Douglas Padgett MD, Ricardo Reina MD, Marco Teloken MD, Emmanuel Thienpont MD, Jonathan H Waters MD

Workgroup 6: Prosthesis Selection

Liaison:

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Leaders:

Javad Parvizi MD, FRCS (US), Yixin Zhou MD (International)

Delegates: 184

Valentin Antoci MD, Paul Ducheyne PhD, Andrew Freiberg MD, Gustavo Garcia Rangel MD, Seung Beom Han MD, Noreen Hickok PhD, Carlos Higuera MD, Constantinos Ketonis MD, Feza Korkusuz MD, Jacek Kruczynski MD, Francisco Macule MD, Jacek Markuszewski MD, Oliver Marín-Peña MD, Dinesh Nathwani MD, Phillip Noble PhD, Kevin Ong PhD, Nelson Ono MD, Mohammad Sadegh Parvizi PhD, Zachary Post MD, Salvador Rivero-Boschert MD, Thomas Schaer VMD, Irving Shapiro DDS, PhD

Workgroup 7: Diagnosis of Periprosthetic Joint Infection

Liaison:

Benjamin Zmistowski BS 202

Leaders:

Craig Della Valle MD (US), Thomas W Bauer MD (US), Konstantinos N. Malizos MD,PhD (International)

Delegates:

Abbas Alavi MD, Hani Bedair MD, Robert E Booth MD, Peter Choong MD, Carl Deirmengian MD, Garth D Ehrlich PhD, Anil Gambir MD, Ronald Huang MD, Yair Kissin MD, Hideo Kobayashi MD, Naomi Kobayashi MD, Veit Krenn MD, Drago Lorenzo MD, SB Marston MD, Geert Meermans MD, Javier Perez MD, JJ Ploegmakers MD, Aaron Rosenberg MD, C Simpfendorfer MD, Peter Thomas MD, Stephan Tohtz MD, Jorge A Villafuerte MD, Peter Wahl MD, Frank-Christiaan Wagenaar MD, Eivind Witzo MD

Workgroup 8: Wound Management

Liaison:

Elie Ghanem MD

Workgroup Leaders:

Volkmar Heppert MD (International), Mark Spangehl MD, FRCSC (US) 224

Delegates:

John Abraham MD, Khalid Azzam MD, Lowry Barnes MD, Federico Jose Burgo MD, Walid Ebeid MD, Nitin Goyal MD, Ernesto Guerra MD, Kirby Hitt MD, Sofiene Kallel MD, Gregg Klein MD, Yona Kosashvili MD, Brett Levine MD, Laura Matsen MD, Michael J Morris MD, James J Purtill MD, Chitranjan Ranawat MD, FRCS, FRCSC, Peter F Sharkey MD, Rafael Sierra MD, Anna Stefansdottir MD, PhD

Workgroup 9: Spacers

Liaison:

Mustafa Citak, MD

Leaders:

Jean-Noel Argenson MD (International), Bas Masri MD, FRCSC (International), Daniel Kendoff MD (International), Bryan Springer MD (US) 251

Delegates:

Volker Alt MD, Andrea Baldini MD, Quanjun Cui MD, Gregory K Deirmengian MD, Hernan del Sel MD, Michael F Harrer MD, Craig Israelite MD, David Jahoda MD, Paul C Jutte MD, Eric Levicoff MD, Enzo Meani MD, Fernando Motta MD, Orestes Ronaldo Pena MD, Amar S Ranawat MD, Oleg Safir MD, Matthew W Squire MD, Michael J Taunton MD, Charles Vogely MD, Samuel S Wellman MD

Workgroup 10: Irrigation and Debridement

Liaison:

Carl Haasper MD, PhD, MSc

Leaders:

Martin Buttaro MD (International), William Hozack MD (US) 274

Delegates:

Craig A Aboltins MD, Olivier Borens MD, JJ Callaghan MD, Pedro Ivo de Carvalho MD, Yuhan Chang MD, Pablo Corona MD, Ferdinando Da Rin MD, Silvano Esposito MD, Thomas K Fehring MD, Xavier Flores Sanchez MD, Gwo-Chin Lee MD, JC Martinez-Pastor MD, SM Javad Mortazavi MD, Nicolas O Noiseux MD, Kuo-Ti Peng MD, Harold Delano Schutte MD, Daniel Schweitzer MD, Rihard Trebše MD, Eleftherios Tsiridis MD, Leo Whiteside MD

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Future Research 363

Societies Represented

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American Academy of Orthopaedic Surgeons (AAOS)
American Association of Tissue Banks AATB
American College of Rheumatology (ACR)
American College of Surgeons (ACS)
American Orthopaedic Association (AOA)
American Shoulder and Elbow Surgeons (ASES)
American Society of Bone and Mineral Research (ASBMR)
American Society of Anesthesiologists (ASA)
American Society of Regional Anesthesia (ASRA)
AO Trauma Clinical Priority Program on Bone Infection
Association Research Circulation Osseuse (ARCO)
Asia Pacific Arthroplasty Association (APAS)
Asia Pacific Knee Society (APKS)
Asia Pacific Orthopaedic Association (APOA)
Asociación Argentina de Ortopedia y Traumatología (AAOT)
Associação Brasileira para o Estudo de Implantes Osteoarticulares (AsBIO)
Association for Study and Application of Methods of Ilizarov (ASAMI)
Association of Bone and Joint Surgeons (ABJS)
Association of Orthopaedic and Trauma surgeons of Russian Federation (AOTRF)
Association of periOperative Registered Nurses (AORN)
Association of Surgeons of Great Britain and Ireland (ASGBI)
Australian Knee Society (AusKS)
Australian Orthopaedic Association (AOA)
Azerbaijan Association of Orthopaedics and Traumatology
Belgian Knee Society (BelKS)
Belgian Orthopaedic and Trauma Society (BVOT)
Brazilian Hip Society (SBQ)
Brazilian Knee Society (BKS)
British Association for Surgery of the Knee (BASK)
British Hip Society (BHS)
British Orthopaedic Association (BOA)
Bulgarian Orthopaedic Association (BulOrtho)
Bulgarian Orthopedics and Traumatology Association (BOTA)
Canadian Orthopaedic Association (COA)
Czech Society for Orthopaedics and Traumatology (CSOT)
Chinese Orthopaedic Association (COA)
Colegio Mexicano De Ortopedia y Traumatología (CMO)
Combined Services Orthopaedic Society CSOS
Croatian Orthopaedic and Traumatology Association (COTA)
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Egyptian Orthopaedic Association (EOA)
European Bone and Joint Infection Society (EBJIS)
European Federation of National Associations of Orthopaedic Sports Traumatology (EFOST)
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Israeli Orthopaedic Association (IOA)
Japanese Orthopaedic Association (JOA)
Korean Hip Society (KHS)
Korean Knee Society (KKS)
Korean Orthopaedic Association (KOA)
Mid American Orthopaedic Association (MOA)
Musculoskeletal Infection Society (MSIS)
Musculoskeletal Tumour Society (MSTS)
New Zealand Orthopaedic Association (NZOA)
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Norwegian Orthopaedic Association (NOA)
Orthopaedic Research Society (ORS)
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Rheumatoid Arthritis Surgical Society (RASS)
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Sociedad Chilena de Ortopedia y Traumatología (SCHOT)
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South African Orthopaedic Association (SAOA)
Southern Orthopaedic Association (SouthOA)
Spanish Orthopaedic Society (SECOT)
Spanish Knee Society (SKS)
Swedish Orthopaedic Association (SOF)
Swiss Orthopaedic and Trauma Association (SGOT/SSOT)
Taiwanese Orthopaedic Association (TaiOA)
The Hip Society (HS)
The International Hip Society (IHS)
The Knee Society (AKS)
Turkish Orthopaedic Association (TOTBID)
Washington State Orthopaedic Association (WSOS)
Weckebach Instituut (WI)
Western Orthopaedic Association (WestOA)
World Orthopaedic Concern (WOC)

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Choong, Peter
Peel, Trisha

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Winkler, Heinz

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Gahramanov, Aydin

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Stuyck, Jose
Thienpont, Emmanuel

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Carvalho, Pedro Ivo
Gomes, Luiz Sérgio Marcelino
Ono, Nelson Keiske
Teloken, Marco

Canada
Backenstein, David
Masri, Bas
Mater, Wadih
Safir, Oleg
Vasarhelyi, Edward

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Diaz-Ledezma, Claudio
Mella, Claudio
Schweitzer, Daniel

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Cai, Xu
Chen, Jiying
Fei, Jun
Huang, Deyong
Lin, Jianhao
Shang, Xifu
Zeng, Yirong
Zhang, Xian Long
Zhou, Yixin

Colombia
Cortes, Luis Emilio
Garcia, Julio Cesar
Higuera, Carlos
Lara, Gilberto
Llinás, Adolfo
Palacio, Julio Cesar
Perez, Javier
Restrepo, Camilo

Costa Rica
Villafuerte, Jorge A.

Croatia
Bicanic, Goran

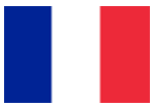
Cyprus
Ketonis, Constantinos

Czech Republic
Gallo, Jiri
Jahoda, David

Denmark
Kirketerpp-Møller, Klaus
Jørgensen, Peter H.

Egypt
Ebeid, Walid

Finland
Huotari, Kasia
Virolainen, Petri



France
Argenson, Jean-Noel
Godefroy, Karine M.
Senneville, Eric

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Alt, Volker
Citak, Mustafa
Frommelt, Lars
Gebauer Matthias
Gehrke, Thorsten
Haasper, Carl
Heppert, Volkmar
Kendoff, Daniel
Krenn, Veit
Lob, Guenter
Lohmann, Christoph H.
Perka, Carsten
Thomas, Peter
Thorey, Fritz
Tohtz, Stephan
Winkler, Tobias
Zahar, Akos

Greece
Babis, George
Malizos, Konstantinos
Papagelopoulos, Panayiotis
Tsiridis, Eleftherios

Hungary
Bucsi, László
Skaliczki, Gabor

India
Malhotra, Rajesh
Sancheti, Parag
Vaidya, Shrinand

Iran
Alijanipour, Pouya
Eslampour, Aidin
Ghazavi, Mohammad Taghi
Hosseinzadeth, Hamidreza
Mortazavi, Javad
Rasouli, Mohammad
Shahcheragh, G. Hossain

Ireland
Cashman, James
Glynn, Aaron
Keogh, Peter
Mulhall, Kevin
O'Toole, Patrick
Sheehan, Eoin

Israel
Heller, Snir
Kosashvill, Yona
Schwaber, Mitchell

Italy
Baldini, Andrea
Catani, Fabio
Da Rin de Lorenzo, Ferdinando
Drago, Lorenzo
Esposito, Silvano
Francheschini, Massimo
Logoluso, Nicola
Meani, Enzo
Romano, Carlo
Traverso, Francesco

Japan
Kobayashi, Hideo
Kobayashi, Naomi
Saito, Tomoyuki
Yamada, Koji

Republic of Korea
Han, Seung-Beom
Kim, Kang-Il
Koo, Kyung-Hoi

Lebanon
Bitar, Diana
Ghanem, Elie
Karam, Joseph
Raphael, Ibrahim

Moldova
Antoci, Valentin

Mexico
Franco-Cendejas, Rafael
Rivero-Boshert, Salvador
Velazquez, Diego

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Altena, Mark
Jutte, Paul C.
Meermans, Geert
Nijhof, Marc W
Ploegmakers, Joris J.W.
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Van den Bekerom, Michel
Vogely, Charles
Wagenaar, Frank-Christiaan

New Zealand
Vince, Kelly George

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Berdal, Erik
Witzø, Eivind

Peru
Pena, Orestes Rolando
Suárez, Rolando

Poland
Bialecki, Jerzy
Kruczynski, Jacek
Marczynski, Wojciech
Markuszeweski, Jacek

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Sousa, Ricardo

Puerto Rico
López, Juan Carlos
Suarez, Juan

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Tikhilov, Rashid

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Lee, Paul

Slovenia
Trebše, Rihard

South Africa
Lautenbach, Charles

Spain
Corona, Pablo
Flores Sanchez, Xavier
Font-Vizcarra, Luís
Guerra, Ernesto
Macule, Francisco
Marín-Peña, Oliver
Martinez-Pastor, J. Carlos
Soriano, Alex

Sweden
Lazarinis, Stergios
Lidgren, Lars
Stefánsdótir, Anna
W. Dahl, Annette

Switzerland
Borens, Olivier
Erhardt, Johannes B.
Ochsner, Peter
Vogt, Markus
Wahl, Pete

Taiwan
Chang, Yuhan
Peng, Kuo-Ti

Tunisia
Kallel, Sofiene

Turkey
Korkusuz, Feza
Tözün, Ismail Remzi
Tuncay, Ibrahim

United Kingdom
Achan, Pramod
Board, Tim N.
Gambir, Anil
Haddad, Fares
Heidari, Nima
Lee, Paul
Morgan-Jones, Rhidian
Nathwani, Dinesh
Parvizi, Sadegh
Stockley, Ian
Townsend, Robert

United States of America
Abboud, Joseph A.
Abraham, John A.
Aggarwal, Vinay K.
Alavi, Abass
Alexander, Bryan T.
Arnold, William V.
Austin, Matthew
Azzam, Khalid
Babic, Maja
Barnes, Lowry
Barsoum, Wael
Bauer, Tom
Bedair, Hany
Belden, Katherine
Bezwada, Hari P.
Bini, Stefano A.
Blaha, J. David
Bolognesi, Michael P.
Booth, Robert E.
Bostrum, Matthias
Bradbury, Thomas L.
Brause, Barry D.
Calhoun, Jason H.
Cardona, Lyssette
Callaghan, John
Chen, Antonia
Conway, Janet
Cui, Quanjun
de Beaubien, Brian C.
Deirmengian, Carl
Deirmengian, Greg
Del Gazio, Daniel
Della Valle, Alejandro
Della Valle, Craig
Dennis, Douglas
Ducheyne, Paul
Esterhai, John
Ehrlich, Garth D.

Fehring, Thomas K.
Freiberg, Andrew A.
Froimson, Mark
Garrigues, Grant
Good, Robert P.
Goodman, Stuart
Goyal, Nitin
Griffin, William
Hamilton, William
Hansen, Erik
Harrer, Michael F.
Hickok, Noreen
Hitt, Kirby D.
Holtom, Paul
Hozack, William James
Huang, Ronald
Huddleston, James
Hume, Eric
Israelite, Craig
Jiraneck, William
Kappadia, Bhaveen
Kates, Stephen L.
Kerr, Glenn J.
Khatod, Monti
Kim,Raymond
Klatt, Brian A.
Klein, Gregg
Krebs, Viktor
Molloy, Robert
Mont, Michael A.
Moore, Christopher C
Morris, Michael J.
Moucha, Calin Stefan
Nana, Arvind D.
Nelson, Charles L.
Nelson, Sandra
Noiseux, Nicolas O
O'Donnell, Richard
Oliashirazi, Ali
Ong, Alvin
Ong, Kevin
Orozco, Fabio
Osman, Douglas R.
Padgett, Douglas E.
Paprosky, Wayne G.
Patel, Preetesh
Patzakis, Michael J.
Polkowski, Michael G.
Post, Zachary
Parsley, Brian
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Question 1A: What are the significant risk factors for development of surgical site infection (SSI) or periprosthetic joint infection (PJI) after elective total joint arthroplasty (TJA)?

Consensus: Active infection of the arthritic joint (septic arthritis), presence of septicemia, and/or presence of active local cutaneous, subcutaneous, or deep tissue infection are all significant risk factors predisposing patients to SSI or PJI and are contraindication to undertaking elective TJA.

Delegate Vote: Agree: 99%, Disagree: 0%, Abstain: 1% (Strong Consensus)

Question 1B: What are the potential risk factors for development of SSI or PJI after elective TJA?

Consensus: The risk factors for SSI or PJI include history of previous surgery, poorly controlled diabetes mellitus (glucose> 200 mg/L or HbA1C>7%), malnutrition, morbid obesity (BMI>40 Kg/m^2), active liver disease, chronic renal disease, excessive smoking (>one pack per day), excessive alcohol consumption (>40 units per week), intravenous drug abuse, recent hospitalization, extended stay in a rehabilitation facility, male gender, diagnosis of post-traumatic arthritis, inflammatory arthropathy, prior surgical procedure in the affected joint, and severe immunodeficiency.

Delegate Vote: Agree: 94%, Disagree: 4%, Abstain: 2% (Strong Consensus)

Justification:

Active Infection of Joint, Bloodstream, or Local Tissue

The presence of active infection in an arthritic joint has been shown to lead to significantly higher rates of PJI after TJA.[1,2] There are also a number of longitudinal studies and case reports which indicate that the presence of active systemic or local tissue infection may result in hematogenous or direct seeding of the implant following TJA.[3-9] Thus, elective arthroplasty should be delayed in patients with active infection until they are adequately treated and infections are confirmed to be eradicated.

History of Previous Surgery

The local wound environment may be compromised in patients who have undergone previous operative procedures, which may contribute to the development of an SSI or PJI following TJA.[10] Peersman et al. matched infected and non-infected patients who underwent total knee arthroplasty (TKA) and reported that a history of prior open surgical procedures was a significant risk factor ($p<0.0001$) for developing PJI following TKA.[11] Although not much literature has been presented correlating history of prior surgery and development of PJI, we recommend that a patient's previous surgical history be documented, along with proper evaluation of the local wound environment. An appropriate infection workup, as discussed elsewhere in this document, should be undertaken in all patients who have had previous surgery at the site of an upcoming arthroplasty. This will allow for any necessary modification of the operative approach and technique to minimize risk of developing infection.[10]

Uncontrolled Hyperglycemia

Numerous studies and meta-analyses indicate that preoperative uncontrolled glucose levels (fasting glucose>180 mg/dL or 10 mmol/L) are associated with increased postoperative complications and adverse outcomes.[12-14] Although less work has been dedicated to the investigation of postoperative glucose control in the arthroplasty literature, there is a suggestion from general surgery that early postoperative hyperglycemia results in a higher rate of SSI.[15] Therefore, efforts should be made to maintain adequately-controlled glucose levels during the entire perioperative time period. Less work has been definitive in elucidating the role of hemoglobin A1C (HbA1C) in predicting joint infection.[16,17] While the optimal HbA1C level at which TJA risks become excessive has not been established, we recommend attempts to pre-operatively optimize diabetic control and would carefully consider offering elective arthroplasty to patients in whom the fasting glucose level is >200 mg/dl (10 mmol/L) and HbA1C>7%.

Further research is needed to evaluate whether patients who are to undergo elective orthopaedic surgery should have routine screening for diabetes and hyperglycemia, as has been done for patients who are to have cardiothoracic surgery.

Malnutrition

Malnutrition has been shown to result in a number of adverse outcomes following TJA, including poor wound healing, longer hospital length of stay, longer anesthesia and surgical time, and persistent wound drainage with increased susceptibility to infections.[18-21] Studies have reported

on the various preoperative tests that may be used to screen patients for malnutrition.[18,21,22] Measures of malnutrition have varied and include transferrin, total lymphocyte count, total albumin, and prealbumin. Currently, parameters to evaluate nutritional status include serum albumin (normal 3.5-5.0 g/dL), serum transferrin (normal 204-360 mg/dL), serum prealbumin (normal 15-35 mg/dL), and total serum lymphocyte count (800-2000/mm^3). Due to the correlation between nutritional status and postoperative recovery, patients suspected of having malnutrition should have their nutritional status checked prior to elective arthroplasty.[23] While the optimal method for correction of malnutrition preoperatively is unknown, options to do so include administration of high protein supplements, vitamin and mineral supplementation,[24] increased consumption of calories, early mobilization, and physiotherapy.[22]

Morbid Obesity

Recent data from the 2010 Centers for Disease Control (CDC) indicate that more than one-third of Americans, or more than 60 million adults aged 20 years or older, are classified as obese (body mass index (BMI)≥30.0 kg/m^2).[25] A number of studies have demonstrated that patients with obesity are at increased risk of poor wound healing and PJI.[26-29] The reason for this increased risk may be related to an increase in operative time, greater need for allogenic blood transfusion, and the presence of other comorbidities, including diabetes.[27,29-31] The decision to perform elective arthroplasty in morbidly obese patients with BMI≥40.0 kg/m^2, should be weighed only after careful consideration of the increased risk of complications including infection. The risk-benefit must be carefully considered and appropriate informed consent/informed choice is paramount as postoperative complications are higher in this patient group.[32] It is important to add that obese patients undergoing surgical procedures are at increased risk of underdosed prophylactic antibiotics[33] and the dose of antibiotic should be accordingly adjusted, as discussed elsewhere in this document.

Smoking

Smoking is associated with postoperative morbidity and mortality.[34] A meta-analysis of 6 randomized trials found that discontinuing smoking prior to surgery led to a decreased risk of total postoperative complications (relative risk (RR)=0.76, 95% confidence interval (CI)=0.69-0.84) .[35] The same meta-analysis also pooled data from 15 observational studies and found that smoking cessation led to fewer wound healing complications (RR=0.73, CI=0.61-0.87).[35] Singh et al. found that current smokers undergoing TJA were more likely to have SSI, whereas prior smokers were not associated with as high a risk for developing wound infection.[34] Longer

periods of smoking cessation prior to surgery have been found to be associated with lower rates of postoperative complications.[35-38] Furthermore, in a study of patients undergoing primary total hip arthroplasty (THA), postoperative complications were significantly higher for those who were heavy tobacco users (>1 pack/day or 25 cigarettes).[39] In the preoperative period it is important to evaluate for tobacco use and offer strategies to quit smoking in order to reduce postoperative wound complications and lower the risk for SSI and PJI. Studies from orthopaedic and non-orthopaedic fields suggest that smoking intervention programs, even when instituted 4-6 weeks prior to elective surgery, may diminish the risk of infectious and wound-healing complications.[40]

Alcohol Consumption

Patients who consume alcohol on a frequent basis may have a significantly increased risk for postoperative complications after arthroplasty.[41] Using the Alcohol Use Disorders Identification Test-Consumption questionnaire on 9,176 male United States veterans who underwent major non-cardiac surgery, Bradley et al. determined that the incidence of SSI and other postoperative infections was significantly associated with excessive alcohol use.[42] The optimal period of cessation of alcohol consumption is unknown for arthroplasty patients, but at least 4 weeks of abstinence may be necessary to reverse physiologic abnormalities that place patients at increased risk of postoperative morbidity.[43] The preoperative period serves as an opportunity to identify patients who abuse alcohol. Although the benefit of directed alcohol cessation programs before surgery is not well established in the literature, it is reasonable to expect patients to reduce alcohol consumption prior to surgery (for non-dependent patients) and to delay elective arthroplasty in alcoholic patients until the issue has been addressed.

Active Renal Disease

Few studies have explored the complications associated with active renal disease in TJA patients. Sunday et al. reported on the complications of TJA in patients with end-stage renal disease on hemodialysis. The authors determined that primary and revision surgeries in this specific cohort were associated with a high rate of complications and death; 29% of patients died from in-hospital complications and 2 patients had overwhelming sepsis (14.5%).[44] These data were supported by Lieberman et al., who also reported a high rate of complications (81%), including a deep infection rate of 19% in patients with chronic renal failure.[45] Sakalkale et al. found that patients with end-stage renal failure had a high mortality and complication rate of 58%, with a deep infection rate of 13%.[46] Overall the risk of developing postoperative infection

after TJA is significantly higher in patients with chronic renal failure, especially in those on hemodialysis.

Active Liver Disease

Several studies explored TJA in patients with either active symptomatic or asymptomatic liver disease. In a matched study of patients undergoing TJA, Pour et al. found that compared to a control group, patients with asymptomatic hepatitis C had a higher rate of surgical complications, including more wound complications.[47] While the underlying mechanism for increased complications is unknown, even patients with asymptomatic hepatitis should be made aware of the potential for higher rates of complications after elective TJA. Hsieh et al. determined that in patients with advanced cirrhosis undergoing TJA, there was a higher rate of complications and especially infectious failures, with a prosthesis survival of 77.8% after 5 years.[48] On the other hand, Cohen et al. report that even in cirrhotic patients, elective TJA could be safely performed with no increase in adverse outcomes.[49] Thus far, routine testing for liver disease preoperatively in patients undergoing elective TJA with no prior history or signs on examination has not been proven to be beneficial.

Immunosuppression

While an association between immunosuppression and an increased incidence of SSI is debated, many surgeons believe that patients with immunosuppression are at an increased risk of PJI. Examples of immunosuppressive agents include glucocorticoids such as prednisone, cytostatics including cyclophosphamide and methotrexate, drugs that act on immunophilins such as tacrolimus, and others agents such as interferons and tumor necrosis factor (TNF)-α inhibiting agents. Berbari et al. created a risk stratification model for SSI and PJI and determined that immunosuppression was a significant risk factor (hazard ratio=1.96, 95% CI=1.37-2.82) for PJI.[50] In addition, Peersman et al. found that immunosuppressive therapy was a significant predisposing factor for SSI.[11] In patients who have undergone organ transplantation, and in particular liver transplant, several studies have reported an increased risk for osteoporotic fractures and osteonecrosis with concurrent immunosuppressive therapy[51,52] However, immunosuppression and simultaneous poor bone quality has led to conflicting opinions surrounding the actual risk for postoperative infection.[53] Part of the difficulty in assessing the risk of immunosuppression on PJI is the current variability in defining immunosuppression. Further work will be needed to delineate the true impact of

immunosuppression on the development of SSI or PJI in patients undergoing elective arthroplasty.

Intravenous Drug Abuse

Patients with previous history of intravenous drug abuse (IVDA) and patients with painful joint arthrosis present a difficult treatment decision. Lehman et al. determined the rate of deep periprosthetic infection in patients with human immunodeficiency virus (HIV) or IVDA after TJA. Twenty-nine patients with HIV or a history of IVDA or both underwent TJA. Of 28 HIV-positive patients undergoing TJA, 4 (14%) developed infections. Two of 8 joint arthroplasties (25%) in the IVDA group developed an infection. Two of 5 joint arthroplasties (40%) with both IVDA and HIV developed a deep infection.[54] These findings were supported by Habermann et al., who reported a septic postoperative complication rate of 28.6% among patients who had a history of intravenous drug abuse.[55] Further work will be needed to determine the direct effects of intravenous drug abuse on the development of SSI or PJI. This workgroup is of the opinion that active IV drug abusers should not be offered elective joint arthroplasty.

Human Immunodeficiency Virus Infection

Recent drug therapies have dramatically improved the life expectancy of HIV-positive patients. HIV-positive patients demonstrate a widely varying progression to AIDS as reflected by the varying rate of decline in CD4 cell counts. Patients with CD4 counts greater than 400 cells/ml and with undetectable viral loads may be appropriate candidates for elective TJA, as the risk of subsequent SSI may be decreased. Habermann et al. reported no difference in functional outcome following TJA between patients with or without HIV.[55] Furthermore, Hicks et al. reported that while rates of deep joint sepsis after primary TJA in HIV-positive patients (18.7%) are higher than in normal populations, long-term survival with marked symptom relief is a reasonable expectation for a large proportion of HIV positive patients following TJA.[56] It is our recommendation that in patients with HIV, orthopaedic surgeons work closely with infectious disease specialists in monitoring CD4 counts and viral loads and that decisions to undertake TJA be made on an individual basis.

Hospital Admission or Extended Rehabilitation Stay

Lee et al. reviewed 169 SSIs in elderly patients who had undergone orthopaedic surgery and compared them to 171 matched controls. Admission from a healthcare facility was

independently associated with a greater risk of infection (odds ratio=4.35; 95% CI=1.64 – 11.11).[57]

Other Risk Factors

It appears that based on numerous studies, male patients are more likely to develop SSI/PJI. In addition, preoperative diagnosis of post-traumatic arthritis with or without prior surgery has also been found to be a risk factor for PJI.[58-60]

Disclaimer: Although elective arthroplasty needs to be withheld for some patients at extreme risk of SSI/PJI, there is inadequate evidence in the literature as to what the exact threshold for making this decision should be. The disability imposed by the degenerative disease needs to be weighed against the potential for development of PJI. Some authorities have attempted to provide a mathematical model that may improve our decision making for subjecting a patient to elective arthroplasty. Dr. Charles Lautenbach has created a scoring system that takes into consideration pain and loss of function and factors predisposing to morbidity and mortality to generate a score that allows surgeons to objectively determine the justification for surgery, even in the face of high risk of morbidity and mortality. A description of the Lautenbach Estimate of the Indication and Contra-indication for Arthroplasty score can be found at www.boneinfection.co.za.

Question 2: What is the role of oral hygiene for patients undergoing an elective arthroplasty?

Consensus: All patients undergoing elective arthroplasty should be screened for evidence of active infection. This may be performed by administration of a questionnaire or dental examination.

Delegate Vote: Agree: 80%, Disagree: 18%, Abstain: 2% (Strong Consensus)

Justification: It has been well established that hematogenous seeding from a remote source of infection can lead to PJI, even years after TJA. Several sources, including data from the CDC National Health and Nutrition Examination Survey, have brought to light the relatively high prevalence of periodontal disease, especially in the elderly.[61] Dental infections can serve as a

potentially dangerous harbor of bacteria and some studies show these bacteria to be microbiologically indistinguishable from pathogens found at sites of PJI.[62] Nonetheless, there is much debate regarding the use of active preoperative screening and treatment of dental pathology to ensure adequate oral hygiene and prevent postoperative bacteremia or PJI in all patients undergoing TJA.

One study by Barrington et al. determined that in 100 consecutive TJA patients, preoperative dental clearance revealed a 23% incidence of dental pathology, yet no patients in their cohort went on to develop a SSI or PJI.[63] Several authors have noted that only a small percentage of joint infections can be accurately attributed to dental pathogens or procedures. Laporte et al. retrospectively reviewed 2,973 patients and of 52 patients with late infections, only 3 were strongly associated with a dental procedure.[64] The incidence of late hematogenous infection in TJA has been quoted as between <0.01% and 0.6% with organisms from a dental source involved in between 0.04% and 0.07%.[65]

Currently, there are no official recommendations from the American Academy of Orthopaedic Surgeons regarding dental clearance prior to TJA to prevent PJI.[66] However, excluding evidence of ongoing oral sepsis or severely poor hygiene, there is little justification for routinely screening and treating all patients for dental abnormalities. Nevertheless, signs and symptoms of active dental infection should be sought prior to subjecting a patient to elective arthroplasty.

A recent prospective study by Tokarski et al. found that administration of a short questionnaire to patients could identify risk factors for active dental disease.[60] In their study, risk factors for failed dental clearance or active dental disease included tobacco use, poor flossing habits, history of one or more tooth extractions, older age, narcotic use, and lack of a dentist visit within 12 months prior to taking the survey. The study found that patients who had 4 of the 6 identified risk factors had a 4-fold increased incidence of failing dental clearance. Based on their study, it appears that selective dental clearance based on patient risk stratification may be a reasonable approach.

Question 3A: What should the process be for methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) screening?

Consensus: While this workgroup does NOT recommend universal screening and decolonization of all patients undergoing joint arthroplasty, it accepts that preoperative

screening for *Staphylococcus aureus* (MSSA and MRSA) and decolonization decreases the rate of SSI and the incidence of staphylococcal and nonstaphylococcal infections.

Delegate Vote: Agree: 85%, Disagree: 11%, Abstain: 4% (Strong Consensus)

Question 3B: What should the treatment regimen be for MRSA and methicillin-sensitive MSSA decolonization?

Consensus: Short-term nasal application of mupirocin is the most accepted current method of decolonization for MRSA and/or MSSA.

Delegate Vote: Agree: 80%, Disagree: 11%, Abstain: 9% (Strong Consensus)

Justification: Extensive literature consistently documents that the carriage of *Staphylococcus aureus* in patients' anterior nares may be an important reservoir for bacteria and can serve as a potential source of hospital-acquired and post-surgical infections.[67] Nasal colonization rates of *S. aureus* have been extensively studied in patients, hospital staff, and the general population.[68,69] Kalmeijer et al. determined that high-level nasal carriage of *S. aureus* was the most important and only significant independent risk factor for developing SSI with *S. aureus.*[70] Many prospective studies and systematic reviews done in the orthopaedic and general surgery population indicate that the number of SSIs with *S. aureus* can be reduced through rapid screening and decolonization of nasal carriers of *S. aureus* on admission.[71,72] Skin decolonization prior to surgery has long been the subject of much debate, with a variety of methods proposed for the eradication process. Mupirocin nasal ointment has been widely accepted for reducing nasal carriage loads for MRSA, yet long-term use of this agent has been shown to lead to development of bacterial resistance.[67,73,74] Other methods of decolonization include photodisinfection therapy, total body chlorhexidine gluconate showers and wipes preoperatively, and iodine-based solutions applied hours before surgery. Chlorhexidine gluconate wipes (2%) eliminate the need to bathe just before surgery and have started to gain popularity and prominence in the orthopaedic literature.[75]

Question 4: Should healthcare workers be screened for MRSA and MSSA?

Consensus: No. Routine MRSA and MSSA screening is not warranted for healthcare workers. MRSA/MSSA screening should be reserved for workers with symptoms associated with bacterial infections.

Delegate Vote: Agree: 82%, Disagree: 15%, Abstain: 3% (Strong Consensus)

Justification: There is ongoing controversy regarding the role of healthcare workers in the transmission of MRSA. Symptomatic MRSA infections among healthcare workers have been described.[76-78] Controversy exists as to the true benefit of screening all healthcare workers. The Dutch Working Party for Infection recommends screening healthcare workers after exposure to MRSA-positive patients; however, German and North American[79-81] specialist associations are against such screening. Opponents of MRSA screening indicate a risk of stigmatization of those affected, potential exposure to toxic decolonization procedures, and high costs associated with such screening.[82] Therefore selective, rather than universal, screening of symptomatic healthcare workers is advised.[83]

Question 5: What is the role of routine urine screening in patients undergoing an elective arthroplasty?

Consensus: Routine urine screening is NOT warranted for patients undergoing elective arthroplasty. Urine screening prior to elective arthroplasty should be reserved for patients with a present history or symptoms of a urinary tract infection (UTI).

Delegate Vote: Agree: 74%, Disagree: 24%, Abstain: 2% (Strong Consensus)

Justification: UTIs have the potential to cause bacteremia and post-surgical wound infections, particularly in patients receiving an elective arthroplasty. Patients with a positive urinalysis and/or urine culture are generally treated with antibiotics prior to elective surgery. However, it is unclear whether a positive preoperative urinalysis and culture with subsequent antibiotic treatment influences the incidence of post-surgical infection. One study in the arthroplasty literature found no significant association between perioperative UTI and deep infection after arthroplasty.[84] Another study found that patients with asymptomatic UTI detected by positive

urinalysis and urine culture had an increased risk of wound infection postoperatively, despite treatment.[85] A cost-effectiveness analysis estimated that with routine urine screening, 4.58 wound infections in non-prosthetic knee operations may be prevented annually, but that it would come at a cost of $1,500,000 per wound infection prevented.[86] Currently, there are no cost-effectiveness analyses or official treatment guidelines from organizations such as the Infectious Diseases Society of America regarding routine urine screening and antibiotic treatment for all patients undergoing TJA.[87,88] Still, it is reasonable to reserve such a preoperative workup for only those patients with a known history of recurrent urinary infection or for those with evidence of ongoing urinary symptoms suspicious for infection.

Question 6: Should disease-modifying agents be stopped prior to elective TJA?

Consensus: Yes. Disease-modifying agents should be stopped prior to elective TJA. The timing of drug discontinuation should be based on the specific medication and the individual patient. The cessation of immunosuppressant medications should be performed in consultation and under the direction of the treating physician.

Delegate Vote: Agree: 92%, Disagree: 5%, Abstain: 3%(Strong Consensus)

Justification: According to a large review of patients in a Medicare database, patients with rheumatoid disease (RA) have been found to be at higher risk of PJI.[89] The infection rate among RA patients undergoing TKA is 1.6 times greater than in patients undergoing the same procedure for osteoarthritis.[90] Patients with RA may have a higher risk of infection due to immunosuppressive therapy including corticosteroids such as prednisone, and disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate.[91,92] High doses of corticosteroids and TNF-α-blocker therapy within one year of surgery was shown to increase the risk of subsequent infection.[93,94] Two studies, one of which was a prospective, randomized controlled trial, failed to show a difference in wound complications and infection rates among TJA patients who continued versus those who discontinued methotrexate prior to their surgery.[95,96] On the other hand, two other studies, one of which was a prospective non-randomized study, showed an increased rate of SSI and PJI in patients who continued their disease-modifying agents prior to TJA.[94,97] We recommend that the management of DMARDs

should be based on the drug half-life. The Canadian Rheumatology Association recommended that these drugs should be stopped prior to surgery for as long as 3 to 5 times the half-life of each individual drug that may last from 0 days to 3 months.[98] It is important to note that corticosteroids should not be abruptly stopped due to the risk of inducing cortisol deficiency from hypothalamic-pituitary-adrenal axis suppression. The cessation of immunosuppressant medications should be performed in consultation and under the direction of the treating physician.

Medication	**Half Life ***	**Recommendation**
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	2-17 hours	Discontinue therapy within 1 week prior to surgery
Methotrexate	0.7 to 5.8 hours	Discontinue therapy within 1 week prior to surgery Continue therapy 2 weeks after surgery (Patients with renal dysfunction, hold 2 weeks prior to surgery)
Sulfasalazine Azathioprine	5 hours 7.6 hours	Discontinue therapy prior to 1 week before surgery
Leflunomide	~2 weeks	Hold for 6 weeks prior to surgery
Hydroxychloroqine	1-2 months	Continue therapy up to and including the day of surgery

Biological Response Modifiers		
Etanercept	4.3 days	Hold for at least 1.5 weeks prior to surgery
Infliximab	8-10 days	Hold for 3 weeks prior to surgery
Golimumab Tocilizumab Abatacept Adalimumab Certolizumab	12-14 days	Hold for 1 month prior to surgery
Rituximab	21 days	Hold for 2 months prior to surgery
Gout Agents		
Allopurinol Colchicine Probenecid	1-2 hours 26-32 hours 26-32 hours	Discontinue therapy within 1 week prior to surgery

Question 7: In patients with prior septic arthritis what strategies should be undertaken to minimize the risk of subsequent PJI?

Consensus: ALL patients with prior septic arthritis should undergo evaluation by serology and aspiration of the joint whenever possible, prior to arthroplasty.

Delegate Vote: Agree: 84%, Disagree: 14%, Abstain: 2% (Strong Consensus)

Consensus: While the optimal timing for performing elective arthroplasty in a patient with prior septic arthroplasty needs further research, surgeons should ensure that no evidence of active infection exists by taking **intraoperative cultures**.

Delegate Vote: Agree: 85%, Disagree: 14%, Abstain: 1% (Strong Consensus)

Consensus: During arthroplasty, if cement is utilized, antibiotics should be added.

Delegate Vote: Agree: 90%, Disagree: 5%, Abstain: 5% (Strong Consensus)

Consensus: If intraoperative cultures are found to be positive, extended intravenous antibiotics should be appropriately administered with input from infectious disease specialists.

Delegate Vote: Agree: 93%, Disagree: 5%, Abstain: 2% (Strong Consensus)

Justification: Septic arthritis can lead to accelerated destruction of the articular cartilage and result in end-stage arthritis. *Staphylococci* most commonly cause bacterial infection of the joint, with *S. aureus* shown to be the primary infecting pathogen in several case series from the United Kingdom, France, and Australia.[99-101] Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly measured in the evaluation of patients with septic arthritis.[102-104] The role of these markers in evaluating the eradication status of infection in patients with prior septic arthritis remains unknown. In some patients with previous septic arthritis, these serological markers were found to be normal. Thus, most patients with prior septic arthritis should undergo joint aspiration prior to elective arthroplasty. The samples should be sent for culture, white cell count, and neutrophil differential. Some authorities also measure the glucose level, procalcitonin level, and other parameters to determine if infection exists. The threshold level for any of the aforementioned parameters for diagnosis of persistent infection in these patients is not known, but based on the arthroplasty literature a cell count>3,000 cells/μl and a neutrophil differential>80% may be indicative of active infection.[105,106] During elective arthroplasty, multiple samples for culture (3-5) should also be taken.[106,107] If cement is being utilized, the surgeon should consider adding antibiotic with appropriate spectrum of activity to cover previously isolated pathogens. The dose of antibiotics added should be kept low to avoid weakening the mechanical strength of the cement. Patients with positive cultures should be treated with an appropriate antibiotic for an extended period of time following elective arthroplasty**.** Patients in whom synovial fluid analysis reveals elevated neutrophil percentage and/or white cell counts should have the cultures maintained for a prolonged period of time following surgery in the hope of isolating a possible infecting organism. Consideration should also be given for the use of molecular techniques (polymerase chain reaction or molecular marker measurements) in these patients.

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Workgroup 2: Perioperative Skin Preparation

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Question 1A: Is there a role for preoperative skin cleansing with an antiseptic?

Consensus: Yes. Preoperative cleansing of the skin with chlorhexidine gluconate (CHG) should be implemented. In the presence of a sensitivity to CHG, or when it is unavailable, it is our consensus that antiseptic soap is appropriate.

Delegate Vote: Agree: 90%, Disagree: 8%, Abstain: 2% (Strong Consensus)

Question 1B: What type and when should preoperative skin cleansing with an antiseptic be implemented?

Consensus: We recommend that whole-body skin cleansing should start at least the night prior to elective arthroplasty. It is a consensus that after bathing patients are advised to sleep in clean garments and bedding without the application of any topical products.

Delegate Vote: Agree: 85%, Disagree: 10%, Abstain: 5% (Strong Consensus)

Justification:

Preoperative showering or cleansing

Two meta-analyses of 7 randomized control trials (RCT) performed by the Cochrane group found that preoperative showering with CHG did not reduce the rate of surgical site infection (SSI) when compared to no shower (3 RCTs) or placebo (4 RCTs).[1] Two observational studies using CHG wipes in total joint arthroplasty patients demonstrated a non-statistically significant reduction in the incidence of SSI.[2,3] Johnson et al. found in a prospective consecutive series that patients who used CHG wipes one day preoperatively and the morning of the operation had a lower incidence of SSI than patients who did not comply with this protocol prior to total hip arthroplasty.[2] These results were reproduced using a similar protocol in total knee arthroplasty patients.[3] In neither study were patients randomized to receive treatment or no treatment; however, the authors compared patients who completely complied with the protocol to patients who did not comply. Patients with partial compliance were excluded from both studies.

Chlorhexidine and methicillin-resistant organisms

A systematic review of the literature conducted by Karki et al. reported on a meta-analysis of two before-and-after studies that showed non-rinse skin cleansing with CHG washcloths was effective in reducing the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) skin colonization in the setting of the intensive care unit. However, a meta-analysis of 4 before-and–after studies showed no evidence that CHG washcloths reduce the risk of MRSA infection.[4] Other studies have shown that CHG cleansing leads to a lower rate of MRSA colonization in the hospital setting.[5,6] One case-control study evaluating a protocol of a 5-day course of intranasal mupirocin and daily CHG cloths (beginning one day before surgery and continuing the day of surgery and postoperative days 1-3) in a non-general surgery population reported statistically significant decreases in the rate of MRSA SSI in the two years following implementation of this protocol.[7] However, in these studies CHG washcloths were used as part of a broader *Staphlylococcus aureus* decolonization protocol. Therefore, it is not possible to determine the impact on SSI of decolonization or CHG wash clothes, independently.

Timing of preoperative shower or cleansing

No studies have focused on the impact of the time or duration of preoperative cleansing with an antiseptic agent. Some studies have implemented protocols of washing the surgical site once on the night prior to surgery and on the morning of the operation,[3,8,9] while other protocols have continued washing through postoperative day 3.[7] One study conducted with a small sample size of volunteers noted decreased microbial colonization with a CHG wash over the course of a 5 day period.[37] Currently, the Centers for Disease Control (CDC) recommends that preoperative showering begin at least the night prior to surgery.[10] Caution should be exercised to ensure that patients do not use preoperative CHG wash excessively, as studies suggest no benefit for such practice that may also lead to skin irritation.[11,12]

Whole body cleansing vs localized surgical site-specific cleansing

One large RCT showed that whole-body cleansing was more effective at reducing the rate of SSI than surgical site-specific washing.[13] We recommend that whole body preoperative skin cleansing be undertaken preoperatively.

Question 2: Which agent, if any, is the optimal agent for surgical skin preparation?

Consensus: There is no clear difference between various skin preparation agents. There is some evidence that combinations of antiseptic agents with alcohol may be important for skin antisepsis**.**

Delegate Vote: Agree: 89%, Disagree: 8%, Abstain: 3% (Strong Consensus)

Justification:

While CHG is the recommended agent for preventing intravenous catheter-related infections,[14] the CDC currently does not recommend one agent over another for prevention of SSI.[10] When compared directly, results are conflicted as to whether CHG or povidone-iodine provides superior skin antisepsis and lowers the rate of SSI. In a large, multicenter RCT, Darouiche et al. showed that CHG in alcohol showed a significant reduction in the rate of SSI when compared to aqueous povidone-iodine scrub and paint; however, the iodine preparation did not use alcohol as a solvent.[15] Conversely, in a single-institution, observational, non-concurrent control study of general surgery patients, Swenson et al. found that when alcohol was used (either as a solvent or a scrub following iodine paint), patients prepped with povidone-iodine had a lower rate of SSI.[16] Other studies have shown that there is no difference in the rate of SSI between patients prepped with either CHG or iodophors.[17,18] To date, there are no prospective randomized studies comparing skin preps in patients undergoing total joint arthroplasty. We therefore have insufficient evidence to recommend a preferred agent for preventing SSI in elective arthroplasty procedures.

Alcohol is used as an antiseptic because of its rapid antimicrobial action.[10] One systematic review of 5 RTCs found that CHG-alcohol formulations were more effective at preventing SSI than aqueous povidone-iodine solutions, and in other studies there was no conclusive evidence that CHG-alcohol solutions were more effective than povidone-iodine products dissolved in alcohol or aqueous solutions.[19] While we cannot make a claim about the superiority of CHG over iodine-based antiseptics, it is suggested that whichever agent is chosen, it be dissolved in alcohol. However, caution should be taken to allow time for adequate drying of alcohol-based products, as operating room fires have been reported.[10,20]

Question 3A: What is the proper method of hair removal?

Consensus: Clipping, as opposed to shaving, is the preferred method for hair removal. We cannot advise for or against the use of depilatory cream for removal of hair.

Delegate Vote: Agree: 92%, Disagree: 3%, Abstain: 5% (Strong Consensus)

Question 3B: When should hair removal be performed?

Consensus: If necessary, hair removal should be performed as close to the time of the surgical procedure as possible.

Delegate Vote: Agree: 94%, Disagree: 4%, Abstain: 2% (Strong Consensus)

Justification:

Clipping is the best form of hair removal: Concern over shaving has been raised because abrasions formed from the shaving process can become sites of bacterial growth. A recent systematic review of randomized and quasi-RCTs showed that clipping lowered the rate of SSI when compared to shaving.[21] Many other studies have shown the superiority of clipping over shaving, using postoperative SSI as the primary endpoint.[22-24] Some institutions utilize depilatory agents as skin preparation.

Hair removal should be performed close to the time of surgery: There is currently no evidence in the literature that shows the most appropriate setting and time in which to remove hair from the surgical site. One study investigated the effects of hair removal the night before surgery compared to hair removal on the day of surgery and found that clipping on the morning of surgery was associated with a lower SSI rate.[25] Another retrospective review demonstrated that shaving immediately before a surgical procedure was associated with a lower SSI rate than shaving 24 hours or greater prior to surgery. However, this study did not include patients who used clipping to remove hair and was designed to test the effect of shaving versus depilatory removal.[26] The CDC recommends not removing hair preoperatively unless the hair at or around the incision site will interfere with the operation. If hair removal is necessary, it should be performed immediately prior to the operation and preferably with electric clippers.[10] Given the overall lack of research specific to the environment in which preoperative hair removal should take place, we recommend that hair removal be performed in the hospital as close to the time of

surgery as possible by either the surgical team or the trained nursing staff. If practical, we suggest that this removal take place outside of the operating room.

Question 4: What special considerations should be given to a patient with skin lesions?

Consensus: Elective arthroplasty should NOT be performed in patients with active ulceration of the skin in the vicinity of the surgical site. It is our consensus that incisions should not be placed through active skin lesions. For certain lesions, such as those due to eczema and psoriasis, surgery should be delayed in these patients until their lesions have been optimized.

Delegate Vote: Agree: 96%, Disagree: 2%, Abstain: 2% (Strong Consensus)

Justification:

Elective arthroplasty in patients with active skin ulcerations: The orthopaedic literature is deficient in studies evaluating SSI in patients with active skin ulcerations. However, one prospective audit showed that active ulceration of the skin was a significant risk factor for wound infection.[27] Therefore, we recommend that elective arthroplasty should not be carried out in patients with active skin ulcerations of the surgical field (active ulcerations defined as breaks in the skin barrier, excluding superficial scratches).

Surgical incisions through eczematous or psoriatic lesions: Likewise, there are no existing studies evaluating the risk of SSI when incisions are placed through eczematous or psoriatic lesions. Some retrospective studies have reported high rates of SSI and periprosthetic joint infection (PJI) in patients with a diagnosis of psoriasis or eczema.[28,29] However, the latter studies did not evaluate whether it was the placement of incision through the affected skin or the overall immunosuppressed status of these patients with psoriasis or eczema that increased the risk of SSI. Given reported poor outcomes as well as increased bacterial load on psoriatic skin,[30] placing surgical incisions through eczematous or psoriatic lesions should be avoided if possible. Surgery should be delayed in these patients until these lesions are optimized.

Question 5A: How should the surgeon and assistants wash their hands?

Consensus: The surgeon and operating room personnel should mechanically wash their hands with an antiseptic agent for a minimum of 2 minutes for the first case. A shorter period may be appropriate for subsequent cases.

Delegate Vote: Agree: 71%, Disagree: 24%, Abstain: 5% (Strong Consensus)

Question 5B: With what agent should the surgeon and assistants wash their hands?

Consensus: There is no clear difference among various antiseptic agents for hand washing.

Delegate Vote: Agree: 80%, Disagree: 15%, Abstain: 5% (Strong Consensus)

Justification:

Duration of hand washing: A review of the literature preformed by Tanner et al. found 4 RCTs comparing different durations of surgical team skin antisepsis.[31-34] All of the studies used colony forming units (CFU) present on the surgical staff's hands, not SSI, as the primary endpoint. One study found no difference between a 2 or a 3 minute scrub and a 1 minute hand washing with soap and water.[34] Another group found that a 1 minute hand washing followed by a 3 minute hand rub using alcohol was more effective in reducing CFUs than a 5 minute hand rub.[31] Pereira et al. found that both a 5 and 3 minute initial scrub with either CHG or povidone-iodine were equally as effective in reducing CFUs.[32,35] Current recommendations vary on the duration of hand antisepsis; the CDC recommends 2-5 minutes,[10] while the Association of Perioperative Registered Nurses states that a 3-4 minute scrub is as effective as a 5 minute scrub.[36] Based on the variability present in the current literature, we recommend that the duration of surgical hand antisepsis last for a minimum of 2 minutes. For the first case, we recommend a mechanical washing (either a scrub or soap-and-water washing) for a minimum of 2 minutes. There is no clear evidence supporting the utility of a particular hand washing method for subsequent cases. If there is a chance of contamination, the process for the first case should be repeated.

Optimum agent for hand washing: Results are inconclusive regarding the most effective agent for surgical hand antisepsis. Only one of 10 RCTs in the systematic review performed by Tanner et al.[33] reported SSI as the primary outcome. One large, multicenter, prospective, equivalence-cluster, randomized crossover study demonstrated that traditional (5 minute) scrubbing methods

and aqueous agents (4% CHG or 4% povidone-iodine) were equally as effective at reducing the incidence of SSI compared to a single hand wash for 1 minute with non-antiseptic soap at the start of the day followed by alcohol-only rubs. The efficacy of CHG compared to povidone-iodine was not directly tested as each institution was able to choose which scrub agent they incorporated into their protocol.[37] A retrospective, observational study that used wound infection as the primary endpoint found no difference between an alcohol-based rub product and a traditional 6 minute brush hand scrubbing; however, the authors did not describe the protocol or agent used for the traditional scrub group arm.[38]

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Workgroup 3: Perioperative Antibiotics

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Question 1: What is the optimal timing of the preoperative dose of antibiotics?

Consensus: The preoperative dose of antibiotics should be administered within one hour of surgical incision; this can be extended to two hours for vancomycin and fluoroquinolones. Furthermore, surveillance measures are critical in ensuring clinician compliance with this objective.

Delegate Vote: Agree: 97%, Disagree: 2%, Abstain: 1% (Strong Consensus)

Justification: The scientific rationale for antibiotic prophylaxis is to inhibit or eliminate contaminating microorganisms that gain access to the surgical site during the procedure, which reduces the probability of an established infection. Thus, the goal of administering preoperative antibiotics is to allow for adequate tissue (blood, soft tissue, and bone) concentrations by the time of incision. These antibiotics should exceed the minimum inhibitory concentration (MIC) for the organisms likely to be encountered for the duration of the operation. This depends on the antibiotic used. There are a number of studies which validate the importance of the preoperative dose of antibiotics in decreasing periprosthetic joint infection (PJI) and surgical site infection (SSI) in total joint arthroplasty (TJA). However, there are conflicting opinions as to the optimal timing of this dose. Some studies suggest that within 2 hours of incision is best, while others recommend scheduling the dose as close to surgical incision as possible. There are several institutional guidelines which support a one hour preoperative dose of antibiotics as a Surgical Care Improvement Project (SCIP) measure. In addition to these guidelines, it is critically important to have surveillance measures in place to document compliance with these protocols.

The American Academy of Orthopaedic Surgeons (AAOS), the Centers for Disease Control (CDC), and SCIP guidelines recommend that prophylactic antibiotics be completely infused within one hour before the surgical incision.[1] The AAOS recommendation for the use of intravenous antibiotic prophylaxis in primary TJA, recommendation 2, states that “timing and dosage of antibiotic administration should optimize the efficacy of the therapy. Prophylactic antibiotics should be administered within one hour before skin incision.” Due to extended infusion time, vancomycin and fluoroquinonlones should be started within 2 hours before incision. When a proximal tourniquet is used, the antibiotic must be completely infused before

inflation of tourniquet.[2] The US advisory statement recommends that antimicrobial prophylaxis be administered within one hour before incision and discontinued within 24 hours after the end of the operation,[3] while European guidelines recommend a single dose within 30 minutes before incision.[4]

Timing < 2hrs

The seminal article on this subject studied the timing of administration of prophylactic antibiotics and the risk of surgical wound infections in clean and clean-contaminated cases at a large community hospital.[5] In a study of 2,847 patients, 313 (11%) received TJA. The authors found that the rate of infection was lowest for patients who received an antibiotic from 0 to 2 hours before the incision.[5] Specifically, of the 1,708 patients who received prophylactic antibiotics during this time frame, only 10 (0.6%) subsequently developed SSI compared to 14 (3.8%) of 369 patients who received antibiotics 2 to 24 hours preoperatively, 4 (1.4%) of 282 patients who received antibiotics within 3 hours after incision, and 16 (3.3%) of 488 patients who received antibiotics 3 to 24 hours following incision. However, this study was conducted in 1985 to 1986, when there was considerable variation in timing of administration of the prophylactic antibiotic, and only 35% of patients received their dose within the contemporary standard of one hour prior to incision. Furthermore, the study did not find a significant difference in SSI rates when antibiotics were administered within 1 to 2 hours prior to incision compared with antibiotics administered 0 to 3 hours postoperatively.

Timing <1 hr

The leadership of the Medicare National Surgical Infection Prevention Projected hosted the Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW) meeting and utilized the available literature to draft a consensus paper. The position of the SIPGWW is that the infusion of the first antimicrobial dose should begin within 60 minutes before incision.[3,6]

Galandiuk et al. combined the results of two prospective randomized controlled trials (RCT) that compared antibiotic prophylaxis (either single-dose piperacillin with multi-dose cefoxitin) in elective surgical procedures of the gastrointestinal tract. The authors found that among other negative predictors, administration of an antibiotic for longer than 60 minutes preoperatively was associated with a higher rate of infectious complications.[7]

In a large, retrospective cohort study using National Veterans Affairs data on prophylactic antibiotics of 32,459 surgical procedures from 2005-2009, Hawn et al. found that higher SSI

rates were observed for antibiotic administration more than 60 minutes prior to incision (unadjusted odds ratio (OR) 1.34, 95% confidence interval (CI) 1.08-1.66) compared with procedures in which antibiotics were administered within one hour of incision. However, in generalized additive models adjusted for patient, procedure, and antibiotic variables, no significant association was seen between prophylactic antibiotic timing and SSI.[8]

Timing 30-60 minutes

In a prospective cohort study at a single academic hospital analyzing the incidence of SSI by the timing of antimicrobial prophylaxis in a consecutive series of 3,836 surgical procedures, Weber et al. determined that administration of single-shot prophylactic cefuroxime is more effective when given 30-59 minutes before incision than administration during the last 30 minutes. The overall SSI rate for this mixed cohort of general, vascular, and orthopaedic surgeries was 4.7% (180), and antimicrobial prophylaxis was administered within the final 30 minutes in 59% of all procedures. Multivariable logistic regression analysis showed a significant increase in the odds of SSI when antimicrobial prophylaxis was administered fewer than 30 minutes (crude OR 2.01; adjusted OR 1.95, 95% CI, 1.4-2.8; $p<0.001$) and 60 to 120 minutes (crude OR 1.75; adjusted OR 1.74; 95% CI 1.0-2.9, $p=0.035$) when compared with the reference interval of 30 to 59 minutes before incision.[9]

Timing <30 minutes

In a large, prospective, multicenter observational study examining the relationship between antibiotic timing and SSI risk, Steinberg et al. determined that SSI risk increased incrementally as the interval of time between antibiotic infusion and creation of the incision increased. The authors analyzed the antimicrobial prophylaxis of 4,472 randomly selected cardiac, hip or knee arthroplasty, and hysterectomy cases from 29 contributing hospitals, and ascertained SSI through the National Nosocomial Infections Surveillance system methodology. When antibiotics requiring long infusion times (eg vancomycin) were excluded, the infection risk following administration of antibiotics within 30 minutes was 1.6% compared with 2.4% associated with administration of antibiotic between 31 to 60 minutes prior to surgery (OR 1.74; 95% CI 0.98-3.04).[10]

In another recent multicenter, observational study from the Netherlands assessing risk factors for postoperative infections in 1,922 total hip arthroplasty (THA) cases, the authors found a similar pattern with a decreased rate of infection in those who received prophylaxis within 30

minutes prior to incision, although it did not reach statistical significance.[4] These authors collected data about SSI and potential risks factors related to prophylaxis, the patient, and procedure from 11 hospitals that participated in the Surgical Prophylaxis and Surveillance Intervention project and used multivariate logistic regression analysis to identify those variables that were predictive of SSI. Although there was a non-significant trend for the lowest SSI rate in those patients who received prophylaxis 30 minutes before surgery, the highest odds ratios for SSI were found in patients who received prophylaxis after incision (2.8, 95% CI 0.9-8.6, p=0.07) and prolonged duration of surgery was the only statistically significant risk factor for SSI following THA.

Timing with Tourniquet Use

In an RCT of 22 patients in which cefuroxime prophylaxis was administered at various intervals (5, 10, 15, or 20 minutes) before inflation of the tourniquet for total knee arthroplasty (TKA), Johnson et al. measured antibiotic levels of bone and subcutaneous fat throughout the operation. They found that an interval of 10 minutes prior to tourniquet inflation was necessary to obtain adequate prophylaxis. While the patients obtained adequate levels in bone at 5 minutes, an interval of 10 minutes or more was required for patients to have therapeutic levels in the subcutaneous fat.[11]

In another similar RCT, 24 patients undergoing TKA were randomized to receive cefazolin 1, 2, or 5 minutes before tourniquet inflation. Serum, soft tissue, and bone samples were measured for adequate cefazolin concentration (defined as 4xMIC 90 (MIC 90=1 microgram/ml). The median percentage of cefazolin penetration into soft tissue and bone for the 5, 2, and 1 minute groups was 14.5% and 4.6%, 6.7% and 3.0%, and 5.9% and 4.6% respectively. The authors also noted that the percentage of patients achieving the ratio of 4xMIC 90 for soft tissue and bone was highest in the 5 minute group compared with either the 2 or 1 minute groups.[12]

In another prospective study by Soriano et al., 908 patients undergoing TKA were randomized to receive either 1.5 g of cefuroxime 30 minutes before inflation of tourniquet and placebo 10 minutes before release of tourniquet (standard group) or placebo 30 minutes before inflation of tourniquet and 1.5 g cefuroxime 10 minutes before release of tourniquet. There was no difference among the patients with regard to various risk factors for SSI/PJI. The authors did not find a significant difference in the incidence of infection at 3.6% for the standard group and 2.6%

for the control group at 12 months. The authors concluded that administration of antibiotics just prior to release of tourniquet was not inferior to a standard prophylactic regimen.[13]

Surveillance Measures

In a study evaluating the impact of a new national project meant to reduce infections in arthroplasty surgery in Sweden, Dahl et al. found that only 57% of patients received preoperative antibiotics during the recommended time frame. In 2009, following the introduction of the World Health Organization surgical checklist and a new Swedish Knee Arthroplasty Register (SKAR) reporting form, which included the time for administration of preoperative antibiotics, the number of patients receiving appropriately-timed doses of preoperative antibiotics increased to 69% in 2009 and 79% in 2010.[14]

Question 2: Is there an optimal antibiotic that should be administered for routine perioperative surgical prophylaxis?

Consensus: A first or second generation cephalosporin (cefazolin or cefuroxime) should be administered for routine perioperative surgical prophylaxis. Isoxazolyl penicillin is used as an appropriate alternative.

Delegate Vote: Agree: 89%, Disagree: 8%, Abstain: 3% (Strong Consensus)

Justification: A first or second generation cephalosporin should be administered for routine perioperative surgical prophylaxis because of its broad spectrum of action, cost-effectiveness, and the need to preserve newer and more expensive therapies for drug-resistant microorganisms and emerging pathogens. These antibiotics cover gram-positive organisms and clinically important aerobic gram-negative bacilli and anaerobic gram positive organisms.[6] Additionally, they have excellent distribution profiles in bone, synovium, muscle, and hematomas.[15] Many studies have documented that minimum bactericidal concentrations for most non methicillin-resistant *Staphylococcus aureus* (MRSA) organisms are achieved rapidly in these tissues-ie within minutes after their administration.[16,17] The optimal prophylactic antibiotic should be bactericidal (penicillin, cephalosporin, vancomycin, or aminoglycosides), not simply bacteriostatic (clindamycin, which is a lincosamide). The agent should also have a half-life that covers the decisive interval (the first 2 hours after incision or contamination) with therapeutic

concentrations from time of incision to wound closure. Failure to maintain tissue concentrations above the MIC increases the risk of wound infection.[18] In Scandinavia and elsewhere, isoxazolyl penicillin, such as cloxacillin, flucloxacillin, nafcilin, or oxacillinis, is used as an appropriate alternative. Some institutions administer carbapenems (namely imipenem/cilastin and meropenem) to patients with penicillin allergy, as they felt that the potential for cross-reactivity between carbapenems and penicillin is less than traditionally believed.[19]

In a multicenter, placebo RCT, Hill et al. convincingly demonstrated the efficacy of cefazolin for antimicrobial prophylaxis in reducing the risk of PJI. In 2,137 THA patients randomized to either 5 days of cefazolin or placebo antibiotic prophylaxis reduced the incidence of deep infection from 3.3% to 0.9% ($p<0.01$).[20]

Tyllianakis et al. performed an RCT comparing cefuroxime to two specific antistaphylococcal agents (fusidic acid and vancomycin) for prophylaxis in THA and TKA in an institution where MRSA and methicillin-resistant *S. epidermidis* (MRSE) prevalence exceeded 25% of orthopaedic infections. In 435 patients (260 hips and 175 knees) followed for a minimum of 2 years, the authors found no statistically significant difference between the treatment groups for either THA or TKA, although the authors concede that the power to detect meaningful statistical differences between the groups was low and it was therefore difficult to provide any definitive conclusions.[21]

The efficacy of one day of cefuroxime vs 3 days of cefazolin on postoperative wound infections was studied by Mauerhan et al. in a double-blind, multicenter trial of 1,354 patients undergoing hip and knee arthroplasty. The authors found no statistically significant difference between the two regimens. For the TKA patients, the rate of PJI was 0.6% (1/178) for those receiving cefuroxime vs 1.4% (3/207) for those receiving cefazolin. For the THA patients, the rate of PJI was 0.5% (1/187) for those receiving cefuroxime as compared to 1.2% (2/168) for those receiving cefazolin.[22]

In a study investigating the bacterial colonization and resistance patterns of a cohort of patients undergoing primary joint arthroplasty in Sweden, Stefansdottir et al. noted that in Scandinavia, isoxazolylpenicillin derivative cloxacillin is the most commonly used prophylactic antibiotic. Moreover, these β-lactams were effective against 99% of the *S. aureus* strains and 80% of the coagulase-negative *Staphylococcus* (CNS) strains colonizing patients undergoing primary TJA. Furthermore, the gentamicin-laden bone cement used in many of these cases covers against most of the additional CNS strains.[23]

Question 3: What is the choice of antibiotic in patients who have pre-existing prostheses such as heart valves?

Consensus: The choice of antibiotics for patients with pre-existing prostheses such as heart valves is the same as that for routine elective arthroplasty.

Delegate Vote: Agree: 94%, Disagree: 3%, Abstain: 3% (Strong Consensus)

Justification: Patients with preexisting prostheses such as heart valves are at risk for infective endocarditis due to bacteremia, which is relatively rare but can lead to catastrophic complications and death. Guidelines for the prevention of infective endocarditis have been published by the American Heart Association (AHA) for more than 50 years. The first 9 guidelines (published between 1955 and 1997) were based on low-level evidence; only more recently have the guidelines been stratified based on lifetime risk of infective endocarditis. Similar to the change in recommendations regarding dental prophylaxis for patients undergoing TJA, the 2007 antibiotic prophylaxis guidelines for infective endocarditis from the AHA and the Infectious Disease Society of America (IDSA) recommend antibiotic prophylaxis only for patients at the highest risk of infective endocarditis and only for selected dental procedures (eg those that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa).[24]

Infections that complicate heart valve replacement and prosthetic joint replacement have several features in common. *S. aureus* and *S. epidermidis* are common pathogens and infection rates are similar.[23-25] It is generally accepted that antimicrobial prophylaxis reduces the frequency of early postoperative infections; however, when such infections do occur, they are difficult to control without removing the prosthesis. The antibiotics that are recommended for endocarditis prophylaxis are similar to that of prophylaxis against PJI. Similarly, if an infection is known or suspected to be caused by *S. aureus*, the antibiotic regimen should contain an antistaphylococcal penicillin or a cephalosporin; whereas vancomycin should be used in those in whom an infection is known or suspected to be caused by MRSA.[25]

While there is literature to support the use of prophylactic antibiotics up to 48 hours postoperatively in cardiac surgery, this is to prevent deep and superficial sternal wound infection and is not relevant to our discussion of TJA surgery in a patient with a preexisting heart valve.[26,27] Interestingly, there have been some studies showing an increase in the routine use of vancomycin for routine valve surgery prophylaxis over the past years. Haydon et al. reviewed the national practice patterns for antibiotic prophylaxis in cardiac surgery in Australia and found that between 2004 and 2008, there was a doubling in the proportion of cardiac units using vancomycin for routine prophylaxis from 31% to 62% ($p<0.001$).[28]

Question 4: What alternatives are available for routine prophylaxis when cephalosporins are not an option?

Consensus: Curently teicoplanin and vancomycin are reasonable alternatives when routine antibiotic prophylaxis cannot be administered.

Delegate Vote: Agree: 73%, Disagree: 22%, Abstain: 5% (Strong Consensus)

Justification: Teicoplanin has proven to be an effective and safe prophylactic agent in prosthetic implant surgery in Europe, but is not yet available in the US, Canada, or China.[29-32] Due to the increased frequency of MRSA and MRSE infections in recent years, the prophylactic use of alternative antibiotics such as glycopeptides (vancomycin and teicoplanin) in hospitals where MRSA/MRSE are prevalent may be justified.[33] As vancomycin is more difficult to administer and has a shorter half-life and poorer tolerability profile than teicoplanin, the latter may be a better choice in these settings.[34] Teicoplanin is notable for having a long half-life (32-176 hours), low toxicity, and good tissue penetration, which allows it to achieve therapeutic concentrations in bone and surrounding soft tissues.[33,35]

Ceftaroline (fifth generation cephalosporin) has the same spectrum of activity as ceftriaxone with additional MRSA activity. The US Food and Drug Administration and the European Medicines Agency have provided indications for the use of ceftaroline for treatment of complicated skin and soft tissue infections only and not for prophylaxis.

In one multicenter RCT, Periti et al. compared administration of a single dose of teicoplanin (400mg intravenous (IV) bolus at time of anesthesia) versus that of 5 doses of cefazolin over a 24 hour period (2g at induction and 1g every 6 hours postoperatively) as prophylaxis in patients undergoing TJA. They randomized 846 patients and noted that 6 patients (1.5%) in the teicoplanin group and 7 patients (1.7%) in the cefazolin group developed a surgical wound infection during their hospital stay, which was a non-significant difference. Additionally, a non-significant difference in adverse events was recorded in the two groups, with 3 (0.7%) of the teicoplanin patients and 9 (2.1%) of the cefazolin patients.[32]

Question 5A: What antibiotic should be administered in a patient with a known anaphylactic penicillin allergy?

Consensus: In a patient with a known anaphylactic reaction to penicillin, vancomycin or clindamycin should be administered as prophylaxis**.** Teicoplanin is an option in countries where it is available.

Delegate Vote: Agree: 88%, Disagree: 10%, Abstain: 2% (Strong Consensus)

Question 5B: What antibiotic should be administered in a patient with a known non-anaphylactic penicillin allergy?

Consensus: In a patient with a reported non-anaphylactic reaction to penicillin, a second-generation cephalosporin can be used safely as there is limited cross-reactivity. Penicillin skin testing may be helpful in certain situations to clarify whether the patient has a true penicillin allergy.

Delegate Vote: Agree: 87%, Disagree: 9%, Abstain: 4% (Strong Consensus)

Justification: When patients present with a penicillin allergy, further information should be obtained to determine whether an Immunoglobulin E(IgE)-mediated response (anaphylaxis) occurred. In patients with a documented IgE-mediated response to penicillin, third and fourth

generation cephalosporins can be used. First and second generation cephalosporins with R1 side chains similar to that of penicillin (cefaclor, cefadroxil, cefatrizine, cefprozil, cephalexin, or cephradine) should be avoided; first and second generation cephalosporins with different R1 side chains can be given.

Vancomycin and clindamycin are recommended as alternative agents for patients who have a true type I β-lactam allergy, manifested by immediate urticaria, laryngeal edema, or bronchospasm.[3] Clindamycin is a preferred alternative for persons with an established β-lactam allergy or with contraindications to its use and at institutions with low rates of MRSA infection. Clindamycin has good bioavailability and at 30 minutes after infusion has been shown to exceed the MICs for *S. aureus* in both animal and human cortical bone samples.[36] However, clindamycin is a bacteriostatic agent. In addition vancomycin alone has a relatively poor activity against *Staphylococcus aureus* and clinical studies implicate that vancomycin as prophylaxis alone increases the risk for SSI. Therefore a second agent should be considered (levofloxacine, moxi-floxacine) in addition to vancomycin. [8]

Cross-reactivity between penicillin and cephalosporin is overestimated and much lower than reported in earlier studies. The 10% estimate of risk of allergic reactions to cephalosporins in penicillin-allergic patients is based on data collected and reviewed in the 1960s and 1970s. It is due in large part to the widely referenced reviews of Dash and Petz, which reported allergic reactions in 7.7% and 8.1% respectively of penicillin-allergic patients (allergy was based on patient history) and only included first generation cephalosporins and second generation cefamandole. [37,38] The high cross-reactivity found in earlier studies may be due in part to contamination of the study drugs with penicillin during the manufacturing process.[39,40] Moreover, the authors of the early studies had a broader definition of allergy and did not account for the fact that penicillin-allergic patients have an increased risk of adverse reactions to any medication.[41,42] Skin testing in penicillin-allergic patients cannot reliably predict an allergic response to a cephalosporin, particularly to compounds with dissimilar side chains.[43] However, skin testing may be useful in determining whether a true allergy to penicillin exists.[44]

Twenty-seven articles on the topic of the cross-reactivity of penicillin and cephalosporin were reviewed, of which 2 were meta-analyses, 12 were prospective cohorts, 3 were retrospective cohorts, 2 were surveys, and 9 were laboratory studies. The authors demonstrated that penicillin has a cross-allergy with first generation cephalosporins (OR 4.8; CI 3.7-6.2) and a negligible cross-allergy with second generation cephalosporins (OR 1.1; CI 0.6-2.1). Moreover,

laboratory and cohort studies indicate that the R1 side chain, not the β-lactam ring, is responsible for this cross-reactivity. The authors conclude that the overall cross-reactivity between penicillin and cephalosporin is lower than previously reported, at 10%, although there is a strong association between amoxicillin and ampicillin with first and second generation cephalosporins that share a similar R1 side chain. The overall cross-reactivity between penicillin and cephalosporin in individuals who report a penicillin allergy is approximately 1% and in those with a confirmed penicillin allergy 2.55%. For penicillin-allergic patients, the use of third or fourth generation cephalosporin or cephalosporins (such as cefuroxime and ceftriaxone) with dissimilar side chains than the offending penicillin carries a negligible risk of cross allergy.[45]

A similar review of 44 articles on the evidence of cross-reactivity between cephalosporin and penicillin in human and animal studies supports the finding that cephalosporin can be safely prescribed to a patient with a non-life threatening reaction to penicillin (including type I anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and angioedema).[46] The relative risk of an anaphylactic reaction to cephalosporin ranges from 1:1,000 to 1:1,000,000 and this risk is increased by a factor of 4 in patients with a history of penicillin allergy.[47]

Based on an analysis of 9 articles that compare allergic reactions to a cephalosporin in penicillin-allergic and non-penicillin-allergic subjects, Pichichero et al. found that first generation cephalosporins have a cross-allergy with penicillin, but cross-allergy is negligible with second and third generation cephalosporins. Specifically, a significant increase in allergic reactions to cephalothin (OR 2.5, 95% CI 1.1-5.5), cephaloridine (OR 8.7, 95% CI 5.9-12.8), and cephalexin (OR 5.8, CI 3.6-9.2) and all first generation cephalosporins plus cefamandole (OR 4.8, CI 3.7-6.2) were observed in penicillin-allergic patients; no increase was observed with second generation cephalosporin (OR 1.1, CI 0.6-2.1) or third generation cephalosporin (OR 0.5, CI 0.2-1.1).[41,42]

In a retrospective cohort of 2,933 patients who received a cephalosporin (usually cefazolin) during their procedure, including 413 who were allergic to penicillin, only one of the penicillin-allergic patients may have had an allergic reaction to the cephalosporin; and one of the non-penicillin-allergic patients developed a rash while the antibiotic was infused, requiring discontinuation of the antibiotic.[48]

In a large, retrospective review of 534,810 patients who received penicillin followed by a cephalosporin at least 60 days later, Apter et al. noted that a total of 3,877 patients had an allergic-like event (ALE) after penicillin administration, but only 43 (1.1%) experienced a second

ALE after receiving cephalosporin (unadjusted risk ratio (RR) 10.0; 95% CI 7.4-13.6). Interestingly, in a separate analysis reviewing sulfonamide antibiotics, 1.6% of penicillin-sensitive patients experienced a second ALE after receiving a sulfonamide (7.2; 95% CI 3.8-12.5), suggesting that patients who are allergic to penicillin are at a higher likelihood of being allergic to other medications in general, not necessarily indicating that cross-reactivity had occurred.[49]

Park et al. performed a retrospective cohort study to determine whether patients with a penicillin allergy were at an increased risk of adverse drug reactions when administered cephalosporin. Eighty-five patients with a history of penicillin allergy and positive penicillin skin test and 726 patients with a history of penicillin allergy and a negative penicillin skin test were administered a first generation cephalosporin. Five (6%) of 85 cases had an adverse drug reaction to cephalosporin compared to 5 (0.7%) of 726 of the control population (p=0.0019). The rate of presumed IgE-mediated adverse drug reactions to the cephalosporin among the cases was 2 (2%) of 85 compared to 1 (0.1%) of 726 among the reference population (p=0.03).[50]

Question 6: What are the indications for administration of vancomycin?

Consensus: Vancomycin should be considered for patients who are current MRSA carriers or have anaphylactic allergy to penicillins.

Consideration should be given to screening high risk patients such as:

- Patients in regions with a high prevalence of MRSA.
- Institutionalized patients (nursing home residents, dialysis-dependent patients, and those who have been in the intensive care unit).
- Healthcare workers.

Delegate Vote: Agree: 93%, Disagree: 7%, Abstain: 0% (Strong Consensus)

Justification: The AAOS recommendation for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, states that “vancomycin may be used in patients with known colonization with MRSA or in facilities with recent MRSA outbreaks.”[51] Similarly, the consensus

position of the Medicare National Surgical Infection Prevention Project's SIPGWW meeting was that "for patients with known MRSA colonization, vancomycin should be considered the appropriate antimicrobial agent for prophylaxis."[6] Additionally, the Society for Healthcare Epidemiology of America recently recommended routine surveillance cultures at the time of hospital admission for patients at high risk for carriage of MRSA.[52]

Question 7: Is there evidence to support the routine use of vancomycin for preoperative prophylaxis?

Consensus: No. Routine use of vancomycin for preoperative prophylaxis is not recommended.

Delegate Vote: Agree: 93%, Disagree: 6%, Abstain: 1% (Strong Consensus)

Justification: Current data suggest that the role of vancomycin in orthopaedic surgery prophylaxis should be limited. There is ample evidence that vancomycin is inferior against methicillin-sensitive strains of staphylococcal species when compared to cephalosporin and penicillinase-resistant penicillin.[8,53]

Several systematic analyses concluded that no clear benefit in clinical or cost effectiveness has been demonstrated for the routine use of vancomycin compared with cephalosporin for prophylaxis. However, most of these studies were conducted before the increasing prevalence of MRSA and may not accurately reflect the current environment. In some hospitals, community-associated MRSA (CA-MRSA) strains are now responsible for a significant portion of SSIs.[54,55] However, there is no consensus about what constitutes a high prevalence of methicillin resistance and no evidence that routine use of vancomycin for prophylaxis in institutions with perceived high risk of MRSA infection results in fewer SSIs than the use of a cephalosporin. Although two RCTs have been conducted in institutions with a high MRSA prevalence, the differences in SSI rates and outcomes were conflicting. Similarly, several studies have utilized decision analysis models to calculate MRSA prevalence thresholds for which vancomycin would have clinical benefit and be more cost-effective than cephalosporin for surgical prophylaxis.

However, these studies all suffer from the lack of randomization to provide baseline probabilities for the clinical effectiveness of each treatment at different rates of MRSA prevalence.

While there is a growing body of evidence to support the routine use of vancomycin for preoperative prophylaxis, this should be tempered by the fact that there is an increasing threat of colonization and infection with vancomycin-resistant *enterococci* (VRE)[56] and an increased prevalence of MRSA strains with reduced susceptibility to vancomycin.[57 58]

The choice of drug prophylaxis should take into account the antibiotic resistance patterns in hospital systems. In a recent study by Fulkerson et al., the susceptibilities of *S. epidermidis* and *S. aureus* to cefazolin at two high-volume academic centers in New York and Chicago were only 44% and 74%, respectively.[59] Of the most common organisms infecting patients undergoing TJA at these hospitals, 26% to 56% were resistant to the standard recommended prophylactic agent. Thirty-three of the 194 infections were diagnosed within a month after the surgery. Of these, 8 were due to *S. epidermidis* and 16 were due to *S. aureus*. Of these, only 2 of the 8 (25%) of the *S. epidermidis* infections and 11 of the 16 (69%) of the *S. aureus* infections were sensitive to cefazolin. However, these infections were 100% susceptible to vancomycin.

In a study of deep infections following hip and knee arthroplasty over a 15-year period at The Royal Orthopaedic Hospital and Queen Elizabeth Hospital in England, 22 of 75 hip and knee infections (29%) were caused by microorganisms that were resistant to the antibiotic used for prophylaxis (cefuroxime). These included all 3 MRSA infections, all 3 *Pseudomonas aeruginosa* infections, and 11 coagulase-negative staphylococcus infections.[60,61] Wiesel and Esterhai recommend administration of vancomycin in institutions where the prevalence of MRSA is greater than 10% to 20%.[62]

In a hospital with a high prevalence of MRSA, Merrer et al. conducted a prospective, observational study comparing the incidence of SSI after vancomycin or cefazolin prophylaxis before femoral neck fracture surgery, as well as the impact of antibiotic prophylaxis on the emergence of VRE and *Staphylococcus aureus*. The authors found no significant difference in the rate of SSI, as a total of 8 (3%) occurred, 4% in the cefazolin group and 2% in the vancomycin group (p=0.47). At one week after surgery, there were a total of 6 patients (2%) who had hospital-acquired MRSA, corresponding to 0.7% in the cefazolin group and 5% in the vancomycin group (p=0.04), none of which were resistant to glycopeptides. Additionally, 3 patients (1%) acquired VRE, all of which were in the cefazolin group (p=0.27).[63]

Cranny et al. used a combination of systematic reviews and economic modeling in order to answer questions about whether there is a level of MRSA prevalence at which a switch from non-glycopeptide to glycopeptide antibiotics for routine prophylaxis is indicated in surgical environments with a high risk of MRSA infection. The effectiveness reviews identified 16 RCTs with a further 3 studies included for adverse events only. They found no evidence to support that glycopeptides are more effective than non-glycopeptides in preventing SSI. Most of the trials did not report either the baseline prevalence of MRSA at the participating surgical units or MRSA infections as an outcome. The cost-effectiveness review included 5 economic evaluations of glycopeptide prophylaxis. Only one study incorporated health-related quality of life and undertook a cost-utility analysis. In conclusion, the authors indicate that there is currently insufficient evidence to determine whether there is a threshold prevalence of MRSA at which switching from non-glycopeptide to glycopeptide antibiotic prophylaxis might be cost effective.[64]

Bolon et al. performed a meta-analysis of 7 RCTs published in the cardiothoracic surgery literature that compared SSIs in subjects receiving glycopeptide prophylaxis with those who received β-lactam prophylaxis. While neither agent proved to be superior for prevention of the primary outcome, occurrence of SSI at 30 days (RR 1.14, 95% CI 0.91-1.42), vancomycin prophylaxis was superior for the prevention of SSI caused by methicillin-resistant gram-positive bacteria (RR, 0.54; 95% CI 0.33-0.90) at 30 days after surgery.[65]

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, states that “vancomycin may be used in patients with known colonization with MRSA or in facilities with recent MRSA outbreaks.”[1] The Hospital Infection Control Practices Advisory Committee guideline also suggests that a high frequency of MRSA infection at an institution should influence the use of vancomycin for prophylaxis but acknowledges that there is no consensus about what constitutes a high prevalence of methicillin resistance.[66]

Two prospective RCTs have evaluated antibiotic prophylaxis in hospitals with a high prevalence of MRSA. Tacconnelli et al. randomized patients undergoing surgery for cerebrospinal shunt placement to receive either vancomycin or cefazolin. The prevalence of MRSA in 2001 for a 1700-bed university hospital was reported as one new case of MRSA infection per 100 hospital admissions. Shunt infections developed in 4% of patients receiving vancomycin (4/88) and 14% receiving cefazolin (12/88, RR, 0.22; 95% CI 0.11-0.99, p=0.03). The infecting pathogen was MRSA in 2 of 4 patients (50%) receiving vancomycin and 9 of 12 (75%) patients receiving

cefazolin.[67] Finkelstein et al. randomized 855 patients undergoing cardiothoracic surgery to either a vancomycin or cefazolin group. The prevalence of new cases of MRSA infection in the cardiac surgery ward was reported to be 3.0 and 2.6 per 100 admissions in 1995 and 1996 respectively. The overall rates of SSI were similar in both groups (9.5% for vancomycin and 9.0% for cefazolin). A trend toward more methicillin-resistant gram-positive infections was observed in the cefazolin group (4.2% vs 2.0%; p=0.09), while more methicillin-sensitive staphylococcus infections were seen in patients receiving vancomycin (3.7% vs 1.3%; p=0.04).[68]

Three other clinical studies have used pre- and post-intervention periods to assess the effect of switching to vancomycin for surgical prophylaxis in patients undergoing cardiothoracic or orthopaedic surgery. Garey et al. demonstrated that a change from cefuroxime to vancomycin prophylaxis decreased the average monthly SSI rate by 2.1 cases/100 coronary artery bypass graft (CABG) procedures when compared with patients undergoing cardiac valve replacement surgery. This was attributed to a lower rate of infections caused by MRSA and CNS during this 4-year study of nearly 6,500 patients.[69] Similarly, Spelman et al. reported a decrease in SSI rates from 10.5% to 4.9% (p<0.001) after switching the antibiotic prophylaxis regimen from cefazolin to vancomycin plus rifampin in 1,114 CABG procedures. This was attributed to a decrease in the incidence of MRSA infections from 67% during the one year pre-intervention period to 0% in the one year post-intervention period.[70] Smith et al. retrospectively reviewed total and MRSA PJI in 5,036 primary TJAs as well as the cure rate of PJI in a 2 year pre-intervention period when cefazolin was the antibiotic prophylaxis of choice to the 2 year post-intervention period when vancomycin was the antibiotic prophylaxis of choice. They found that with the use of vancomycin the total rate of PJI was significantly reduced (1.0% vs 0.5%, p=0.03) and the rate of MRSA PJI was also reduced (0.23% vs 0.07%, p=0.14). Furthermore, PJIs were more successfully treated with irrigation and debridement only, not requiring antibiotic spacers (76.9% vs 22.2%, p=0.002).[71]

A study published on Australian Surveillance Data (Victorian Healthcare Associated Surveillance System) of over 20,000 cardiac and arthroplasty procedures identified 1,610 case in which vancomycin was administered as compared to 20,939 cases in which a β-lactam was used. The adjusted OR for an SSI with methicillin-sensitive *Staphylococcus aureus* (MSSA) was 2.79 (95% CI 1.6-4.9) when vancomycin prophylaxis was administered (p<0.001), whereas the unadjusted OR for an SSI with MRSA was 0.44 (OR 0.19-1.004; p=0.05).[72]

Several recent studies have developed decision analysis models to determine the threshold of MRSA prevalence at which vancomycin would minimize the incidence and cost of SSI. For CABG surgery, the authors of two studies have recommended a MRSA prevalence threshold of 3% among infections caused by *S. aureus*.[73-75]. Miller et al. suggested that lower rates of MRSA prevalence (eg 3%-10%) were within the error of their model and that surgical prophylaxis with vancomycin would have a modest effect in reducing the incidence of SSI. For vascular surgery, a MRSA prevalence of 50% was suggested before a β-lactam agent is replaced with vancomycin for surgical prophylaxis.[76] The authors also suggested that an aminoglycoside should be added to the prophylactic regimen once the prevalence of MRSA reaches 10%, which is in agreement with the recent guidelines from the British Society of Antimicrobial Chemotherapy.[77] Elliot et al. developed an economic model to explore the cost-effectiveness of vancomycin and/or cephalosporin for surgical prophylaxis in patients undergoing THA. Vancomycin was recommended when the rate of MRSA SSIs is ≤ 0.15% and the rate of non-MRSA SSIs is ≥ 0.1%, or when the rate of MRSA infections is ≤ 0.2% and the rate of other infections is > 0.2%.[78] Each of these decision analysis studies noted that their biggest limitation was the lack of available evidence from RCTs, with a high prevalence of MRSA infections as one of the most important factors that influenced modeling assumptions.

Question 8: Is there a role for routine prophylactic use of dual antibiotics (cephalosporins and aminoglycosides or cephalosporins and vancomycin)?

Consensus: Routine prophylactic use of dual antibiotics is not recommended.

Delegate Vote: Agree: 85%, Disagree: 14%, Abstain: 1% (Strong Consensus)

Justification: Clinical studies have used pre- and post-intervention periods to assess the effect of switching to vancomycin for surgical prophylaxis in patients undergoing cardiothoracic surgery. Walsh et al. implemented a comprehensive MRSA bundle program in which vancomycin was added to the routine cefazolin prophylaxis regimen for patients who tested positive for nasal MRSA carriage. Other components of the program included decolonization of all cardiothoracic staff who screened positive for nasal MRSA, application of nasal mupirocin ointment for 5 days in all patients starting one day before surgery, application of topical

mupirocin to exit sites after removal of chest and mediastinal tubes, and rescreening of patients for MRSA colonization at the time of hospital discharge. This program resulted in a significant reduction in the SSI rate (2.1% to 0.8%, p<0.001) as well as a 93% reduction in postoperative MRSA wound infections (from 32 infections/2,767 procedures during the 3-year pre-intervention period to 2 infections/2,496 procedures during the 3-year post-intervention period).[79]

Dhadwal et al. conducted a double-blind RCT to compare the efficacy of a 48 hour, weight-based dosing of vancomycin plus gentamicin and rifampin versus a 24 hour cefuroxime regimen for antibiotic prophylaxis of sternal wound infections in a high-risk group of patients undergoing CABG surgery. The infection rates significantly decreased from 23.6% (25/106) in the cefuroxime group to 8.4% (8/95) in the combination vancomycin group (p=0.004).[80] Patrick et al. conducted an RCT to compare cefazolin and combinations of cefazolin and either vancomycin or daptomycin in 181 low-risk patients undergoing vascular surgery. Only 6 postoperative MRSA infections were reported (2 in the cefazolin group, 4 in the vancomycin plus cefazolin group, and 0 in the daptomycin plus cefazolin group), making the interpretation of the differences between antibiotic regimens difficult.[81]

Sewick et al. retrospectively reviewed 1,828 primary TJAs that received either a dual antibiotic regimen of cefazolin and vancomycin or received cefazolin alone in order to determine the rate of SSI as well as the microbiology of subsequent SSI. There was a total of 22 SSIs (1.2%) with no significant difference in the infection rate between the dual antibiotic prophylaxis group compared to the single antibiotic regimen (1.1% and 1.4% respectively, p=0.636), while the prevalence of subsequent MRSA infection was significantly lower (0.002% vs 0.08%, p=0.02).[82] Ritter et al. administered a single prophylactic dose of vancomycin and gentamicin in a cohort of 201 consecutive TJA patients and documented bactericidal blood concentrations during and for 24 hours after surgery with no postoperative infections.[83]

Elliot et al. developed an economic model to explore the cost effectiveness of vancomycin and/or cephalosporin for surgical prophylaxis in patients undergoing THA. Combination therapy (such as vancomycin plus a cephalosporin) was recommended when the rate of MRSA SSIs is ≥ 0.25% and the rate of non-MRSA SSIs is ≥ 0.2%).[78]

Thus, based on the available literature, this workgroup feels that dual antibiotics may be utilized to allow broad coverage in institutions or regions where there is a high rate of MRSA infection for which prophylactic vancomycin use is deemed appropriate under question 6 above.

Question 9: What should be the antibiotic of choice for patients with abnormal urinary screening and/or an indwelling urinary catheter?

Consensus: The presence of urinary tract symptoms should trigger urinary screening prior to TJA. Asymptomatic patients with bacteriuria may safely undergo TJA provided that routine prophylactic antibiotics are administered. Patients with acute urinary tract infections (UTI) need to be treated prior to elective arthroplasty

Delegate Vote: Agree: 82%, Disagree: 12%, Abstain: 6% (Strong Consensus)

Justification: There is sparse literature on the risk of deep joint infection in patients with abnormal perioperative urinalysis. While several case reports in the 1970s linked postoperative UTIs to PJI,[84 85] the literature supporting the correlation between preoperative UTIs and PJI following TJA is inadequate.[86] Only 3 studies have directly addressed the relationship between preoperative bacteriuria and PJI following TJA, none of which observed a positive correlation.[87-89] To our knowledge there are no studies of patients with symptomatic UTI undergoing TJA with routine perioperative prophylactic antibiotics. There is no evidence either in support of or against proceeding with surgery in this cohort of patients.

The presence of UTI symptoms should serve as a preliminary screening tool for surgical clearance of the TJA candidate. Symptoms can then be classified as either irritative or obstructive. Irritative symptoms (such as dysuria, urgency, or frequency) may or may not be related to bacteriuria and a noncentrifuged clean catch midstream urine sample should be evaluated for white blood cells (WBCs) in these patients. In patients with $>10^4$ WBC/mL, a bacterial count and culture should be obtained and in patients with >4 WBC/high power field and bacterial count $>10^3$/mL, surgery should be postponed until an appropriate course of microbe-specific antibiotics is administered and repeat urinalysis is obtained. On the other hand, asymptomatic patients with bacteriuria may safely undergo TJA provided routine prophylactic antibiotics are administered. Patients with obstructive symptoms should undergo urologic evaluation before arthroplasty, as postoperative urinary retention has been shown to be a risk factor for PJI. [86,90,91]

In a prospective, multicenter study of 362 knee and 2,651 hip arthroplasty cases, the authors reported a deep joint infection rate of 2.5% for knee and 0.64% for hip cases at one year follow-up. While univariate analysis showed no association between deep joint infection and preoperative UTI (>10^5 CFU/mL), multivariate regression analysis indicated that postoperative UTI increased the risk of hip PJI.[88]

Of 1,934 surgical cases (1,291 orthopaedic surgeries) performed at a Veterans Administration hospital, a preoperative urine culture was obtained in 25% (489) of cases. Of these, bacteriuria was detected in 54 (11%) patients, of which only 16 received antimicrobial drugs. The incidence of SSI was similar between those with bacteriuria and those without (20% vs 16%, p=0.56), while the rate of postoperative UTI was more frequent among patients with bacteriuria than those without (9% vs 2%, p=0.01). Among the 54 patients with a positive urinary culture, treated and untreated patients were compared. Unexpectedly, a greater proportion of treated patients developed an SSI (45% vs 14%, p=0.03). This effect was greatest among patients with high count bacteriuria (>10^5 CFU/mL), with SSI occurring in 4 of 8 (50%) of treated vs 1of 15 (7%) of untreated (p=0.03). These results led the authors to conclude that in this system preoperative urinary cultures were inconsistently ordered and that when they were, they were rarely positive for bacteriuria. Even when bacteriuria was detected, it was usually not treated. The authors noted that treating bacteriuria associated with SSI is likely confounded by factors that contributed to the initial decision to administer antimicrobials in the first place.[92]

A retrospective study of 274 THAs found that 5 patients with PJI had perioperative UTIs. However, the same organism was isolated from the urinary tract and hip in only 3 patients. Of these, only one had a documented preoperative urinalysis.[93] A retrospective analysis of 277 patients (364 TJAs) showed that 35 patients had evidence of preoperative or perioperative UTI with colony counts greater than 10^5 CFU/mL on preoperative clean-catch urine specimens. Only 3 patients (1.1%) developed joint infections at 9, 19, and 45 months respectively, and none was thought to be due to perioperative UTI.[87] Another retrospective analysis found 57 (55 asymptomatic, 2 symptomatic) of 299 arthroplasty patients had bacteriuria on admission. Twenty of the 57 patients went to surgery before the routine culture results were available, but postoperatively received appropriate antibiotics for treatment of the UTI. Another 18 patients underwent surgery during their treatment course for preoperatively-diagnosed UTI, while the other 19 patients completed an appropriate antibiotic course prior to surgery. None of the patients developed a PJI, which led the authors to conclude that a treatment course of antibiotics can be implemented at any time perioperatively once culture data are obtained.[89]

The incidence of bacteriuria rises from 0.5% to 1% for a single in-and-out catheterization, 10% to 30% for catheters in place for up to 4 days, and up to 95% for catheters in place for 30 days or more.[94,95]

Question 10: Should the preoperative antibiotic choice be different in patients who have previously been treated for another joint infection?

Consensus: The type of preoperative antibiotic administered to a patient with prior septic arthritis or PJI should cover the previous infecting organism of the same joint. In these patients, we recommend the use of antibiotic-impregnated cement, if a cemented component is utilized.

Delegate Vote: Agree: 84%, Disagree: 10%, Abstain: 6% (Strong Consensus)

Justification: There is no evidence that septic arthritis or a PJI can be completely cured. Jerry et al. conducted a study of 65 patients who underwent TKA and had a history of prior sepsis or osteomyelitis around the knee. They reported rates of deep PJI of 4% and 15% respectively.[96]

Lee et al. studied a consecutive series of 20 primary TKAs in 19 patients with a history of prior septic arthritis or osteomyelitis around the knee. They performed a preoperative workup to evaluate for infection that included serologies and plain radiographs in all patients, while 8 patients additionally had tagged WBC scans and 7 patients had a knee aspiration. Intraoperatively, frozen section for evidence of acute inflammation was used to guide decisions on whether the procedure was done as a single or staged procedure. All TKA components were implanted with antibiotic cement containing 1g of vancomycin and 1.2g of tobramycin/batch of Simplex bone cement. Of the 17 patients with a minimum of 2 years follow-up, only one developed a PJI approximately 3.5 years from the index arthroplasty. Of note, this was one of the two patients that had been treated in a staged manner and additionally had immunosuppressive comorbidities, including rheumatoid arthritis, insulin-dependent diabetes mellitus, and was taking daily doses of prednisone.[97]

Larson et al. performed a retrospective matched case control study to review the clinical results of 19 patients who underwent TKA after infected tibial plateau fractures, comparing them to 19 control subjects matched for age, gender, and arthroplasty year, who underwent TKAs for tibial

plateau fractures without a history of infection. Of the 19 case patients, 13 underwent one-stage TKA, while the remainder underwent a staged TKA with either an antibiotic spacer or debridement and intravenous antibiotic therapy. Antibiotic cement was used in the majority of patients. Previously infected knees were 4.1 times more likely to require additional procedures for complications compared with knees with no previous infection (95% CI 1.2-18.3, p=0.02). The 5 year infection-free survival was 73%±10% in the case group compared with 100% in the control group (p=0.023). The authors recommended that in patients at high risk less than one year since active evidence of infection, a two-stage TKA be performed, with antibiotic therapy and a 4 to 6 week delay between procedures.[98]

Question 11: Should postoperative antibiotics be continued while a urinary catheter or surgical drain remains in place?

Consensus: No. There is no evidence to support the support the continued use of postoperative antibiotics when urinary catheter or surgical drains are in place. Urinary catheters and surgical drains should be removed as soon as safely possible.

Delegate Vote: Agree: 90%, Disagree: 7%, Abstain: 3% (Strong Consensus)

Justification: Short-term use of an indwelling catheter after surgery reduces the incidence of urinary retention and bladder over-distension without increasing the rate of UTI and is therefore common practice in many hospitals.[99] However, it has been shown that there is an increased risk of UTIs when a catheter is employed for more than 48 hours.[100,101] Urinary retention as well as catheterization can both lead to bacteriuria,[101-103] which increases the risk of deep PJI from 3 to 6 times.[87,88,104,105]

Literature in the field of surgical oncology demonstrates that bacterial colonization of surgical drains used in breast and axillary procedures is a significant risk factor for the development of SSI and the microorganisms that caused SSIs were the same as those that colonized the drainage tube in 83% of cases.[106] Other studies have demonstrated that there is an association between longer duration of drain use and increased incidence of SSI.[107]

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 3, states that the “duration of prophylactic antibiotic administration should not

exceed the 24 hour postoperative period. Prophylactic antibiotics should be discontinued within 24 hrs of the end of surgery. The medical literature does not support the continuation of antibiotics until all drains or catheters are removed and provides no evidence of benefit when they are continued past 24 hours."[2]

Colonization of drains by skin organisms can certainly occur, but in only 10% of cases with positive drain tip culture does overt infection develop.[108] Michelson et al. conducted an RCT of 100 TJA patients using two methods of bladder management: short term (<24 hour) indwelling catheters and intermittent catheterization. All patients received the same perioperative cefazolin prophylaxis. The authors reported a lower incidence of urinary retention in the indwelling catheter group (27% vs 52%, $p<0.01$) and a lower rate of bladder distension (7% vs 45%; $p<0.01$). Moreover, patients who had an indwelling catheter for more than 48 hours had a significantly higher rate of bladder infection (35%) than patients who were straight catheterized and/or who had an indwelling catheter for fewer than 48 hours (6%, $p<0.01$).[99]

Van den Brand et al. performed a prospective RCT to determine whether an indwelling catheter for 48 hours or intermittent catheterization leads to less postoperative bacteriuria or a UTI with a single dose of cefazolin prophylaxis in primary hip and knee arthroplasties. In their protocol, patients received 48 hours of IV prophylactic cefazolin during the postoperative period. Patients who had an indwelling catheter in place after the IV antibiotics were completed were treated with oral antibiotic prophylaxis (nitrofurantoin) until catheter removal. Of the 99 patients who completed the study, 14 patients (5 men, 9 women) developed postoperative bacteriuria. The indwelling catheter group had a bacteriuria rate of 24% (11/46) compared with 6% (3/53) in the intermittent catheterization group ($p=0.018$).[109]

Similar findings were reported by Oishi et al., who reviewed 95 consecutive patients who had been managed with either an indwelling catheter (72 hours) or intermittent catheterization. Patients who were treated with an indwelling catheter had significantly lower incidences of urinary retention (7% vs 84% respectively; $p<0.005$) and bladder distension (7% vs 41%; $p<0.005$) than those who were treated with straight catheterization. While not statistically significant, though no patient in the indwelling catheter group developed infection, in the intermittent catheterization group one patient (2%) had bacteriuria and one patient (2%) had a UTI ($p>0.1$).[110]

Koulouvaris et al. performed a retrospective case control study to determine whether a treated preoperative or postoperative UTI or asymptomatic bacteriuria increases the risk of deep PJI

and whether the organisms are the same for the UTI and PJI. The authors matched 58 patients who had wound infections with 58 patients who did not develop wound infection based on age, gender, surgeon, joint, year of surgery, and length of follow-up. The authors found no association between preoperative UTI and wound infection (OR 0.34; 95% CI 0.086-1.357, p=0.13), and no association between postoperative UTI and wound infection (OR 4.22; 95% CI 0.46-38.9, p=0.20). Only one patient had the same bacteria (*E. faecalis*) cultured in the urine and the wound.[111]

In a survey of the members of the American Society of Breast Surgeons regarding the use of perioperative antibiotics for breast operations requiring drains, respondents continued antibiotic prophylaxis for 2-7 days or until all drains were removed (38% and 39% respectively) in cases without reconstruction, while in reconstruction cases 33% of respondents continued antibiotic prophylaxis for 2-7 days or until all drains were removed.[112] A similar study surveying the American and Canadian societies of Plastic Surgeons regarding drain use and perioperative antibiotic prophylaxis in cases of breast reconstruction found that 72% of plastic surgeons prescribed postoperative outpatient antibiotics in reconstruction patients with drains, with 46% continuing antibiotics until drains were removed.[113]

Question 12: What is the evidence for the optimal duration of postoperative antibiotics in decreasing SSI or PJI?

Consensus: Postoperative antibiotics should not be administered for greater than 24 hours after surgery.

Delegate Vote: Agree: 87%, Disagree: 10%, Abstain: 3% (Strong Consensus)

Justification: Many studies across surgical specialties have been performed to compare durations of antibiotic prophylaxis and the overwhelming majority have not shown any benefit in antibiotic use for more than 24 hours in clean elective cases.[114-116] Prolonged postoperative prophylaxis should be discouraged because of the possibility of added antimicrobial toxicity, selection of resistant organisms, and unnecessary expense.[24]

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 3, states that “duration of prophylactic antibiotic administration should not exceed the 24 hour postoperative period. Prophylactic antibiotics should be discontinued within 24 hours of surgery.”[1]

Mcdonald et al. performed a systematic review across surgical disciplines to determine the overall efficacy of single versus multiple dose antimicrobial prophylaxis for major surgery. They included only prospective RCTs which used the same antimicrobial in each treatment arm whose results were published in English. Regardless of fixed models (OR 1.06, 95% CI 0.89-1.25) or random effects (OR 1.04; 95% CI 0.86-1.25), there was no significant advantage of either single or multiple dose regimens in preventing SSI. Furthermore, subgroup analysis showed no significant differences in the type of antibiotic used, length of the multiple dose arm (>24 hr vs ≤24 hr), or type of surgery (obstetric-gynecological vs other).[117]

Mauerhan compared the efficacy of a one-day regimen of cefuroxime with a 3-day regimen of cefazolin in a prospective, double-blinded, multicenter study of 1,354 patients treated with arthroplasty and concluded that there was no significant difference in the prevalence of wound infections between the two groups. In the group treated with primary THA, the prevalence of deep wound infection was 0.5% (1/187) for those treated with cefuroxime compared with 1.2% (2/168) for those who had received cefazolin. In the group treated with a primary TKA, the rate of deep wound infection was 0.6% (1/178) for those treated with cefuroxime compared with 1.4% (3/207) for those who had received cefazolin.[22]

Heydemann and Nelson, in a study of hip and knee arthroplasty procedures, initially compared a 24-hour regimen of either nafcillin or cefazolin with a 7-day regimen of the same and found no difference in the prevalence of infection. They then compared a single preoperative dose with a 48-hour regimen and again found no difference in infection prevalence. A total of 466 procedures was performed during the 4-year study. No deep infections developed in either the one-dose or 48-hour antibiotic protocol group. A deep infection developed in one (0.8%) of the 127 patients in the 24-hour protocol group and in two (1.6%) of the 128 patients in the 7-day protocol group for an overall infection rate of 0.6% (3/466). The authors recognized that as a result of the small sample sizes, the study lacked the power to compare the one dose and the more than one dose categories.[118]

Stone et al. performed two separate prospective, placebo RCTs of variable-duration antibiotic prophylaxis in patients undergoing elective gastric, biliary, or colonic surgery and then in

patients undergoing emergency laparotomy and found that in both cases no significant difference was seen in the rate of SSI. Specifically, in a prospective RCT of 220 patients undergoing elective general surgery who were randomized to either perioperative cefamandole plus 5 days of placebo or perioperative plus 5 postoperative days of cefamandole, there was no significant difference in the rate of wound infection (6% and 5% respectively). In a second prospective RCT of patients undergoing emergent laporatomy in which cephalothin was utilized perioperatively, there was no significant difference in the rate of peritoneal infection between those who received perioperative therapy only (8 and 4% respectively) compared to those who had 5 to 7 days of additional postoperative therapy (10% and 5% respectively).[119]

In a retrospective review of 1,341 TJAs, Williams and Gustilo found no difference in deep infection rates between a 3 day and 1 day course of prophylactic antibiotics, but emphasized the importance of the preoperative dose, which was 2g of cefazolin.[120]

Clinical studies have used pre- and post-intervention periods to assess the effect of antibiotic duration for surgical prophylaxis. One institution launched a surgical wound infection surveillance program to monitor all orthopaedic surgeries and changed the prophylactic antibiotic regimen from intravenous cefuroxime (one preoperative and 2 postoperative doses every 8 hours) to one single preoperative dose of intravenous cefazolin for all clean orthopaedic surgeries. The authors of this study found no significant difference in the superficial and deep wound infection rates in 1,367 primary arthroplasties performed with a single preoperative dose of cefazolin versus 3 doses of cefuroxime. The deep wound infection rate for THA was 1.1% (95% CI, 0%-3.3%) in the cefuroxime group and 1.1% (95% CI, 0%-2.2%) in the cefazolin group (p=1.0). The deep wound infection rate of TKA was 1.6% (95% CI, 0%-3.8%) in the cefuroxime group and 1.0% (95% CI, 0.3%-1.7%) in the cefazolin group (p=0.63).[121]

Question 13: Until culture results are finalized, what antibiotic should be administered to a patient with a presumed infection?

Consensus: In a patient with a presumed infection when culture results are pending, empiric antibiotic coverage should depend on the local microbiological epidemiology. Culture data should assist in the tailoring of antibiotic regimens.

Delegate Vote: Agree: 96%, Disagree: 1%, Abstain: 3% (Strong Consensus)

Justification: Guidelines based on individual institutional microbiological epidemiology should be developed.[124] In the US, vancomycin is recommended for gram-positive coverage due to a high rate of resistance to methicillin in many cases and gentamicin or a third or fourth generation cephalosporin is recommended for gram-negative coverage. However, in areas with low MRSA prevalence, vancomycin should not be recommended as the first choice of drug until culture results are obtained and other antibiotics should be chosen instead.

Sharma et al. classified the spectrum and antibiotic susceptibility of bacteria isolated from revision hip and knee arthroplasty specimens in order to recommend appropriate empiric perioperative antibiotics before definitive cultures are obtained. They identified 147 patients with positive specimens, yielding 248 microorganisms from 195 tissue specimens, 43 fluid specimens, and 10 swabs. Of the 248 isolated microorganisms, *staphylococcus* species was the most common genus encountered (53%), followed by gram-negative isolates (24%). Eighty-eight percent of gram-negative organisms were detected within 48 hours of inoculation and 94% of gram-positive organisms within 96 hours. Overall, 46% of isolates were susceptible to cephalothin, while only 35% of CNS were sensitive to cephalothin. No gram-positive vancomycin resistance was encountered. Therefore the authors concluded that empiric prophylactic antibiotics for revision hip and knee arthroplasty should include vancomycin for gram-positive organisms and gentamicin for gram-negative bacteria; and if infection is suspected, vancomycin and gentamicin should be continued postoperatively for 96 and 48 hours respectively, unless culture or histology results suggest otherwise.[122]

Knee: In a retrospective review of 121 patients who underwent revision TKA for infection between 1994 and 2008 in the United Kingdom, the most common organism was CNS (49%) and *S. aureus* (13%). The prevalence of CNS appears to be increasing, while that of *S. aureus* and other organisms is decreasing. Vancomycin and teicoplanin were the most effective antibiotics, with overall sensitivity rates of 100% and 96% respectively. Also, the authors reported that based on their theoretical model of comparing microorganism sensitivities against specific antibiotics, gentamicin combined with vancomycin or teicoplanin is the most effective empirical regimen. While the authors recognized the potential serious nephrotoxic side effects, these antibiotics may be added to bone cement relatively safely. The authors also suggested that this empirical regimen can potentially allow for a one-stage revision procedure to be conducted when deep infection arises.[123]

In early, delayed, and late infections observed from data from the SKAR from 1986-2000 in 426 surgically revised cases, CNS was most prevalent (105/299, 35.1%) and twice as common as *S. aureus* (55/299, 18.4%). In hematogenous infections, *S. aureus* was the dominating pathogen (67/99, 67.7%), followed by streptococci and gram-negative bacteria. Methicillin resistance was found in 1/84 tested isolates of *S. aureus* and 62/100 tested isolates of CNS. During the study period of 1986-2000, methicillin resistance among CNS increased (p=0.002). Gentamicin resistance was found in 1/28 tested isolates of *S. aureus* and 19/29 tested CNS isolates. Therefore, the authors conclude that empiric antibiotics should cover CNS, as most early infections were caused by this organism. They also raised the concern that due to high rate of gentamicin resistance among CNS in infected TKA, other antibiotics should be used in bone cement at revision.[23]

Data from the SKAR have previously been used to report on the microbiology of 357 TKA infections in patients operated on before 1986. *S. aureus* was the most common pathogen (45.4%) followed by CNS (18%).[124] In later studies, staphylococci continued to be the most common pathogens, with *S. aureus* reported to account for 13%-51% of the infections and CNS accounting for 15%-49%.[123,125,126]

Hip: Rafiq et al. retrospectively reviewed the microbiology of 337 one-stage revision hip replacements for deep infection and found that CNS was the predominant organism (67%) and that *Staphylococcus* (13%) is becoming more prevalent. The authors also noted an increase in antimicrobial resistance (24% resistance to gentamicin), which lead the authors to suggest that other antibiotics such as erythromycin or fusidic acid be added to bone cement during these procedures.[127]

In a study examining the microbiology of contaminating bacteria during primary THA, Al-maiyah et al. cultured the gloved hands (n=627 impressions) of the surgical team in 50 THA cases after draping, at 20 minute intervals, and then before cementation. They found contamination present in 57 (9%) of impressions and a total of 106 bacterial isolates, with CNS being the most frequent (68.9%), micrococcus (12.3%) and diptheroids (9.4%) following, and *S. aureus* only representing 6.6% of cases. Interestingly, only half (52%) of the CNS isolates were sensitive to cefuroxime, the institutional prophylactic agent of choice, suggesting alternate agents may be indicated.[128]

Phillips et al. reviewed the microbiology of deep infection following hip and knee arthroplasty at a specialist orthopaedic hospital in the United Kingdom over a 15 year period. At their institution, CNS was the most common infecting organism (36%), followed by *S. aureus* (25%), *enterococcus* (9%), and MRSA (4%). Of the infecting organisms, 72% were sensitive to routine prophylactic agents. There was no significant change in microbiology over that time period at this institution.[129]

Timing of Infection: A retrospective analysis of 146 patients who had a total of 194 positive cultures obtained at time of revision total hip or knee arthroplasty was performed. Seventy percent of the infections were classified as chronic, 17% as acute postoperative, and 13% as acute hematogenous. Gram-positive organisms caused the majority of the infections (87% or 168/194). The microorganisms were sensitive to cefazolin in 61% of cases, gentamicin in 88% of cases, and vancomycin in 96% of cases. The most antibiotic-resistant bacterial strains were from patients in whom prior antibiotic treatment had failed. Acute postoperative infections had a greater resistance profile than did chronic or hematogenous infections. Bacteria isolated from a hematogenous infection had a high sensitivity to both cefazolin and gentamicin. This led to the following recommendations:

- Until final cultures are available, acute hematogenous infections should be treated with cefazolin and gentamicin.
- All chronic and acute postoperative infections with gram-positive bacteria and all cases in which a gram stain fails to identify bacteria should be managed with vancomycin.
- Infections with gram-negative bacteria should be managed with third or fourth generation cephalosporin.
- Infections with mixed gram-positive and gram-negative bacteria should be managed with a combination of vancomycin and third or fourth generation cephalosporin.
- As 93% (180) of the 194 cultures tested positive by the fourth postoperative day, the authors recommend that if culture results are not positive by the fourth postoperative day, termination of empiric antibiotic therapy should be considered.[59]

In a retrospective review of 97 patients (106 infections in 98 hips), Tsukayama et al. noted that aerobic gram-positive cocci accounted for 109 (74%) of the 147 isolates; gram-negative bacilli, 21 (14%); and anaerobes, 12 (8%). Of the CNS species 27 (48%) were oxacillin-resistant, while

all 33 (100%) of the coagulase-positive staph species were sensitive to oxacillin. The authors noted that most of the gram-negative isolates came from the early postoperative and late chronic infections, while isolates from the acute hematogenous infections were exclusively gram-positive cocci.[130]

Irrigation and Debridement (I&D): A retrospective review was conducted to describe the microbiological spectrum of PJI in 112 patients managed with I&D or arthroscopic washout of infected prosthetic joints between 1998 and 2003 in order to guide the choice of empirical antibiotics. Overall, the most frequently isolated organisms were CNS (47%) and methicillin-sensitive *Staphylococcus aureus* (MSSA) (44%), while 8% were MRSA and 7% were anaerobes. In their series, 60% of CNS isolates were resistant to methicillin. Most gram-negative isolates were resistant to cefuroxime and all were sensitive to meropenem. Based on the high rate of early polymicrobial infection, cephalosporin resistance among gram-negative organisms, β-lactamase resistance among gram-negative organisms, and β-lactam resistance among CNS, the authors recommend glycopeptides with a carbapenem in the initial regimen, with modification when culture and sensitivity results are available.[131]

Question 14: What is the appropriate preoperative antibiotic for a second-stage procedure?

Consensus: The appropriate preoperative antibiotic for the second stage should include coverage of the prior organism(s). Cemented arthroplasty components should be inserted with antibiotic-laden bone cement.

Delegate Vote: Agree: 66%, Disagree: 31%, Abstain: 3% (Strong Consensus)

Justification: Patients undergoing reimplantation surgery following a two-stage exchange procedure are at risk of developing recurrent infection.[132,133] The recurrent infection may be either due to incomplete eradication of the prior bacteria during the antibiotic spacer exchange or to a new infection. In order to properly address both potential scenarios, the appropriate preoperative antibiotics should include coverage of the prior organism as well as the most common infecting microorganisms.

Antibiotic-laden bone cement has been shown to decrease septic failure following TJA in high-risk individuals and it is US Food and Drug Administration-approved for use during reimplantation of components in a two-stage exchange. While there is no evidence to support the practice, it makes theoretical sense to add antibiotics that are effective in treating the index infection.

In a systematic review of 31 studies that compared the clinical outcomes achieved with one- and two-stage revision TKA with different types of spacers, the authors noted that after the index revision for infection, deep joint infection was detected in 0%-31% of cases. Of these, the infection was considered recurrent in 0%-18% of cases, while new infection rates varied from 0 to 31%. While the length of follow-up did not appear to influence the rate of recurrent infections, the studies with <4 years of clinical follow-up had fewer new infections.[134]

Azzam et al. retrospectively reviewed 33 patients who had failed an initial two-stage exchange arthroplasty, of whom 18 eventually went on to undergo a second two-stage procedure. Of this cohort, the isolated organism was different from the previous infecting organism in only one of 18 patients.[132]

In a similar study, Kalra et al. retrospectively reviewed 11 patients who developed reinfection after two-stage revision for infected THA and were subsequently treated with a two-stage re-revision. In their series, the infecting microorganisms were polymicrobial in 3 patients and only 2 had reinfection by the initial offending microbe.[133]

In a review of the outcomes of 69 patients with PJI in TKA, Mont et al. determined that in 8 of 9 cases reinfections were from the organism that had caused the initial infection, although in 6 of the 8 patients the sensitivity of the organism to antibiotics had changed.[126]

Kubista et al. published results on 368 patients treated with a two-stage revision for infected TKA. Of this cohort, 58 (15.8%) developed reinfection and a causative organism was identified in 47/58 (81%) of patients.[135]

In a retrospective review of 117 patients who underwent two-stage exchange arthroplasty for PJI of the knee, 33 of 117 patients (28%) required reoperation for infection. At the time of reimplantation, antibiotic-laden bone cement (1.2g tobramycin and 1g vancomycin per 40g of cement) was used for fixation of the prosthesis, but there was no note of the parenteral or perioperative antibiotics utilized at the second stage.[136]

Question 15: For surgeries of longer duration, when should an additional dose of antibiotic be administered intraoperatively?

Consensus: An additional dose of antibiotic should be administered intraoperatively after two half-lives of the prophylactic agent. The general guidelines for frequency of intraoperative antibiotic administration are provided. We recommend that re-dosing of antibiotics be considered in cases of large blood volume loss (>2000 cc) and fluid resuscitation (>2000cc). As these are independent variables, re-dosing should be considered as soon as the first of these parameters are met.

Delegate Vote: Agree: 94%, Disagree: 5%, Abstain: 1% (Strong Consensus)

Justification: In cases of large blood volume loss and fluid resuscitation there is a remarkable loss of the prophylactic agent that can result in levels below the MIC. The same is true for longer surgeries that extend beyond the half-life of the agent. Thus, additional antibiotic treatment is needed to re-establish antibiotic levels that exceed the MIC. An additional dose of antibiotic has been shown to reduce SSI rates in cardiac patients and should be administered intraoperatively after two half-lives of the prophylactic agent.[3,74,75]

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, states that "timing and dosage of antibiotic administration should be such to optimize the efficacy of the therapy."[1] Both the IDSA and AAOS state that "Additional intraoperative doses of antibiotic are advised when the duration of the procedure exceeds one to two times the antibiotic's half-life or when there is significant blood loss during the procedure." The general guidelines for frequency of intraoperative antibiotic administration are as follows: cefazolin every 2-5 (4) hours, cefuroxime every 3-4 hours, clindamycin every 3-6 hours, isoxazoyl penicillin every 3 hours, and vancomycin every 6-12 hours.[2,137,138]

In a prospective multicenter study exploring the relationship between timing, duration, and intraoperative redosing of surgical antimicrobial prophylaxis and the risk of SSI, Steinberg et al. determined that intraoperative dosing was associated with a lower infection risk only when the preoperative antibiotic was given in the recommended time frame. In 1,062 (24%) cases, the

surgical procedure lasted for at least 4 hours. Because of a longer half-life and the reduced need for redosing, cases that received vancomycin or fluoroquinolones were excluded from the analysis of the impact of redosing on infection risk (n=372). Intraoperative redosing was given in 21% of 690 of these long operations. Of the group that had a surgical procedure with a duration of >4 hours and who received the preoperative dose within one hour, 2 of 112 (1.8%) patients who were redosed intraoperatively developed infection, compared to 22 of 400 (5.5%) of those who were not re-dosed (OR 3.08, p=0.06).[10]

Scher et al. randomized 801 patients undergoing clean contaminated operations to one of three antibiotic regimens: 1g of cefazolin preoperatively, 1g of cefazolin preoperatively and another dose 3 hours later, and 1g of cefotetan preoperatively. While all regimens demonstrated similar wound infection rates for surgeries lasting less than 3 hours, for those that exceeded 3 hours, the group that only received the single preoperative cefazolin dose had a statistically significant higher wound infection rate than those who received the second cefazolin dose (6.1% vs 1.3%, p<0.01).[139]

Shapiro et al. performed a placebo-controlled RCT to test the efficacy of perioperative cefazolin in preventing infection after abdominal or vaginal hysterectomy. The authors sub-analyzed the effect of surgery duration on the efficacy of perioperative prophylaxis by calculating adjusted relative odds of infection with and without prophylaxis for different durations of surgery and found that the efficacy of prophylaxis diminishes rapidly with increasing length of surgery; by 3 hours, 20 minutes prophylaxis had no measurable effect (OR=1).[140]

Polk et al. prospectively analyzed the antibiotic levels of 3 cephalosporins (cefazolin, cephaloridine, and cephalothin) given as a single preoperative dose and found that acceptable concentrations of cefazolin were maintained near the incision site until 3 hours post-administration, whereas cephalothin did not maintain wound levels consistent with effective antimicrobial activity.[141]

Ohge et al. prospectively examined the pancreatic tissue concentrations of cefazolin in 10 patients undergoing pancreatectomy and determined the optimal intraoperative time to repeat the dose of cefazolin. Based on their results, the authors recommended a second dose of kefzol be given 3 hours after first administration in order to maintain adequate levels of antibiotic activity. They measured MIC for 4 bacterial species, namely 360 isolates of MSSA, 204 isolates of *K. pneuomoniae*, 314 isolates of *E. coli*, and 30 isolates of streptococci species; and measured tissue levels of cefazolin. Antibiotic concentrations in adipose tissue and peritoneum

3 hours after administration of kefzol were lower than the MIC 80 for *K. pneumoniae*, *E. coli*, and streptococcal species.[142]

In a retrospective review of 131 patients with primary colorectal cancer in prolonged operations exceeding 4 hours, the surgical wound infection rates were 8.5% and 26.5% respectively for those with (n=47) and without (n=49) intraoperative repeated dosing, which were significantly different based on both a univariate (p=0.031) and a multivariate analysis (p=0.008).[143]

Zanetti et al. retrospectively compared the risk of SSIs in 1,548 patients who underwent cardiac surgery lasting >240 minutes after preoperative administration of cefazolin prophylaxis. The overall risk of SSI was similar among patients with (43 (9.4%) of 459) and without (101 (9.3%) of 1089) intraoperative redosing (OR 1.01, 95% CI 0.7-1.47). However, redosing was beneficial in procedures lasting >400 minutes; infection occurred in 14 (7.7%) of 182 patients with redosing and in 32 (16.0%) of 200 patients without (adjusted OR 0.44, 95% CI 0.23-0.86). Intraoperative redosing of cefazolin was associated with a 16% reduction in the overall risk for SSI after cardiac surgery, including procedures lasting >240min.[74,75]

Blood Loss: Swoboda et al. attempted to determine the effect of intraoperative blood loss on prophylactic cefazolin and gentamicin serum and tissue concentration in a prospective study of elective spinal surgical procedures with expected large blood loss. At 60 minutes after the incision, blood loss correlated with cefazolin tissue concentrations (r=-0.66, p=0.05) and the clearance of gentamicin from the tissues (r=0.82, p=0.01). Based on their measured pharmacokinetic values, additional doses of cefazolin should be administered when the operation exceeds 3 hours and blood loss is greater than 1500mL. A dose of gentamicin greater than 1.8mg/kg should be administered more than 30 minutes prior to the surgical incision.[144]

Blood Loss/Volume Replacement: Markantonis et al. investigated the effects of surgical blood loss and fluid volume replacement on gentamicin concentrations in serum and in 3 tissue types (subcutaneous fat, epiploic fat, and colonic wall) in patients in undergoing colorectal surgery. Gentamicin was administered at a standard dose of 2 mg/kg and blood and tissue samples were obtained concurrently at specific times throughout each procedure. The mean concentration at first surgical incision was 7.83 (0.82) µg/mL and decreased to 2.60 (0.28) µ/mL at skin closure, resulting in borderline effectiveness even for susceptible gram-negative microorganisms (MIC-1.0). A strong negative correlation was found between the intravenously-administered fluids and gentamicin concentrations in serum and tissues (p≤0.04).[145]

Klekamp et al. prospectively studied orthopaedic patients with either large or small blood loss who also received vancomycin prophylaxis to determine the effect of intraoperative volume shifts on serum vancomycin concentrations. There were 6 index patients in the large blood loss group (greater than 2L) and 7 in the control group (less than 2L), with mean estimated blood loss for index and controls was 4.4L and 1.0L; and the mean intraoperative fluid resuscitation, excluding blood products, was 12.4L and 5.1L respectively. There was a modest inverse correlation between blood loss and the intraoperative serum half-life of vancomycin. Although controls maintained slightly higher intraoperative vancomycin concentrations at each time point, there was no statistically significant difference between the groups with regard to absolute concentrations or rate of decline. After 8 hours, the serum concentration of vancomycin exceeded the MIC-90 for *S. aureus* by approximately eightfold in all but one case patient, who was morbidly obese and had massive blood loss. Thus blood loss during orthopaedic procedures has a minimal effect on the intraoperative kinetics of vancomycin and administering vancomycin every 8 to 12 hours seems appropriate for most patients.[146]

Two well-controlled studies of surgical prophylaxis with cefazolin similarly demonstrated minimal effects of blood loss on drug concentrations during THA and spine fusion procedures. Meter et al. examined the effect of intraoperative blood loss and volume resuscitation during THA on serum levels of cefazolin in 18 patients. At 4 hours after administration, the serum level of cefazolin was 45 mcg/mL, which far exceeded the MIC for *S. aureus* (0.5mcg/mL), despite an average intraoperative blood loss of 1137±-436 mL. This led the authors to conclude that even with blood losses of 2L, it is not necessary to redose cefazolin any earlier than 4 hours in order to maintain the MIC for most common infecting organisms.[147] The authors repeated the study in 19 patients undergoing instrumented posterior spinal fusion and found that there was no significant difference between preoperative and intraoperative cefazolin clearance and there was no correlation between blood loss and cefazolin level.[148]

Question 16: Should preoperative antibiotic doses be weight-adjusted?

Consensus: Preoperative antibiotics have different pharmacokinetics based on patient weight and should be weight-adjusted.

Delegate Vote: Agree: 95%, Disagree: 4%, Abstain: 1% (Strong Consensus)

Justification: Because of the relative unpredictability of pharmacokinetics in obese individuals, doses are best estimated on the basis of specific studies for individual drugs carried out in this population. Only a few antibiotics (aminoglycosides, vancomycin, daptomycin, and linezolid) have been studied in the obese population.

AAOS recommendation for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, states that "timing and dosage of antibiotic administration should optimize the efficacy of the therapy. Dose amount should be proportional to patient weight; for patients >80 kg, the doses of cefazolin should be doubled."[2]

The recommended dose of cefazolin is based on patient's body mass index (BMI), with 1.0g for people who weigh <80 kg and 2.0g for those who weigh >80 kg. The adult dose of cefuroxime is 1.5g. The recommended dose of clindamycin is 600 to 900mg.[61] The recommended dose of vancomycin, which is based on BMI, is 10-15mg/kg, up to a limit of 1g, in patients with normal renal function.[149] However, there is literature to support the use of higher doses of vancomycin, with emphasis that doses >4g/day have been associated with increased risk of nephrotoxicity. A trough level is obtained prior to the fourth scheduled dose and in certain occasions there may be a need to shorten dosing interval to maintain therapeutic trough level (eg q12h to q8h dosing).

Because 30% of adipose is water, an empirical approach is to use the Devine formula to calculate ideal body weight (IBW), to which is added a dosing weight correction factor (DWCF) of 0.3 times the difference between actual body weight (ABW) and IBW (IBW + 0.3 x [ABW-IBW]) to arrive at a weight on which to base dosage of hydrophilic antibiotics. No studies confirm this approach for β-lactam drugs. Clinical studies suggest a DWCF of 0.4 for aminoglycosides and 0.45 for quinolones.[150]

For aminoglycosides, some suggest using ABW using a dosing correction factor,[151,153] while others suggest dosing based on lean body weight (LBW) with appropriate monitoring with the first dose.[152] Current guidelines for vancomycin administration are based on loading doses of vancomycin on the total body weight (TBW) of the patient and maintenance doses on the calculated creatinine clearance (CrCl) of the patient.[153,154] However, deciding whether to base CrCl calculations on ABW, IBW, or another measure is still to be determined. As a general rule, obese and morbidly obese patients require higher doses of cephalosporin to achieve similar

outcomes; however, there are fewer absolute dosing recommendations. At least one study demonstrated that a dose of 2g of cephazolin should provide adequate levels for at least 4 hours, even in super morbid obesity (MO) (BMI ≥ 50kg/m2).[155]

Other studies confirm that vancomycin should be given on the basis of ABW, with dosage adjustments based on serum concentrations[156] whereas aminoglycoside dosing requires calculation of adjusted body weight via a correction factor.[157]

Forse et al. conducted a prospective RCT in MO patients undergoing gastroplasty and found that the blood and tissue levels of cefazolin were significantly lower for all MO patients who received 1g cefazolin compared with the blood and tissue levels of the drug found in normal weight patients who received a similar dose of antibiotic. Moreover, the MO patients who only received 1g of cefazolin had antibiotic levels below the MIC of 2mcg/mL for gram-positive cocci and 4mcg/mL for gram-negative rods. The serum and tissue concentrations were adequate only when 2g of cefazolin were administered. Also, relative to 1g, the administration of cefazolin 2g decreased the wound infection rate from 16.5 to 5.6% in these MO patients.[18]

Van Kralingen et al. studied the influence of body weight measures and age on pharmacokinetic parameters and evaluated unbound cefazolin concentrations over time in obese patients. Twenty MO patients (BMI 38-79 kg/m^2) were studied following the administration of 2g of cefazolin at induction of anesthesia. Blood samples were collected up to 4 hours post dosing to determine the total and unbound plasma cefazolin concentrations. Cefazolin clearance was 4.2±1.0 L /h (mean ± standard deviation) and showed a negative correlation with age ($p=0.003$) but not with body weight measures ($p>0.05$). In all patients, unbound cefazolin concentrations remained above 1mg/L (MIC 90) of MSSA until 4 hours post dosing.[158]

Ho et al. attempted to determine an optimal dosing regimen for cefazolin as a prophylactic antibiotic in surgery for patients with MO. Twenty-five patients undergoing elective surgical procedures were given a single dose of cefazolin: 10 with MO (BMI 40-50 kg/m2) received 2g via intravenous push (IVP), 5 with MO received 2g via 30 minute infusion, 5 with super morbid obesity (SMO, BMI >50 kg/m^2) received 2g via infusion, and 5 with SMO received 3g via infusion. The protective duration, determined using a pharmacodynamic target for fT>MIC of 70%, was 5.1 hours for MO2-IVP, 4.8 hours for MO2-INF, 5.8 hours for SMO2-INF, and 6.8 hours for SMO3-INF. The authors concluded that a single 2g dose of cefazolin appears to provide antibiotic exposure sufficient for most common general surgical procedures of <5 hr duration regardless of BMI.[155]

In contrast, Edmiston et al. concluded that 2g of cefazolin may not be sufficient for patients with a BMI >50 kg/m^2, based upon measurements of total serum concentrations in morbidly obese patients undergoing gastric bypass. The authors assigned 38 patients to one of 3 BMI groups: A) BMI=40-49 kg/m^2 (n=17), B) BMI=50-59 kg/m^2 (n=11), and C) BMI>=60 kg/m^2 (n=10) and measured serum and tissue concentrations of cefazolin. They determined that therapeutic tissue levels were only achieved in 48.1%, 28.6%, and 10.2%% in groups A, B, and C respectively. The authors measured concentrations in the serum skin, adipose tissue, and omentum, but did not evaluate unbound cefazolin concentrations, which may be expected to migrate across tissues rapidly.[159]

Table: Recommended dosing of preoperative antibiotics by weight:

Antimicrobial	**Actual Body Weight (ABW; kg)**	**Recommended Dose (mg)**	**Perioperative Redosing Schedule**	**Indication**
Cefazolin	< 60	1000	every 4 hours	Primary Perioperative Prophylaxis
	60-120	2000	every 4 hours	
	> 120	3000	every 4 hours	
Cefuroxime	No adjustments	1500	every 4 hours	Primary Perioperative Prophylaxis
Vancomycin	Weight based dosing recommended	15 mg/kg (Maximum dose 2000 mg)	one dose pre-op, one dose 12 hours post-op, one dose 24 hours post-op	Perioperative Prophylaxis for current MRSA carriers and/or patients with β-lactam allergy
Clindamycin	No adjustments	900	every 3 hours	Perioperative Prophylaxis for patients with β-lactam allergy

Teicoplanin	No adjustments	400	NA	Perioperative Prophylaxis for current MRSA carriers and/or patients with β-lactam allergy

Question 17A: What type of perioperative antibiotic prophylaxis is recommended for current MRSA carriers?

Consensus: For current MRSA carriers, vancomycin or teicoplanin is the recommended perioperative antibiotic prophylaxis.

Delegate Vote: Agree: 86%, Disagree: 12%, Abstain: 2%(Strong Consensus)

Question 17B: Should patients with prior history of MRSA be re-screened? What should the choice of perioperative prophylactic antibiotics be in these patients?

Consensus: Patients with prior history of MRSA should be re-screened preoperatively. If patients are found to be negative for MRSA, we recommend routine perioperative antibiotic prophylaxis.

Delegate Vote: Agree: 76%, Disagree: 23%, Abstain: 1% (Strong Consensus)

Justification: Implementation of a MRSA prevention program may significantly reduce MRSA SSIs. However, it is unlikely that any single MRSA-specific intervention (such as adding or switching to vancomycin) can optimally prevent SSIs. Several studies provide convincing data on the clinical effectiveness of vancomycin in preventing SSIs when MRSA prevalence is high.[69,70,79] Further research is needed to determine which components of a MRSA prevention program are essential in successfully preventing MRSA SSIs.[160] It is uncertain whether

decontamination should alter the type of antibiotic prophylaxis, as few studies have retested patients' MRSA status immediately prior to surgery.

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, states that "vancomycin may be used in patients with known colonization with MRSA or in facilities with recent MRSA outbreaks."[1] Additionally, the Society for Healthcare Epidemiology of America recently recommended routine surveillance cultures at the time of admission to the hospital for patients at high risk of MRSA.[52]

Walsh et al. implemented a comprehensive MRSA program in which vancomycin was added to the routine cefazolin prophylaxis regimen for patients who tested positive for nasal MRSA carriage. Other components of the program included decolonization of all cardiothoracic staff who screened positive for nasal MRSA carriage, application of nasal mupirocin ointment for 5 days in all patients starting one day before surgery, application of topical mupirocin to exit sites after removal of chest and mediastinal tubes, and rescreening of patients for MRSA colonization at the time of hospital discharge. This program resulted in a significant reduction in the SSI rate (2.1% vs 0.8%, $p<0.001$) as well as a 93% reduction in postoperative MRSA wound infections (from 32 infections/2,767 procedures during the 3 year pre-intervention period to 2 infections/2,496 procedures during the 3 year postintervention period). The data suggest that a bundled approach to preventing MRSA SSIs may be more critical than a single intervention.[79]

Pofahl et al. published on the impact of introducing MRSA screening programs and treatment of subsequent MRSA SSIs. After a MRSA surveillance program was instituted, the rate of MRSA SSI decreased from 0.23% to 0.09%, with the most pronounced reduction seen in TJA procedures (0.30% to 0%, $p=0.04$). However, the authors note that changes in perioperative antibiotics in MRSA-positive patients was at the discretion of the attending surgeon.[161]

Question 18: What is the recommended prophylaxis in patients undergoing major orthopaedic reconstructions for either tumor or non-neoplastic conditions using megaprosthesis?

Consensus: Until the emergence of further evidence, we recommend the use of routine antibiotic prophylaxis for patients undergoing major reconstruction.

Delegate Vote: Agree: 93%, Disagree: 6%, Abstain: 1% (Strong Consensus)

Justification: Deep infection has been reported as being one of the most common complications following endoprosthetic replacement of large bone defects, ranging between 5%-35% in some series.[162-166] Reinfection rates after revision surgery for endoprosthetic infection have been reported as high as 43%.[165] Despite this there is insufficient evidence to suggest that a different perioperative antibiotic regimen is warranted. Recently a multicenter, blinded, randomized, controlled trial, using a parallel two-arm design has been set up that will evaluate 920 patients from Canada and the USA who are undergoing surgical excision and endoprosthetic reconstruction of a primary bone tumour. The patients will receive either short (24 h) or long (5 days) duration postoperative antibiotics. The primary outcome will be rates of deep postoperative infections in each arm. Secondary outcomes will include type and frequency of antibiotic-related adverse events, patient functional outcomes and quality-of-life scores, reoperation and mortality.[167]

Another area of development involves silver coating of foreign materials, such as heart valves, cardiac catheters, and urinary catheters, that has shown the ability to reduce the infection rate of medical devices; therefore, a logical extension of this work was to translate this concept to the field of endoprosthetics.[168,169] Both basic science and clinical research suggests a decreased incidence of SSI and PJI in endoprostheses coated with silver. Recently iodine-supported titanium implants have been also effective for preventing and treating infections after major orthopaedic surgery.[170,171]

In a rabbit study, the infection rate of silver-coated versus noncoated prostheses after inoculation with *Staphylococcus aureus* was determined and the silver concentrations in blood, urine, and organs with possible toxic side effects were documented. The authors convincingly demonstrated that megaprostheses coated with silver showed a significantly lower infection rate (7% vs 47%, $p<0.05$) in comparison with a titanium group.[173] Furthermore, measurements of C-reactive protein, neutrophilic leukocytes, rectal temperature, and body weight showed significantly lower ($p<0.05$) signs of inflammation in the silver group. In a second study, authors analyzed the potential toxicological side effects of these implants and found that the silver concentration in blood (median 1.883 parts per billion (PPB)) and in organs (0.798-86.002 PPB) showed elevated silver concentrations, without pathologic changes in laboratory parameters and without histologic changes of organs.[172]

In a prospective observational study, Hardes et al. compared the infection rate in 51 patients with sarcoma (proximal femur, n=22; proximal tibia, n=29) who underwent placement of a silver-coated megaprosthesis to 74 patients (proximal femur, n=33; proximal tibia, n=41) in whom an uncoated titanium megaprostheses was used. The authors reported a substantial reduction in the infection rate from 17.6% in the titanium group compared to 5.9% in the silver group (p=0.06). Furthermore, while 38.5% of patients ultimately underwent amputation when PJI developed, this was not necessary in any case in the study group. However, the authors note that the operating time required for the proximal tibia replacement was significantly shorter in the silver-coated prosthesis group (p=0.034) and that prolonged operating time was associated with a higher rate of PJI (p=0.025).

The same group reported a lack of toxicological side effects of silver-coated megaprostheses in 20 patients with bone metastases.[173] They reported that silver levels in the blood did not exceed 56.4 PPB and can be considered non-toxic. They further excluded significant changes in liver and kidney function based on laboratory values; and histopathologic examination of the periprosthetic environment in two patients showed no signs of foreign body granulomas or chronic inflammation, despite effective silver concentrations up to 1,626 PPB directly related to the prosthetic surface.[173]

Tsuchiya et al reported that iodine-supported implants were used to prevent infection in 257 patients with compromised status. Acute infection developed only in 3 tumor cases and one diabetic foot among the 257 patients. Abnormalities of thyroid gland function were not detected. None of the patients experienced loosening of the implant. Excellent bone ingrowth was found around all hip and tumor prostheses. The results indicate that iodine-supported titanium has favorable antibacterial activity, biocompatibility, and no cytotoxicity.[170]

Gosheger reviewed 197 patients with megaprostheses and discovered that those with cobalt chrome implants had more infections than those with titanium implants.[176] Reviewing 197 patients (77 patients with a cobalt chrome alloy system and 120 patients with a titanium alloy system) who underwent lower extremity reconstruction with a megaprosthesis, the authors reported a 31.2% infection rate in the cobalt chrome group compared to 14.2% in the titanium group ($p<0.01$). When they performed a secondary analysis matching two identical subgroups, the cobalt chrome group was still associated with a significantly higher infection rate, with 5 infections of 26 megaprostheses vs one infection of 36 titanium megaprostheses ($p<0.05$).[174]

Question 19: Should antibiotic prophylaxis be different in patients who have reconstruction by bulk allograft?

Consensus: We recommend the use of routine antibiotic prophylaxis in patients who have reconstruction by bulk allograft.

Delegate Vote: Agree: 93%, Disagree: 5%, Abstain: 2% (Strong Consensus)

Justification: The periprosthetic area is inherently a locus minoris resistance. Bulk allograft is in essence is a large foreign body and therefore represents a nidus for deep infection following surgery, apart from the prosthetic components. Additionally, bulk allografts are used most often in the setting of revision arthroplasty when there is frequently additional local soft tissue and vascular compromise, which compounds the risk for infection. Therefore, it would seem reasonable to want to modify the perioperative antibiotic protocol to protect these reconstructions. Unfortunately, there is insufficient literature to support altering antibiotic regimens, as most studies on the use of bulk allograft do not indicate or detail the antibiotic regimens utilized. Even if this data were available, it would not be accurate to properly compare the infection rates of different clinical series based on their perioperative antibiotic protocols because of the heterogeneity of patient populations. However, there is a growing body of literature to support the use of antibiotic-impregnated allograft in the revision setting as a means of decreasing infection rates. In addition, there are several reports of using antibiotic-impregnated graft substitute or grafts as a way to fill bony defects and promote bony ingrowth while delivering supratherapeutic doses of antibiotics to the local environment in cases of osteomyelitis. While there is no current literature applying this technology to the use of bone defects in infected revision arthroplasty, it may be a promising technique.

Witso et al. used netilmicin-impregnated allografts for reconstruction in revision hip and knee surgery and found no adverse effects.[175] Buttaro et al. favorably used vancomycin-supplemented cancellous grafts for reconstruction after infected THA [176,177] Michalak et al. and Khoo et al. impregnated segmental allografts with gentamicin and flucloxacillin respectively.[178,179] However, all these groups used antibiotic impregnated grafts only in the second stage of a two-stage revision, after resolution of clinical and laboratory evidence of infection.

Winkler et al. performed 37 one-stage uncemented revision THAs using cancellous allograft bone impregnated with antibiotics and noted a 92% success rate, defined as recurrent infection at a mean follow-up of 4.4 years (range 2-8 years). In addition, no adverse effects were seen and the incorporation of bone graft was comparable to unimpregnated grafts.[180]

In a similar series, Buttaro analyzed the incidence of infection after one-stage aseptic revision hip reconstruction using acetabular and/or femoral vancomycin-impregnated impacted bone allograft and a THA fixed with cement containing no antibiotic. In 75 consecutive patients (80 hips), followed for a mean of 36 months (range 24-59 months), deep infection occurred in one patient for an incidence of infection of 1.25%, which occurred 2 years after the index procedure and was thought to be hematogenous in origin.[181]

Cancellous bone allograft can store and release high initial local amounts of vancomycin without compromising incorporation of the graft, and some favorable results have been published following two-stage revision of infected THA with this technique.[176,177,182-184]

Question 20: Do patients with poorly controlled diabetes, immunosuppression, or autoimmune disease require a different perioperative antibiotic prophylaxis?

Consensus: No. Routine antibiotic prophylaxis is recommended in these patients.

Delegate Vote: Agree: 90%, Disagree: 9%, Abstain: 1% (Strong Consensus)

Justification: Several studies have demonstrated that diabetes mellitus (DM), especially uncontrolled DM, is a risk factor for postoperative infection in THA and TKA.[185-188] A recent retrospective cohort study within the Kaiser Healthcare system found no significant increase in risk of revision or deep infection or revision whether patients had controlled (HbA1c<7%) or uncontrolled diabetes (HbA1c>7%). Specifically, compared with patients without DM, there was no association between controlled DM and risk of revision (OR 1.32; 95% CI 0.99-1.76). Similarly, compared to patients without DM, there was no association between uncontrolled DM and risk of revision (OR 1.03; 95% CI 0.68-1.54).[189]

Obesity has also been associated with a significant increase in rate of postoperative infection following TJA.[190-192]

Human immunodeficiency virus (HIV) has also been associated with an alarming rate of postoperative complications, including infection. Parvizi et al. reported on 6 deep infections in 21 HIV-positive patients undergoing TJA. The authors remarked that the immune status of the patients was related to their risk of deep PJI, in that 5 of the 6 patients ultimately developed Acquired Immune Deficiency Syndrome (AIDS) and the CD4 count was significantly lower at 239±112μL at latest follow-up for patients who developed infection compared to 523±171μL for the study population as a whole ($p<0.001$). In this study the authors reported using prophylactic antibiotics (cephalosporins) preoperatively and 3 doses postoperatively and added antibiotic powder (vancomycin and tobramycin) to the cement in 2 patients thought to be at high risk for infection.[193]

Similarly, Ragni et al. found a very high postoperative infection rate (26.5%) in 34 TJA in HIV-positive hemophiliacs, all of whom had CD4 counts less than 200/μL at time of surgery.[194] Haberman et al. noted an infection rate of 12.7% in their cohort of 41 patients with HIV undergoing TJA, but did not identify any difference in the outcomes relating to CD4 count.[195] Their perioperative antibiotic protocol was a 5 day course of cefuroxime and in all procedures antibiotic-containing cement (Palacos R, Zimmer, Warsaw, IN) was used. In a smaller series of 6 HIV-infected patients undergoing TJA, Wang et al. noted no infectious or other complications. The authors again used antibiotic (vancomycin)-impregnated bone cement in all cemented cases.[196] Unger et al. evaluated the results of 26 TKAs in HIV-positive hemophiliacs and found no cases of deep infection, but it is interesting to note that the average CD4 count of these patients was 463μL.[197]

Hemophilia has historically been considered a risk factor for PJI, due in part to its relation to HIV and AIDS, but also as an independent risk factor. An article by Silva et al. reviewed the long-term results of primary TKA in patients with hemophilia and noted an overall prevalence of PJI of 16% with a rate of infection in HIV-positive and HIV-negative patients of 17% and 13% respectively ($p=0.5$). The authors' perioperative protocol included 3 to 5 days of prophylactic antibiotics and antibiotic cement was not used.[198] In contrast, Rodriguez-Marchan reported an infection rate of only 3% of 35 TJA in hemophiliac patients, but used antibiotic-laden bone cement and 2 days of perioperative antibiotic prophylaxis.[199]

Asplenic patients are at increased risk of infection by encapsulated bacteria; and although there is evidence to support vaccinations and penicillin prophylaxis in patients under 16 and over 50 years of age, there is no consensus on the appropriate perioperative management of these immunocompromised patients. In a single case report by Shaarani et al. of an asplenic patient who underwent a TKA, the patient ultimately developed a MRSA infection. In this case standard polymethylmethacrylate (PMMA) was used for cementing components and the patient received intravenous prophylactic dose of second generation cephalosporin preoperatively.[200]

Renal disease (including renal failure, dialysis dependence, and renal transplant) has been implicated as increasing the risk of PJI. McCleery et al. analyzed the Scottish Arthroplasty Registry in order to determine the rates of PJI in patients with renal failure, those undergoing dialysis, and those with a renal transplant. They found that patients with renal failure had a significantly increased risk of early infection (1.6%, RR 1.52, p=0.02) and late infection (4.47%, RR 2.2, p<0.001). Patients on dialysis had a significantly increased risk of late infection (8.0%, RR 3.99, p<0.001) and early revision (3.7%, RR 4.4, p<0.001). Renal transplant patients had a significantly increased risk of late infection, despite whether the transplantation occurred before TKA (9.1%, RR 4.5, p=0.03) or at any time (8.0%, RR 4.0, p=0.05).[201] Lieberman et al. documented a deep infection rate of 19% in 16 chronic renal dialysis patients and more favorable outcomes in renal transplant patients.[202] Sakalkale et al. reported a deep infection rate of 13% in 12 patients with end-stage renal failure on dialysis who underwent THA. In this study, perioperative prophylactic antibiotics were administered for 2 to 5 days.[203] In contrast, other authors have reported no increased rate of infection in patients on chronic hemodialysis undergoing THA.[204,205]

Similarly, liver disease has been associated with increased morbidity following TJA. Pour et al. performed a case control study of 71 non-cirrhotic patients with hepatitis C undergoing TJA and found that this cohort had higher rates of wound drainage following THA when compared to matched controls (15 vs 3.8%, p=0.03).[206] Orozco et al. recently published a case control study to analyze the effect of fibrosis and thrombocytopenia on the diagnosis of hepatitis C and clinical outcomes. Analyzing 72 patients (77 joint replacements), the authors found that fibrotic hepatitis C patients had higher deep infection rates (21% vs 0%, p =0.047) and rates of cellulitis (21% vs 0%, p =0.047), while thromobocytopenia showed a trend towards greater infection.[207]

Solid organ transplant (SOT) is a risk factor for PJI due to the need for chronic use of immunosuppressant medications. Vergidis et al. performed a case control study of patients with

SOT who developed PJI and compared them to non-infected controls matched by transplant type, prosthetic joint type, and order of organ transplantation or joint implantation. Of 367 patients with both a joint replacement and SOT, there were 12 cases of PJI, of which 8 were renal transplants, 3 were liver transplants, and 1 was a heart transplant patient. Eight infections were caused by gram-positive organisms, 2 were caused by nontuberculous mycobacteria, and the remaining 2 were culture-negative. Of note, patients received perioperative cefazolin, or in cases of colonization or prior infection with MRSA, vancomycin.[208] Tannenbaum et al. reported results on 35 TJA in 19 patients with renal or liver transplant and documented an infection in 5 patients who had the joint replacement after the transplantation. There were no infections in patients who had TJA before the organ transplantation. In this series, prophylactic antibiotics were administered for at least 48 hours or until the drains were removed and bone cement when used was not impregnated with antibiotics.[209]

Question 21A: Should preoperative antibiotics be different for primary and revision TJA?

Consensus: No. Perioperative antibiotic prophylaxis should be the same for primary and uninfected revision arthroplasty.

Delegate Vote: Agree: 89%, Disagree: 10%, Abstain: 1% (Strong Consensus)

Question 21B: Should preoperative antibiotics be different for hips and knees?

Consensus: Perioperative antibiotic prophylaxis should be the same for hips and knees.

Delegate Vote: Agree: 99%, Disagree: 1%, Abstain: 0% (Strong Consensus)

Justification: Patients undergoing revision TJA are at higher risk of developing PJI than primary arthroplasty and those undergoing revision knee procedures are at even highest risk.[210-212] One recent study has effectively demonstrated targeting infection prevention programs at high-risk surgical patients that take into account an institution's local epidemiology and antibiogram.[213]

Liu et al. determined the impact of adding vancomycin to cefazolin as antimicrobial prophylaxis in 414 patients undergoing revision TKA based on a notable increase in PJI in revision TKA patients, with many being methicillin-resistant. Following introduction of vancomycin to the routine preoperative antibiotic prophylaxis, the infection rate decreased from 7.89% to 3.13% (p=0.046). In particular, a significant reduction in PJI resulting from methicillin-resistant organisms over this time period was seen (4.2% to 0.9%, p=0.049).[219]

Question 22: What is the best antibiotic prophylaxis to choose in patients with colonization by carbapenem resistant enterobacteriaceae or multi-drug resistant (MDR)-Acinetobacter spp?

Consensus: There is insufficient data to recommend expanded antibiotic prophylaxis in patients known to be colonized or recently infected with MDR pathogens.

Delegate Vote: Agree: 76%, Disagree: 8%, Abstain: 16% (Strong Consensus)

Justification: There is an increasing awareness of the threat posed by *K. pneumoniae* strains with decreased susceptibility to carbapenems worldwide.[214] This resistance is conferred by *K. pneumo carbapemenase* (KPC), which is a β-lactamase that also confers resistance to broad-spectrum cephalosporins, as well as commercially available β–lactam/β-lactamase inhibitor combinations.[215] As there are few antimicrobial options, prevention of *K. pneumo carbapemenase K. pneumoniae* (KPC-KP) has become a major priority of those studying nosocomial infections.[216]

While there is no evidence on the management of surgical antimicrobial prophylaxis in a patient with past infection or colonization with a resistant gram-negative pathogen, it is logical to provide prophylaxis with an agent active against MRSA for any patient known to be colonized with this gram-positive pathogen who will have a skin incision; specifically, prophylaxis for a resistant gram-negative pathogen in a patient with past infection or colonization with such a pathogen may not be necessary for a purely cutaneous procedure.

In a literature review, KPC-producing microbes are resistant to many non-β-lactam molecules. Most isolates are resistant to fluoroquinolones, aminoglycosides, and co-trimoxazole. Some

isolates are susceptible to amikacin and gentamicin and most are susceptible to colistin and tigecycline.[214,217-219]

In a prospective RCT, De Smet et al. studied the elimination of colonization with MDR organisms using selective oropharynegeal and/or digestive tract decontamination (SOD/SDD) in a multicenter crossover study using cluster randomization of 5,939 intensive care unit patients in the Netherlands. SOD included 4 days of intravenous cefotaxime and topical application of tobramycin, colistin, and amphotericin B in the oropharynx and stomach. SDD consisted of oropharyngeal application only of the same antimicrobials. Using a random effects logistic regression analysis, the OR for death at day 28 in the SOD and SDD group, as compared with the standard care group, were 0.86 (95% CI 0.74-0.99) and 0.83 (95% CI 0.72-0.97) respectively.[220]

Perez et al. used a mouse model to examine the effect of antibiotic treatment on the establishment and elimination of intestinal colonization of KPC-KP. They administered 3 days of antibiotics (clindamycin, zosyn, tigecycline, ertapenem, cefepime, and ciprofloxacin) before KPC-KP was administered orogastrically. The authors reported that of the 4 antibiotics with minimal activity against the KPC-KP strain (MIC >16mcg/mL), those that suppressed total anaerobes and Bacteroides (ie clindamycin and zosyn) promoted colonization by KPC-KP ($p<0.001$), while agents that did not suppress total anaerobes and bacteroides (ie ciprofloxacin and cefepime) did not ($p=0.35$). Of the antibiotics with moderate activity against KPC-KP, ertapenem (MIC 4mcg/mL) did not promote colonization by KPC-KP, while tigecycline (MIC 3mcg/mL) did ($p<0.001$), despite not reducing levels of total anaerobes and bacteroides. Orgogastric administration of gentamicin and polmyxin E-suppressed KPC-KP was at undetectable levels in the majority of mice. The authors posited that antibiotics that disturb the intestinal anaerobic microflora lack significant activity against KPC-KP promote colonization, while the administration of non-absorbed oral antibiotics may be an effective strategy to suppress colonization with this microorganism.[221]

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Workgroup 4: Operative Environment

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Question 1: Do numbers of bacteria arriving in the surgical wound correlate directly with the probability of surgical site infection (SSI)?

Consensus: We recognize that the probability of SSI correlates directly with the quantity of bacteria that reach the wound. Accordingly we support strategies to lower particulate and bacterial counts at surgical wounds.

Delegate Vote: Agree: 97%, Disagree: 2%, Abstain: 1% (Strong Consensus)

Justification: Postoperative SSIs are believed to occur via bacterial inoculation at the time of surgery or as a result of bacterial contamination of the wound via open pathways to the deep tissue layers.[1-3] The probability of SSI is reflected by interaction of parameters that can be categorized into three major groups.[2] The first group consists of factors related to the ability of bacteria to cause infection and include initial inoculation load and genetically determined virulence factors that are required for adherence, reproduction, toxin production, and bypassing host defense mechanisms. The second group involves those factors related to the defense capacity of the host including local and systemic defense mechanisms. The last group contains environmental determinants of exposure such as size, time, and location of the surgical wound that can provide an opportunity for the bacteria to enter the surgical wound, overcome the local defense system, sustain their presence, and replicate and initiate local as well as systemic inflammatory reactions of the host.

The use of iodine impregnated skin incise drapes shows decreased skin bacterial counts but no correlation has been established with SSI. However, no recommendations regarding the use of skin barriers can be made (See Workgroup 4 Question 27).

Question 2: Do numbers of bacteria in the operating room (OR) environment correlate directly with the probability of SSI?

Consensus: We recognize that airborne particulate bacteria are a major source of contamination in the OR environment and that bacteria shed by personnel are the predominant

source of these particles. The focus of our recommendations is to reduce the volume of bacteria in the OR with particular attention to airborne particles.

Delegate Vote: Agree: 93%, Disagree: 5%, Abstain: 2% (Strong Consensus)

Justification: Air is a potential source of contamination in the OR.[2, 4] Studies have demonstrated that the number of airborne bacteria around the wound is correlated to the incidence of periprosthetic joint infection (PJI).[1] It has been suggested that if it was possible to measure accurately the number of bacteria present in the wound it should constitute the most precise predictor of subsequent infection.[5] Bacteria can be considered as part of the total mass of particulates in the air. Some studies have suggested that the airborne particulate count should be considered as potential surrogate for airborne microbial density.[6] Others have found a correlation between the number of particulates larger than 10 micrometers with the density of viable bacteria at the site of surgery (measured by colony forming units).[7] It has been suggested that monitoring particulate count be used as a real-time proxy for increased risk of wound contamination or infection.[7] Persons in the OR are a major source of bacterial load and shed bacterial particulates. These particulates circulate through the OR via air currents. Movements of personnel and objects (including OR equipment) and opening and closing doors can generate significantly marked air currents and increase the probability of bacteria being deposited in the surgical site.[3, 8]

Question 3: Should the OR in which an elective arthroplasty is performed be fitted with laminar air flow (LAF)?

Consensus: We believe that arthroplasty surgery may be performed in operating theaters without laminar flow. Laminar flow rooms and other strategies that may reduce particulates in operating rooms would be expected to reduce particulate load. Studies have not shown lower SSI in laminar flow rooms and some cases are associated with increased rates of SSI. These are complex technologies that must function in strict adherence to maintenance protocols. We recommend further investigation in this field.

Delegate Vote: Agree: 85%, Disagree: 7%, Abstain: 8% (Strong Consensus)

Justification: The most cited studies supporting the use of LAF were conducted in the 1970s and 1980s by Charnley and Lidwell et al.[9, 10] However, several recent studies have shown no clear benefit of LAF in reducing the incidence of deep SSI.[11-14] Breier et al. conducted a nationwide study in Germany, controlling for confounding factors with multivariate analysis, and found no independent effect of LAF on SSI rates, even when considering LAF rooms with large ceiling sizes (at least 3.2m x 3.2m).[11]

A recent study by Hooper et al. that was based on the New Zealand joint registry evaluated the subject on a wide basis.[13] The authors analyzed 51,485 total hip arthroplasties (THA) and 36,826 total knee arthroplasties (TKA) and revealed increased early infection rates with laminar flow use, especially for THA patients. This increase was found to be independent of patient characteristics, operative time, surgeon, or institution. Unfortunately, except for the study performed by Salvati et al. in which horizontal LAF was found to increase the risk of PJI in TKA, other studies, including those supporting the use of LAF,[10] those opposing its use,[13] and those with indifferent results,[15-17] did not conduct any sub-analysis to distinguish influence of different types of LAF on PJI.

Question 4: Is there enough evidence to enforce the universal use of body exhaust suits during total joint arthroplasty (TJA)?

Consensus: There is currently no conclusive evidence to support the routine use of space suits in performing TJA.

Delegate Vote: Agree: 84%, Disagree: 11%, Abstain: 5% (Strong Consensus)

Justification: Similar to the situation with laminar flow, the use of space suits during TJA has become a subject of controversy. A recent study by Miner et al. showed no benefit in the use of body exhaust suits[14] and a study by Hooper et al. evaluating the use of a space suit and its effect on early infection rates identified an increased rate of early infection with the use of space

suits both in conventional and in laminar flow theaters.[13] However, there is some suggestion that space suits should be worn in laminar flow-fitted rooms to prevent contamination.[18, 19]

Question 5: What strategies should be implemented regarding OR traffic?

Consensus: We recommend that OR traffic should be kept to a minimum.

Delegate Vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification: Personnel are the major source of air contamination in the OR, both by traffic that creates turbulence and contaminates ultraclean air and by bacterial shedding. Ritter et al. showed that bacterial counts in OR air increased 34-fold in an operating room with 5 people compared to an empty room.[17] Keeping the OR door open also significantly increased bacterial air contamination of the room in the same study. Andersson et al. showed a positive correlation between traffic flow rates and air bacterial counts in orthopaedic procedures.[15] They also identified a direct correlation between the number of people present in the OR and bacterial counts. Quraishi et al. further demonstrated a direct correlation between the activity level of OR personnel and bacterial fallout into the sterile field. [20] Panahi et al. observed door openings during primary and revision TJA cases.[21] They identified 0.65 and 0.84 door openings per minute in primary and revision cases, respectively. The main personnel responsible for door openings were implant technical representatives and circulating nurses. Lynch et al. showed an exponential relationship between the number of door openings and the number of personnel in the OR. In their series, information requests (an easily avoidable cause) was the reason for the majority of door openings.[22] Multiple door openings can result in a drop in the pressure gradient requiring more air being pumped through LAF systems and therefore the high efficiency particulate air filters are consumed more quickly. It has been proposed by experts that OR personnel pass through a sub-sterile hallway every time they enter or leave the OR, although evidence regarding this practice is lacking. If preoperative templating is possible, available sizes of the implants should be in the OR at the start of the surgery.

Question 6: Should operating lights be controlled with a foot pedal as opposed to reaching above eye level?

Consensus: We recommend a general awareness that light handles can be a source of contamination and to minimize handling of lights as much as possible. Other strategies for light control need to be developed in the future to minimize contamination.

Delegate Vote: Agree: 91%, Disagree: 4%, Abstain: 5% (Strong Consensus)

Justification: Davis et al. identified a 14.5% rate of contamination of sterile light handles during TJA cases.[23] Hussein et al. showed no evidence of contamination of the sterile light handle (autoclaved plastic or metallic) after 15 cases of primary TJA.[24] However, we were unable to identify other studies in the literature addressing the risk of contamination of the surgeon's gown or of parts of the sterile field when compared with reaching up for light adjustment, or studies that looked at air disruptions secondary to the movement of the surgeon reaching above eye level.

Question 7: Is there a role for ultraviolet (UV) light use in the prevention of infection after TJA?

Consensus: We agree that UV light environments can lower infection rates, but recognize that this can pose a risk to OR personnel. We recognize that the benefit of UV might be the inhibition of operating traffic.

Delegate Vote: Agree: 74%, Disagree: 13%, Abstain: 13% (Strong Consensus)

Justification: Even though UV light use has been shown to significantly decrease the number of bacterial counts in the OR, as well as the occurrence of postoperative infection, its use is harmful for OR personnel and increases the risk of corneal injuries and skin cancer; as such, current guidelines from the Centers for Disease Control (CDC) recommend against the use of UV lights in the OR to prevent SSIs.[5, 25-30]

Question 8: Do UV decontamination/sterilization lights or portable units in unoccupied ORs (nights and weekends) make a difference in the sterility of the OR environment?

Consensus: UV would be expected to lower bacterial load in ORs, but the technology has not been studied in this application. It might be considered an adjunct but not a replacement for conventional cleaning. There are potential risks to staff by UV technology inadvertently left on at the start of the work day.

Delegate Vote: Agree: 84%, Disagree: 3%, Abstain: 13% (Strong Consensus)

Justification: After a thorough literature search, we were unable to identify evidence to support or refute the use of UV light to keep the OR environment sterile outside operative times.

Question 9: Should the patient and OR personnel wear a mask to avoid contamination of the OR air?

Consensus: Despite the absence of conclusive studies that show a reduction in SSI when surgical masks are worn properly and uniformly by all staff, we believe there is reason to expect particulate airborne bacteria counts to be reduced by disciplined use of surgical masks. Until evidence appears that shows an advantage to NOT wearing a mask, we believe that it is in the interest of patient safety that all personnel wear surgical masks at all time that they are in the OR. There is insufficient evidence to support the use of masks by patients that outweighs the benefit of airway access.

Delegate Vote: Agree: 85%, Disagree: 7%, Abstain: 8% (Strong Consensus)

Justification: Several authors have questioned the utility of face masks worn by OR personnel in preventing air and wound contamination.[31-33] A study by Lipp and Edwards included 3 randomized controlled trials (RCTs)with a total of 2,113 subjects and concluded that the use of face masks had no significant effect on surgical wound infections in patients undergoing clean

surgery.[32] Sellden et al. decided to refrain from the use of face masks for unscrubbed personnel in the OR.[34] A recent RCT by Webster et al. showed that if none of the non-scrubbed OR personnel wore a face mask, there was no increase in the rate of SSIs. However, this study included non-orthopaedic as well as orthopaedic procedures and followed patients for only 6 weeks postoperatively.[35] Furthermore, it was not clear if orthopaedic procedures included implantation procedures. We were unable to identify studies looking specifically at face masks worn by the patient undergoing TJA or studies evaluating the benefit of this practice in reducing OR air contamination.

Question 10: What garments are required for OR personnel?

Consensus: We recommend that all personnel wear clean theater attire including a disposable head covering, when entering an OR. Garments worn outside of the hospital should not be worn during TJA.

Delegate Vote: Agree: 98%, Disagree: 1%, Abstain: 1% (Strong Consensus)

Justification: Some aspects of the appropriate attire for surgical personnel (such as surgical gowns and gloves) have been addressed in other sections. Controversy has been raised regarding the utility of surgical masks or head coverings in the prevention of SSI based on inconsistent results from experimental and clinical investigations in the field of general surgery, gynecology, and cardiology (cardiac catheterization).[36-42] Nevertheless, as affirmed by CDC guidelines,[28] use of surgical masks by all OR personnel is an advantageous and harmless behavior that provides a mechanical obstacle for OR personnels' oro- and nasopharyngeal secretions. These secretions may contain bacterial particulates and all efforts should be made to decrease the risk of exposure of surgical wound to these particulates. Moreover, masks can also be beneficial in protecting the personnel from patients' blood or other bodily fluids.

Question 11: What restrictions should be placed on the use of portable electronic devices (such as mobile phones, laptops, tablets, or music devices) in the OR?

Consensus: We recognize that portable electronic devices may be contaminated with bacteria. We also recognize that increased levels of talking are associated with higher levels of bacteria in the OR environment. Accordingly we recommend that portable electronic device usage be limited to that which is necessary for patient care.

Delegate Vote: Agree: 84%, Disagree: 14%, Abstain: 2% (Strong Consensus)

Justification: Many studies have shown a high rate of contamination of cell phones and other portable electronic devices used in hospitals by healthcare workers, from 44% to 98%, with a high percentage of resistant strains, namely extended-spectrum β-lactamase-producing gram-negative bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA).[43-49] Ulger et al. demonstrated that 52% of *Staphylococcus aureus* strains isolated from cell phones were methicillin-resistant.[48] Brady et al. showed that cleaning mobile phones with an alcohol-based solution significantly reduced contamination of mobile phones,[43] similar to what was previously observed by Singh et al. for pagers[50] and Hassoun et al. for personal digital assistants.[51] Thus, regular cleaning of portable electronic devices with alcohol is highly recommended, as efforts towards maintaining hand hygiene to prevent nosocomial infections, including SSI, may be compromised by the use of handheld electronic devices that act as reservoirs of pathogens. Limitation of portable electronic devices in the OR is also advised, although no evidence in the literature is able to link their use to an increased risk of SSI.

Question 12: Does prolonged surgical time predispose to an increased risk of PJI?

Consensus: We recognize that SSI rates increase directly with the duration of surgery. We recognize that some surgeries present a marked and inescapable level of complexity that will require more time. We recognize that minimizing the duration of surgery is an important goal and a cooperative effort on the base of the entire surgical team as well as the institution. We recommend that a coordinated effort be made to minimize the duration of surgery without technical compromise of the procedure.

Delegate Vote: Agree: 96%, Disagree: 3%, Abstain: 1% (Strong Consensus)

Justification: Numerous studies have linked increased operative time to the risk of infection after TJA with statistical significance.[52-65] Skramm et al. investigated the incidence of SSI following THA and TKA for fractures after the implementation of surveillance policies. When considering the risk factors for infection, the duration of surgery was the only significant independent factor in a logistic regression model, also taking into account age, American Society of Anesthesiologists' physical status score, and level of emergency.[61] The study by van Kasteren et al. supported the use of duration of surgery more than the 75th percentile as a risk factor for PJI,[64] as previously suggested by the National Noscomial Infections Surveillance risk index.[66] In a population-wide study based on the Danish national hip arthroplasty registry that included 80,756 cases of primary THA, surgical time was a significant independent risk factor for revision due to infection.[57] Similar results were reported in countries such as Norway and England.[60, 62] Peersman et al. suggested using operative times as a predictive risk factor for infection after TKA in a risk stratification model.[58] In a systematic review of only observational studies that investigated deep SSI in THA and included more than 100 patients, Urquhart et al found just two studies that examined operative time.[54, 60] After merging data from these two studies, they reported duration of surgery as an independent risk factor for SSI. In addition, in a recent analysis of 56,216 primary TKAs, Namba et al. identified a 9% increase in the risk of deep SSI per 15 minute-increment increase in operative time.[56]

Nevertheless, methodological concerns exist regarding the studies that support the role of operative time as a risk factor for PJI, including missing data,[9] failure to consider potential confounding factors,[57, 58] and statistical considerations.[59-61] On the other hand, there are studies that failed to demonstrate such a correlation[67] or even found an opposite relationship.[68] Moreover, none of the previous studies considered the potential confounding role of repeat doses of antibiotic prophylaxis during prolonged procedures. Procedure duration may be an indicator of complexity of surgery (extensive surgical exposure and more severe tissue damage), surgical indication (previous procedures and indications other than osteoarthritis), inexperienced surgical team, surgeon with slow pace, perioperative complications, inadequate optimal standardization program, or patient's preexisting medical conditions.[57, 69, 70] Perhaps staff education in how to operate efficiently and follow systematically defined steps might decrease the risk of SSI. It has also been demonstrated that procedures with a longer duration are at increased risk for revision due to aseptic failure.[62]

Question 13: Should the scheduling of elective TJA be ordered so that clean cases are not preceded by known infected, dirty, or contaminated cases?

Consensus: We recognize the concern regarding risk of infection to a clean surgery following a contaminated surgery. We recognize that studies have not demonstrated increased infection rates in clean surgery performed subsequent to contaminated cases. We recommend thorough cleaning after contaminated surgery and before further surgery, as defined by local institutional standards.

Delegate Vote: Agree: 89%, Disagree: 8%, Abstain: 3% (Strong Consensus)

Justification: Although performing an infected arthroplasty procedure before non-infected procedures is theoretically risky for cross-contamination between procedures, there is inadequate evidence to support or oppose this practice. However, this policy may allow the hygiene staff a thorough clean down procedure at the end of the OR working day when there is no economical concern regarding the duration of time that might be required for a compliant OR disinfection.

A common practice in orthopaedic surgery, especially in arthroplasty, is to organize the OR in a manner so that confirmed or suspicious cases of infection are operated on at the end of the OR session after clean procedures. Whether the practice of performing a clean arthroplasty procedure following an infected case increases the probability of infection or not has not been adequately studied. Microbiologic studies have demonstrated long-term survivorship of common nosocomial pathogens on inanimate surfaces.[71] This may support the theoretical risk of cross-contamination between procedures if there is no efficient preventive strategy for disinfection of these surfaces after every procedure. There are only two retrospective studies that have addressed this issue, but both had inadequate power and inconsistent conclusions.[72, 73] Despite the lack of evidence, a sound practice consists of thoroughly addressing this potential factor of PJI, even though there is inadequate evidence for cross-contamination between procedures.

Abolghasemian et al. evaluated 85 primary and revision cases performed after TJA resection for PJI and evaluated the risk of infection in those patients.[72] After a minimum follow-up of 12 months, an increased rate of superficial or deep infections was not witnessed in this cohort

when compared to 321 patients matched for demographic factors who did not undergo TJA after an infected TJA in the same OR. The one patient who developed a deep PJI in the study group had a different infecting organism than the one responsible for the PJI of the preceding surgical case. Cleaning the OR after an infected case did not differ from cleaning after an aseptic case. Namdari et al. undertook a similar endeavor when they evaluated the development of infection in 39 cases of primary TJA performed after dirty cases. They identified one case of PJI in this cohort when the causative infecting organism (*Propionibacterium acnes*) was the same as the one causing the infection in the preceding septic case. However, no advanced microbiological testing was performed to certify that both organisms were of identical strains.[73]

Question 14: Does patient normothermia have an essential role in preventing infectious complications?

Consensus: We recognize the significance of patient normothermia and the data from non-orthopaedic procedures. We support general recommendations from the general surgery literature and identify this as a field that requires further research.

Delegate Vote: Agree: 92%, Disagree: 1%, Abstain: 7% (Strong Consensus)

Justification: Kurz et al. undertook an RCT of major colorectal surgery patients and demonstrated significant decrease in SSI rates in patients receiving warmed fluids and forced-air warming (FAW) blankets compared to patients who did not receive aggressive maintenance of normothermia.[74] Melling et al. conducted an RCT in non-orthopaedic clean surgery and identified a significant role for patient warming in preventing SSI.[75] A systematic protocol using FAW blankets or local warming protocols using a radiant heat dressing led to a significant decrease in SSI. No such RCT was identified specifically for TJA or orthopaedic procedures in general.

Question 15: Do FAW blankets increase the risk of SSI?

Consensus: We recognize the theoretical risk posed by FAW blankets and that no studies have shown an increase in SSI related to the use of these devices. We recommend further study but no change to current practice.

Delegate Vote: Agree: 89%, Disagree: 5%, Abstain: 6% (Strong Consensus)

Justification: Recent studies have raised concern about the possibility of bacterial air contamination by FAW devices. Some authors evaluated disruptions in airflow. McGovern et al. conducted an experimental study where they found that FAW blankets lead to a disruption in the airflow at the surgical site under LAF conditions when compared to conductive fabric warmers in simulated THA and spine surgery.[76] Legg et al. found increased air particles above the surgical site when using FAW compared to radiant warming.[77] On the contrary, Sessler et al. did not identify any worsening in air quality with use of FAW under laminar flow conditions.[78] Memarzadeh et al. reported the results of a computational study conducted by the National Institutes of Health which showed negligible disruption of laminar flow by FAW.[79]

Other authors have investigated the bacterial contamination of OR air. Moretti et al. undertook air sampling in experimental conditions and demonstrated increased bacterial contamination of air after turning FAW blankets on; however, this was much lower than worsening of air quality induced by personnel placing a patient in the OR.[80] Tumia et al. undertook air sampling under LAF conditions in orthopaedic procedures and failed to identify any significant rise in air bacterial counts with the use of FAW.[81] Sharp et al. also performed air sampling in LAF-equipped ORs to study the effect of FAW on air quality using volunteer patients with psoriasis who had increased shedding of skin cells.[82] Air at 30cm from a theoretical operating site was sampled and there were no positive cultures. In addition, a smoke test that was used to visually assess airflow found no disturbance by the FAW device. Zink et al. were also concerned by possible contamination of the OR environment with FAW, but did not resort to air sampling. Instead, they placed culture plates on the abdomen of volunteers with use of FAW and failed to identify increased contamination rates with this method.[83]

Albrecht et al. found that the intake filters used in air blowers were not optimally efficient and resulted in colonization of the internal parts of the device. Overall, 92% of the devices they tested resulted in positive bacterial growth with organisms that are typically implicated in PJI (mostly Staphylococci species).[84] However, there is no concrete evidence to link the use of FAW system with SSI/PJI. McGovern et al studied a change of a warming system from forced

air to an alternative system in 1,437 patients. A significant increase in deep joint infection, as demonstrated by an elevated infection odds ratio (3.8, p=0.024), was identified during a period when FAW was used compared to a period when conductive fabric warming was used. The authors conceded that the study was observational and may have been affected by other infection prevention measures instituted by the hospital.[76]

Question 16: Should OR personnel be required to decontaminate their hands with at least an alcohol-based foam every time their hands have been in contact with inanimate objects (including medical equipment) located in the immediate vicinity of the patient?

Consensus: We support current recommendations for hand hygiene in patient care.

Delegate Vote: Agree: 86%, Disagree: 8%, Abstain: 6% (Strong Consensus)

Justification: Properly performed hand hygiene affords protection to both the patient and healthcare worker from cross transmission of infectious agents. Hand hygiene should be performed by OR personnel involved in examination, manipulation and placement of the patient, in accordance with the World Health Organization's (WHO) 5 Moments for Hand Hygiene.[85] There is ample evidence to confirm that transmission of pathogens from/to a patient to/from their immediate environment, defined below, occurs. However, there is inadequate evidence to show the influence of hand decontamination on this sequence. High-quality clinical investigations are required to study the efficiency of hand decontamination on prevention of SSI and PJI. Frequent hand decontamination has been suggested,[86] but concerns have been expressed regarding skin irritation and contact dermatitis.[87] Moreover, some risk of change of bacterial flora to colonizing bacteria with skin damage might exist.[88]

Five sequential steps for cross-transmission of microbial pathogens have been described.[86] These steps include shedding of skin flora to inanimate objects surrounding the patients, transfer of the bacteria to the healthcare worker's hands, adequate survival of the microbes on the healthcare worker's hands, inadequate hand antisepsis technique by the healthcare worker, and transmission of bacteria from the healthcare worker's hands to other patients or inanimate

objects that can potentially be in contact with patients.

Approximately 10^6 skin squames containing microorganisms are shed daily from normal skin.[89] Therefore, surfaces located in the close vicinity of the patient (such as floor, bed lines, gowns, furniture, and medical equipment such as blood pressure cuffs) can become contaminated with patients' skin flora.[86, 90-92] Hands or gloves of healthcare workers can be contaminated after contact with inanimate objects in patient rooms.[93, 94] Laboratory-based studies have demonstrated that many bacteria, including *Staphylococcus aureus*, gram-negative bacilli, and *Enterococci*, can be transferred to the hands by touching contaminated surfaces.[86, 94, 95] Microorganisms can survive on hands for different lengths of time varying between a few minutes to several hours and healthcare workers' hands can be progressively colonized due to poor hygiene, longer duration of care, and higher quantity of contamination.[86] In one study, the use of an alcohol gel hand wash was associated with a 36% decrease in nosocomial infection rates.[96] There is substantial evidence that demonstrates improvement in the rate of healthcare-associated infections with hand hygiene promotional programs that include the use of an alcohol-based hand rub, although studies with improved design methodology are needed.[86]

Question 17: What are the guidelines for hand hygiene and glove use for personnel in contact with the patient for examination, manipulation, and placement on the OR table?

Consensus: We support current recommendations in patient care in accordance with the principles of Standard Precautions.

Delegate Vote: Agree: 92%, Disagree: 1%, Abstain: 7% (Strong Consensus)

Justification: Gloves should be used by OR personnel as dictated by the principles of Standard Precautions.[97] Added protection to the healthcare worker, via glove use, is required in the event of potential contact with blood, body fluids, secretions, excretions, mucous membranes, non-intact skin or contaminated equipment.[97] Glove use does not preclude the need for application of hand hygiene principles. In the event that the patient is on contact precautions, gloves should be used for all contact with the patient and/or the immediate patient environment. The dynamics

of contamination are similar between gloved and ungloved hands.[86] Gloves can be contaminated after touching the patient or inanimate objects in patient rooms.[92, 93, 98, 99] Risk of cross-contamination through contaminated gloves is similar to that of naked hands.[92, 99] Therefore, when gloves are used in patient care, hand hygiene must be performed prior to donning gloves and following glove removal. A single pair of gloves may not be used in the care of more than one patient.

Question 18: Should triple gloving be used to prevent contamination during TJA?

Consensus: We recommend double gloving and recognize the theoretical advantage of triple gloving.

Delegate Vote: Agree: 89%, Disagree: 7%, Abstain: 4% (Strong Consensus)

Justification: A relatively high rate of inner glove contamination has been identified with double-gloving in TJA, leading to the consideration of triple-gloving practices.[100, 101] Hester et al. compared the rate of inner glove perforation with 3 different gloving protocols in TJA: latex/cloth, latex/latex, and latex/cloth/latex.[102] They found a reduced rate of perforation when the outer glove was a cloth glove compared to a latex glove, and interposing a cloth glove between two latex gloves yielded the lowest rate of perforation. While double-gloving with an outer cloth glove had a notable impact on tactile sensation and was troublesome when manipulating cement, triple-gloving with a cloth glove between two latex gloves was not perceived as having such an important impact. However, reported differences in rates were not shown to be statistically significant. Sebold et al. demonstrated that the use of a cloth glove between two latex gloves was able to reduce inner glove perforation rates to zero in their institution.[103] According to their observations, surgeon dexterity was not affected by this gloving practice. In addition, the authors showed that the use of orthopaedic outer gloves yielded lower inner glove puncture rates than regular latex gloves. Sutton et al. showed that a triple-gloving protocol with a cut-resistant liner interposed between the two latex gloves significantly reduced the rate of perforation compared to double-gloving with two latex gloves.[104] Overall, triple-gloving seems to decrease inner glove perforation rates; however, this is at the expense of a decrease in surgical dexterity and tactile sensation.

Question 19: How frequently should gloves be changed during surgery?

Consensus: We recognize the advantage of glove changes at least every 90 minutes or more frequently and the necessity of changing perforated gloves. Permeability appears to be compromised by the exposure to methacrylate cement and gloves should be changed after cementation.

Delegate Vote: Agree: 89%, Disagree: 6%, Abstain: 5% (Strong Consensus)

Justification: Al-Maiyah et al. conducted an RCT on THA procedures where the study group consisted of changing outer gloves every 20 minutes and before implant cementation, compared to changing only before cementation in the control group.[105] This change in practice led to a significant reduction in perforation and contamination rates of outer gloves. Kaya et al. reported that glove perforations occurred after 90 minutes on average and suggested changing gloves every 90 minutes.[106] Dawson-Bowling et al. evaluated glove contamination after draping and before opening the final components and found 12% and 24% contamination rates respectively.[107] Beldame et al. identified a significantly higher rate of glove contamination before prosthesis implantation and advised changing gloves before this surgical step.[108] The authors also showed that when the outer gloves were contaminated, changing them lead to non-contaminated outer gloves in 80% of cases. Furthermore, in a prospective study, Carter et al. found that a surgeon's outer glove perforation occurred in 3.7% and 8.3% of primary and revision arthroplasty procedures, respectively. They also found that inner glove perforation was ignored in 19% of double glove perforations and recommended careful inspection of the inner glove whenever outer glove perforation is noted.[100]

Question 20: When should instrument trays be opened?

Consensus: We recommend that the timing of opening trays should occur as close to the start of the surgical procedure as possible with the avoidance of any delays between tray opening and the start of surgery.

Delegate Vote: Agree: 98%, Disagree: 1%, Abstain: 1% (Strong Consensus)

Justification: Dalstrom et al. recently demonstrated a direct correlation between the duration of open exposure of instrument trays and the risk of bacterial contamination.[109] Some trays were found to be contaminated immediately after opening. After eliminating those trays, they reported contamination rates of 4% at 30 minutes, 15% at 1 hour, 22% at 2 hours, 26% at 3 hours, and 30% at 4 hours. Brown et al. demonstrated that bacterial air counts during preparation and draping were 4.4 times higher than during surgery, leading them to recommend opening instruments after patient preparation and draping.[110]

Question 21: Should trays be covered with sterile drapes/towels when not in use?

Consensus: We recognize a theoretical advantage to covering trays when not in use for extended periods, and that larger covers may be disadvantageous, if they are moved from contaminated areas across the sterile field. We recommend further study of this question regarding timing and techniques.

Delegate Vote: Agree: 90%, Disagree: 4%, Abstain: 6% (Strong Consensus)

Justification: Chosky et al. demonstrated that covering the instruments with sterile drapes reduced bacterial contamination rates 4-fold.[111] The Association of Perioperative Registered Nurses guideline for maintaining a sterile surgical field does not recommend covering the sterile table with sheets that fall below the table top because such a practice may cause air currents that can transfer micro-organisms from a nonsterile area (below the table level) to the sterile field over the table at the time of drape removal[112] Nevertheless, Dalstrom et al. showed that

covering trays significantly reduced the risk of contamination and did not identify any increased risk of contamination when uncovering them.[109]

Question 22: After skin incision, should the knife blade be changed for deeper dissections?

Consensus: We recognize high contamination rates in studies of scalpel blades that have been used for the skin incision and recommend changes after skin incision.

Delegate Vote: Agree: 88%, Disagree: 8%, Abstain: 4% (Strong Consensus)

Justification: In the majority of institutions, separate blades are used for incision of the skin and the deeper tissues during TJA. However, several studies have questioned the necessity of such a practice.[113-115] When comparing contamination of skin and deep knives, Ritter et al. were unable to identify any difference in contamination rates in both conventional and LAF conditions.[115] Furthermore, organisms retrieved from deep wound cultures did not correlate with those that were on the knife blades, thus refuting deep wound contamination by the blades. Other authors subsequently corroborated these findings.[113, 114] However, Davis et al. identified a 9.4% contamination rate of superficial blades and supported the routine practice of changing blades after incision.[23] Schindler et al. reported a 15.3% contamination rate for skin blades, 74% of which grew coagulase-negative *Staphylococcus* (CNS), one of the most frequent causes of PJI.[116] In this study, 10.8% of deep blades were contaminated, 50% of which with CNS. Based on their findings, the authors supported changing the skin blade after incision.

Question 23: Should electrocautery tips be changed during TJA? If so, how often?

Consensus: In the absence of evidence we recommend further study and no specific behavior.

Delegate Vote: Agree: 95%, Disagree: 0%, Abstain: 5% (Strong Consensus)

Justification: After review of the literature, there were no studies relevant to the necessity and frequency of change of electrocautery disposable tips during elective TJA.

Question 24: Should suction tips be regularly changed during surgery? If so, how frequently? Should suction tips enter the femoral canal?

Consensus: We recommend changing suction tips every 60 minutes based on studies showing higher rates of contamination. Suction tips can be introduced into the femoral canal for the time necessary to evacuate fluid but should not be left in the canal, where they circulate large amounts of ambient air and particles that may contaminate the surgery.

Delegate Vote: Agree: 85%, Disagree: 8%, Abstain: 7% (Strong Consensus)

Justification: Several studies have demonstrated high rates of contamination of suction tips during the intraoperative period.[23, 117-123] In 1988, Strange-Vognsen et al. identified a 54% contamination rate in orthopaedic procedures.[123] Twenty years later, Givissis et al. found the same rate of contamination, with 78% of cases growing *Staphylococcus* species.[117] The authors reported one case of deep SSI where the organism was the same as the one isolated from the suction tip. When looking at procedure duration, they showed a 9% contamination rate in procedures lasting less than an hour compared to a 66.7% in procedures lasting over an hour, which led them to advise changing of the catheter tip every hour. Similarly to Strange-Vognsen et al., they recommended turning the suction off when not in use. However, there are concerns that turning off the suction might impose risk of contamination of the surgical field due to backflow of the material along the suction tube and tip.

Greenough et al. found a 37% rate of contamination of operative suctions used in THA.[118] However, when evaluating the suction tips used only for cleaning the femoral shaft, only one of those (out of 31) was contaminated. The authors advised changing the suction tip before preparing the femur in THA. The same conclusion was drawn by Robinson et al. who conducted a similar study among patients undergoing THA in laminar flow rooms and identified a 41% contamination rate of suction tips.[122]

Question 25: Should splash basins be used, as they are known to be a source of contamination?

Consensus: We recommend against the use of fluid filled basins that sit open during the surgery.

Delegate Vote: Agree: 88%, Disagree: 3%, Abstain: 9% (Strong Consensus)

Justification: Andersson et al. showed that 13 out of 21 irrigation solutions stored in basins were contaminated at the end of the procedure in conventional ventilation rooms.[15] Baird et al. revealed a contamination rate of 74% in their series among specimens taken from splash basin fluids. In their series, *Staphylococcus epidermidis* was the most prevalent organism.[124] Anto et al. demonstrated a 24% rate of contamination of liquid samples removed from the basins.[125] Conversely, Glait et al. recently showed much lower rates of contamination of samples taken from basins that were used to wash and store instruments with only one contaminated case out of 46 (2.17%).[126] However, they used culture swabs as opposed to culturing fluid in other studies.

Question 26: Do disposable instruments and cutting guides reduce contamination and subsequent PJI?

Consensus: We recognize the possible theoretical advantages of disposable instrumentation but in the absence of data we can make no recommendations.

Delegate Vote: Agree: 95%, Disagree: 2%, Abstain: 3% (Strong Consensus)

Justification: Mont et al. have recently demonstrated a decreased contamination rate of 57% in non-navigated and 32% in navigated cases of TKA when using single-use instruments, cutting blocks, and trials.[127]

Patient specific instrumentation can shorten the duration of surgery in TKA.[128] However, there are no studies that have specifically evaluated the incidence of subsequent PJI in patients that received custom cutting guides or disposable instruments versus those undergoing TJA using conventional instruments and cutting guides. Thus, this issue remains unresolved.

Question 27: Is there a role for incise draping? What type of incise draping should be used (impregnated or clear)?

Consensus: We recognize the presence of studies that show iodine-impregnated skin incise drapes decreased skin bacterial counts but that no correlation has been established with SSI. We do not make any recommendations regarding the use of skin barriers but do recommend further study.

Delegate Vote: Agree: 89%, Disagree: 7%, Abstain: 4% (Strong Consensus)

Justification: There is concern about the recolonization of skin and surgical site with the host flora during surgery.[129-132] Incise drapes are intended to provide a sterile barrier at the beginning of the surgical procedure. They are used on prepped surgical sites to provide additional protection and minimize the risk of recolonization. While it has been shown that impregnated incise drapes decrease the recolonization rate of skin flora, there have been inconsistent conclusions about the existing evidence regarding the value of drapes in preventing SSI. High-quality evidence with PJI as an endpoint is lacking. Use of adhesive incise drapes impregnated with iodine should be avoided in patients with systemic or topical allergy to iodine.

The bactericidal action of iodine-containing incise drapes is inferior to conventional skin preparation solutions such as betadine. The sole use of incise drapes as a substitute for conventional skin preparation is not recommended.[133]

In an experimental study on the skin of normal individuals, use of an iodophor-incorporated drape was significantly associated with a lower rate of recolonization of skin bacteria compared with skin-site preparation methods, with or without non-impregnated drape.[131] However, another experimental study on an animal model found that after contamination of skin samples with *Staphylococcus aureus* suspension, iodine-containing adhesive drapes were as inefficient as the control group in reducing the number of colony-forming units.[134] Another experimental study

found that non-impregnated drapes can facilitate the rate of recolonization of skin after antiseptic preparation.[135] In contrast, in an earlier investigation, bacteria did not multiply underneath a plastic adhesive drape and lateral migration of bacteria did not occur.[136]

In a prospective RCT, Chiu et al. could not demonstrate a difference between the wound contamination rates after surgery of acute hip fractures with and without the use of plastic incise drapes (4/65 versus 1/55 for with and without drapes, respectively).[137]

In another prospective RCT in abdominal surgery, within the group of clean and clean-contaminated procedures, iodophor-impregnated incise drapes significantly reduced the contamination of the surgical wound by normal skin flora organisms, but the study was unable to detect any significant difference in the rate of SSI compared with the control group in whom no drape was utilized (5.9% vs 5.6% for procedures performed with and without drapes, respectively).[138]

In a prospective study comparing 122 patients undergoing hip surgery in which Ioban (3M Company, USA) was applied to the operative site 24 hours before surgery, bacterial sampling of the wound at the end of the procedure showed that the wound contamination rate was reduced from 15% to 1.6% by this method.[139]

One review combined the results of clinical trials of a wide range of clean and clean-contaminated surgical procedures (caesarean sections, abdominal, and hip fracture procedures), most of which did not meet criteria for high quality evidence. In these studies plastic (defined as polyethylene, polyurethane, or polyvinyl) adhesive drapes (eg Op-Site (Smith and Nephew), Ioban (3M), Steridrape (3M, United Kingdom) were utilized. The authors concluded that adhesive drapes are not associated with a reduced infection rate compared with no adhesive drapes and appear to be associated with an increased risk of infection.[140] However, the quality of the few studies included in this systematic review was not high. The authors concluded that if adequately disinfected prior to surgery, the patient's skin is unlikely to be a primary cause of SSI; therefore, attempts to isolate the skin from the wound using an adhesive drape may be pointless and potentially harmful, as excessive moisture under plastic drapes may encourage bacteria residing in hair follicles to migrate to the surface and multiply.[137, 140]

Another issue that should be considered is that the type of skin preparation affects drape adhesion.[141] A few studies demonstrated that addition of Duraprep (3M) enhanced the adhesive capacity of drapes.[129, 130] Choosing a skin preparation that enhances drape adhesion may

minimize drape lifting and the potential for wound contamination. It has been concluded that the separation of incise drapes from the skin was associated with a 6-fold increase in the infection rate compared with surgical procedures in which the incise drape was not lifted.[142] A prospective RCT on patients with TJA confirmed that Duraprep solution was associated with significantly better drape adhesion than povidone-iodine scrub and paint. However, the study was not able to demonstrate a significant difference in skin contamination between the groups, although Duraprep was associated with slightly lower rate of contamination.[130]

Allergic reactions to povidone-iodine can occur and there is at least one case report of allergic contact dermatitis associated with the use of iodophor-impregnated incise draping.[143, 144]

Question 28: Does the application of towels or other sterile materials to wound edges and subcutaneous fat during an operation, clipped securely to the edges of the wound, diminish the chances of wound contamination and wound infection?

Consensus: We recognize the traditional practice of covering skin edges with sterile draping but there is wide variation in clinical practice and we make no recommendations.

Delegate Vote: Agree: 94%, Disagree: 2%, Abstain: 4% (Strong Consensus)

Justification: Evidence regarding the application of sterile material to wound edges is mainly available for abdominal open surgery.[145] There is no evidence regarding its use in orthopaedic surgery and we found no recommendation regarding their use for PJI. Towels can serve to support the drapes against instrument strike-through. They may also protect the wound edges from trauma by instruments such as retractors or broaches.

Wound edge protection devices (wound protectors or wound guards) have been used in abdominal surgery to avoid contamination and trauma of the wound edges during laparotomy.[145, 146] There are two main types of protectors: (1) wound protectors with an external and internal ring connected by an impermeable plastic that covers the wound edges and (2) those with an internal ring connected to a drape that extends outward and over the abdomen and is fixed by adhesive material or clips.[146] They provide a physical barrier to protect the incision site from contamination. In contrast, adhesive drapes do not cover the edges of the

wound. Wound protectors have only been used in abdominal surgery.[145] Two meta-analyses of RCTs compared the use of wound protectors with no protection in abdominal laparotomy. The authors concluded that their use seems to be protective against SSI.[145, 146] However, the quality of those RCTs has been poor. Two multicenter trials on abdominal laparotomy procedures have been registered and are being conducted at the time of writing.[147, 148]

Question 29: What type of draping should be used (reusable or disposable)?

Consensus: We recognize that penetration of drapes by liquids is believed to be equivalent to contamination and recommend impervious drapes. In the absence of data on disposable versus cloth drapes, we make no recommendation except for further study.

Delegate Vote: Agree: 90%, Disagree: 6%, Abstain: 4% (Strong Consensus)

Justification: The available evidence is solely experimental. Most of the studies have been performed in models with rigorous conditions that are unusual in real-life situations. Clinical trials with PJI as an endpoint are lacking.

In addition to the physical properties of material applied for fabricating drapes, factors such as pressure, friction, contact time with contaminated material, state of moisture/dryness, and the moisturizing agent (blood, normal saline, or antiseptic solutions) can affect the bacterial permeability of drapes.[149, 150] While passage of bacteria through dry drapes does happen, the strike-through rate of bacteria is enhanced when wetted by normal saline or blood and diminished when wetted by antiseptic solutions (iodine or chlorhexidine).[149] Moreover, drape material may demonstrate different levels of impermeability depending on the penetrating particle (aqueous fluids, albumin, or bacteria).[151-153] Woven and non-woven materials vary in their ability to resist bacterial strikethrough. Disposable nonwoven drapes are superior to reusable woven cotton/linen drapes in resisting bacterial penetration. When wetted by normal saline, reusable woven drapes were penetrated by bacteria within 30 minutes, while the majority of disposable nonwoven drapes were not.[151] Being impervious does not necessarily mean being absolutely impenetrable to bacteria and impermeability can vary between different disposable

drape brands. However, disposable drapes considerably decrease bacterial load passing through them.[154]

Two RCTs were conducted comparing reusable and disposable drapes and gowns in coronary artery bypass graft and elective abdominal surgery, with SSI as their main outcome. None of these studies found differences between the two types of gowns and drapes.[155, 156]

Question 30: Is there evidence that the use of sticky U drapes, applied before and after prepping, effectively seals the non-prepped area from the operative field?

Consensus: We recognize that adhesive U-drapes to isolate the perineum has been traditional practice but in the absence of data we make no recommendations.

Delegate Vote: Agree: 83%, Disagree: 11%, Abstain: 6% (Strong Consensus)

Justification: There are no published or unpublished reports that we could identify that were related to this issue.

Question 31: Is irrigation useful? How should the delivery method for irrigation fluid be (high pulse, low pulse or bulb)?

Consensus: We recognize the theoretical basis for irrigation to dilute contamination and non-viable tissue and that a greater volume of irrigation would be expected to achieve greater dilution. We recognize advantages and disadvantages of different methods of delivering fluid but make no recommendations of one method over another.

Delegate Vote: Agree: 91%, Disagree: 4%, Abstain: 5% (Strong Consensus)

Justification: There are indirect data regarding the optimal volume of irrigation in TJA. In both animal and human studies, increasing the volume of irrigation solution removes more particulate matter and bacteria, but the effect plateaus depending on the system. There have been no reported human clinical studies related to the volume of irrigation.[157, 158] High-quality studies with

PJI as endpoint are lacking. No evidence was found regarding differences in irrigation in primary and revision TJA. Use of high-pressure pulsatile lavage may have potential benefits of being time-saving and removing necrotic tissue and debris more effectively.[159-164] It also improves the mechanical stability of cemented arthroplasty by allowing better cement penetration in cancellous bone tissue. However, there are some concerns regarding damage to tissue structures and propagation of bacteria into the deeper layers of soft tissues with the use of high pressure lavage. High-pressure pulsatile lavage should perhaps be reserved for severely contaminated wounds or for open injuries for which treatment will be delayed. Low-pressure irrigation might be useful if contamination is minimal or treatment is immediate. High-quality evidence is lacking regarding optimum lavage pressure in primary or revision TJA.

Decreases in the amount of bacteria present in the surgical site have been observed with normal saline lavage,[165] indicating that a component of physical removal for every irrigating solution should be considered. For a clean contaminated surgery (appendectomy) irrigation with normal saline was found to decrease SSI in comparison with no irrigation.[166, 167] In one study that used pulsatile lavage with normal saline after cemented TKA, particles larger than 1 μm were collected consecutively after each liter of lavage up to 8 liters. The weight of these particles peaked in the first 1L lavage fluid and gradually decreased until the eighth lavage fluid. Significant differences were found between the first and second, second and third, and third and fourth lavage. However, no significant differences were found beyond the fourth lavage. The results of this study indicated that 4L of pulse lavage is effective for removing the bone and cement particles during cemented TKA. The authors suggested that if bacteria are considered as particles of approximately more than 1 μm, 4L of pulse lavage may be effective for removal of bacterial particles.[158]

The precise definition of high- and low-pressure lavage is not established in the literature. Generally below 15 psi (103.4 kPa) and over 35 psi (241.3 kPa) are considered low or high pressure, respectively.[168] High-pulsatile lavage has been shown to improve cement penetration in cancellous bone and increase mechanical strength at the cement-bone interface during in vitro studies.[169-174] *In vivo* studies have also demonstrated fewer radiolucency zones in follow up x-rays evaluation.[175] In addition, a relationship between the pressure of irrigation and the quantity of cellular material removed from the bony trabeculae has been demonstrated.[176] However, there is no agreement on a cut-off point for high-pressure lavage. Some studies suggest that even lavage pressures that were considered to be too low to have macroscopic

influence may still have an effect on bone marrow mesenchymal cells and direct them to differentiate into adipocyte tissues, thus declining the content of osteoblasts in marrow.[159]

High-pressure lavage may result in tissue damage in cancellous bone, cortical bone, and muscle; and can negatively influence the healing process and early formation of new bone.[91, 176-178] Pulsatile lavage (either high or low pressure) results in greater deep bacterial seeding in bone than does brush and bulb-syringe lavage in *in vitro* models[162, 179] and can spread the contamination to nearby tissues.[179] High-pressure pulsatile lavage results in deeper bacterial penetration in muscle tissue in comparison with low-pressure pulsatile lavage.[168]

There is a considerable body of evidence regarding open fractures and contaminated wounds. A few early and recent studies, including *in vitro* and *in vivo* human and animal studies, demonstrated that high-pressure pulsatile lavage is more effective than low-pressure pulsatile lavage for removing particulate matter, bacteria, and necrotic tissue, particularly in contaminated wounds that had delayed treatment.[159-164] Moreover, in an experimental model it was demonstrated that low-pressure pulsatile lavage was more effective and efficient than bulb-syringe irrigation in reducing bacterial removal.[180]

One prospective RCT showed that pulsatile lavage in comparison with normal lavage by syringe or jug leads to a lower incidence of PJI after cemented hemiarthroplasty for hip fracture (3/164 versus 10/192 for pulsatile and syringe lavage groups, respectively).[181]

In another study, the use of high-pressure pulsatile lavage during open debridement for the treatment of acute orthopaedic implant infections (mainly TKA, THA, and hip hemiarthroplasty) was associated with a similar success rate compared with the conventional manual low-pressure lavage (n=79).[182]

Question 32: What type of irrigation solution should be used? Should antibiotics be added to the irrigation solution?

Consensus: We recognize the mechanical advantage of irrigation as per question 31 but that conflicting evidence exists supporting the use of one agent over the other and make no recommendation regarding type of solution.

Delegate Vote: Agree: 90%, Disagree: 7%, Abstain: 3% (Strong Consensus)

Justification: Detergents such as castile soap or benzalkonium chloride are effective in decreasing the burden of bacteria in musculoskeletal wounds because of their surface-active properties. The detergents act by disrupting hydrophobic and electrostatic forces, thereby inhibiting the ability of bacteria to bind to soft tissue and bone. It is possible that some detergents act on some bacteria more efficiently than on others.[157, 183]

Weak evidence is available for the benefit of irrigation with diluted betadine solution before closure of surgical wound. However, no deleterious influence on wound healing or any other major adverse effects have been associated with their use. Concerns for its potential chondrocytotoxicity are supported by experimental evidence only. Lower concentrations (0.35% to 0.5%) with a short time of lavage might avoid potential chondrocytotoxic effects in partial knee arthroplasty. Further clinical evidence is required to define optimal concentration and length of exposure.

The pharmacodynamic profiles of antibiotics vary depending on the type, dose, and method of delivery.[184] A variation of these factors, a difference in surgical settings in which studies have been performed, and a lack of specific efficacy criteria make it difficult to reach a conclusion regarding whether topical antibiotics are efficacious; and if so, what type should be used and which formulations are optimal for prophylaxis of SSI and PJI. Moreover, the safety of using topical antibiotics has been questioned. Evidence regarding wound irrigation with antibiotic solutions mainly comes from non-orthopaedic surgical specialties with clean-contaminated surgeries. Most of these RCTs found that adding antibiotics to irrigation solutions did not decrease the incidence of SSI significantly in comparison with irrigation with normal saline solution.[160, 185-189] This finding has also been supported by some experimental studies.[157, 190] Further high-level evidence with SSI or PJI as endpoints is required to evaluate the efficacy and potential adverse effects of local irrigation with antibiotic solutions on the surgical site.

In vitro studies show that Castile soap is more effective than antibiotic solutions at removing *Staphylococcus aureus, Staphylococcus epidermidis, and Pseudomonas aeruginosa* from metallic implants and bone.[191, 192] In an RCT on open fractures, soap and bacitracin solution did not result in any difference in the incidence of SSI, although bacitracin was associated with more wound complications.[193]

In one RCT in general surgery, there were more wound infections in the saline group (39/258) in comparison with the povidone-iodine solution group (7/242).[194] Irrigation with dilute povidone-

iodine solution (0.35%) before closure of the surgical wound in THA and TKA was associated with significant decrease in PJI.[195] The same solution was associated with a significant decrease in deep SSI in spine surgery (6/206 deep SSIs in the no betadine group versus 0/208 in the betadine group).[196] Ten of 15 studies (11 RCTs and 4 prospective comparative studies) in a systematic review of different surgical specialties (2 studies of spine surgery) demonstrated that povidone-iodine irrigation was significantly more effective at preventing SSI than the comparative interventions of saline, water, or no irrigation.[197] The other 5 studies did not detect any significant difference. This study has considerable methodological limitations, such as considerable variety in the types of surgeries, quality of clean or contaminated interventions, inconsistent concentration of povidone-iodine, and variable use of prophylactic antibiotics. There is no reported complication with the use of dilute betadine irrigation and no adverse effect on wound healing, bone union, or clinical outcome has been reported.[196] One study demonstrated an increased postoperative serum iodine which was not related to any adverse effects.[197] The cytotoxicity of povidone-iodine solution is controversial: Chondrocyte ability for DNA synthesis significantly decreased after 5 minutes of exposure to povidone-iodine 1%. Other studies similarly show toxic effects of povidone-iodine solution on fibroblasts, keratinocytes, synovial cells and chondrocytes.[198, 199] Cytotoxicity has been related in bovine chondrocytes with length of exposure, regardless of concentration, although higher concentrations were associated with less viability of chondrocytes. A concentration of 0.35% povidone-iodine was the least chondrotoxic but still reduced the cell viability when applied for longer than one minute. Cytotoxicity has been observed in cultured embryonic chicken tibia osteoblasts at a betadine concentration of 5%. Less cytotoxic effect occurs at a povidone-iodine concentration of 0.5%.[200] Povidone-iodine preparations of 1%, 5%, or 10% do not have a deleterious effect on wound healing in animals and humans.[201] Povidone-iodine irrigation should not be used in patients with iodine sensitivity, burns, and thyroid or renal disease.[197] The sterility of povidone-iodine solution before its use should be meticulously monitored because its contamination has been associated with infectious complications.[202, 203] One experimental study showed that there was no difference in the quality of cement fixation when irrigation was done with povidone-iodine or normal saline, although both solutions were inferior to hydrogen peroxide solution.[204]

Topical antibiotics should have a broad spectrum and low systemic absorption and be relatively inexpensive and harmless to the tissue. The most commonly used topical antibiotics include cephalosporins, aminoglycosides (neomycin), glycopeptides, chloramphenicol, polymyxin, and bacitracin.[184, 205] The potential advantages of topical antibiotic use are their limited potential for

systemic absorption and toxicity, low potential for development of antibiotic resistance, and the fact that their effect is essentially independent from the local physiological changes that may affect the efficacy of systemic antibiotics.[206] However, topical antibiotics may produce contact dermatitis or hypersensitivity and their use has been reported to be associated with serious systemic effects such as anaphylaxis with bacitracin and deafness and renal failure with a neomycin-bacitracin-polymixin combination.[207-209] Earlier studies demonstrated that prophylactic topical administration of antibiotics in the surgical incision during various orthopaedic and non-orthopaedic procedures is more efficacious than normal saline. However, consistent results have not been reported regarding their efficacy.[165] *In vitro* and animal studies using bone or metal surfaces failed to show better performance for neomycin and bacitracin solutions in comparison with normal saline for removing bacteria from bone, titanium, and stainless steel.[190-192] Despite evidence that topical antibiotics decrease bacterial inoculum in clean surgical wounds,[210] it has not been shown that they offer any advantage over intravenous antibiotic prophylaxis, nor that they have been proven to decrease the incidence of SSI.[184, 186] A study of a canine model for TJA reported a reduction in the SSI rate with neomycin containing irrigation solution.[211] There is concern regarding the adverse effect of topical antibiotic solutions on wound and bone healing. An RCT on open fractures found that topical irrigation with bacitracin solution did not decrease the incidence of SSI in comparison with soap, yet it was associated with a higher rate of wound complications.[193]

Question 33: Is there a role for intraoperative application of autologous blood-derived products to the wound in preventing infection?

Consensus: In the absence of data we make no recommendation regarding autologous blood derived products to the wound to prevent infection.

Delegate Vote: Agree: 94%, Disagree: 2%, Abstain: 4% (Strong Consensus)

Justification: Although some benefits have been observed regarding the intraoperative application of autologous blood-derived products in TJA, the majority of the studies were not sufficiently powered to be able to detect difference for PJI. Only one RCT demonstrated that use

of these products directly decreased the incidence of postoperative wound infection.[212] Larger-scale trials with PJI as an endpoint are required.

In TKA, application of autologous platelet gel and fibrin sealant together on the wound tissues at the end of surgery was associated with a higher postoperative hemoglobin level and decreased the need for blood transfusion. The incidences of wound leakage, wound healing disturbance, and wound infection (0/85 versus 4/80) were significantly less in patients managed with platelet gel and fibrin sealant.[212]

In a multi-center study (n=58) topical spraying of fibrin tissue adhesive (non-autologous cryoprecipitate-based fibrinogen) was added to standard hemostatic measures in TKA and resulted in a decrease in blood loss and reduced blood transfusion requirements. There were 3 cases of superficial wound infection (2/29 and 1/29 for the treatment and control groups, respectively) without any significant difference.[213] Other similar RCTs on TKA (n=53)[214] and THA (n=81)[215] reported similar findings regarding blood loss.

In one RCT using autologous fibrin sealant in THA, there was an association with less wound drainage and blood loss (no significant difference), yet the transfusion rate and hospital stay remained similar to the control group.[216]

One review included 6 trials[213-218] that studied the use of fibrin sealants in orthopaedic surgery. In these trials 482 patients were included, of whom 235 were randomized to receive fibrin sealants. The review found use of fibrin sealant in the context of orthopaedic surgery that was associated with a reduced postoperative blood loss on average around 223 mL per patient, and reduced the risk of exposure to allogeneic red blood cell transfusion by 32%. Fibrin sealant treatment was not associated with an increased risk of wound infection, any infection, hematoma formation, or death. Hospital length of stay was not reduced in patients treated with fibrin sealant.[219]

Question 34: Do staples or the type of suture have an effect on infectious events? If so, what is the best closure method to prevent infectious events?

Consensus: In the absence of conclusive data and the wide variability in surgical practice, we make no recommendation regarding specific sutures or staples to prevent infection.

Delegate Vote: Agree: 92%, Disagree: 3%, Abstain: 5% (Strong Consensus)

Justification: We are unable to draw a clear conclusion about the best method for closure to prevent infectious complications due to inadequate definitions for infection complications of surgical wounds. In addition, the majority of the studies reviewed were underpowered. Evidence is lacking regarding patients whose health may interfere with wound healing and in surgical sites of high tension. Tissue adhesives should be considered as a biological sealant rather than a closure method of mechanical strength.

In an RCT that included 90 patients who underwent TKA, no significant differences in infection, dehiscence, general health, and functional and clinical assessments were observed. The study compared the following: (1) combined suture tissue adhesives defined by sutures for capsule and subcutaneous layers and tissue adhesive (2-octyl or nbutyl-2) for the final cutaneous layer, (2) staples, and (3) conventional subcuticular suture approach (sutures used for the capsule, subcutaneous, and cutaneous layers). It was observed that the length of hospital stay was higher with the staple group.[220]

Another trial included 187 patients who underwent TKA (n=85) and THA (n=102) and compared wound closure with 2-octylcyanoacrylate (OCA), staples, and sutures.[221] Early wound discharge (less than 24 hours postoperatively) was reduced with OCA in both THA and TKA. In TKA, prolonged wound discharge was observed with OCA. No significant difference was observed in the incidence of superficial wound infections between groups. No deep infection was detected. Sealing of the wound as measured by blood strike-through onto the dressing was significantly improved with OCA in both joints. The authors concluded that for more mobile surgical wounds (such as with TKA), OCA might not be appropriate for skin closure because it does not provide adequate resistance for withstanding early rehabilitation.

In another trial including 90 patients with THA, skin adhesive and surgical staples were both effective skin closure methods. Staples were quicker and easier to use than skin adhesive and less expensive. No significant difference was found regarding the occurrence of complications, although the study was not adequately powered to detect any case of deep infection.[222]

A review of RCTs in a wide range of non-orthopaedic surgical specialties with pediatric and adult patients[223] concluded that sutures were significantly better than tissue adhesives for minimizing dehiscence. Sutures were also found to be significantly faster to use. No differences

were found between tissue adhesives and tapes for minimizing dehiscence or infection. Tapes and staples were significantly faster to use than tissue adhesives. For all outcomes of dehiscence and infection there were no statistically significant differences between high- and low-viscosity adhesives.

Smith et al. performed a meta-analysis to compare the clinical outcomes of the use of staples and sutures in orthopaedic surgery.[224] The authors included 6 small-sized studies and noted major methodological drawbacks including inadequate definitions for superficial and deep infections in most of them. Based on these studies, they found a significantly higher risk of developing wound infection when the wound was closed with staples rather than sutures (17/350 versus 3/333 superficial or deep infections for staples and sutures, respectively). Five of the 6 studies included data on patients who underwent hip surgery. A higher risk of infection with staples also existed in patients who underwent hip surgery. At this point there is need for future studies to evaluate this issue further.

Question 35: Does the use of a surgical safety checklist and time-out affect the rate of SSI in arthroplasty patients?

Consensus: We support the surgical checklist protocol as beneficial to patient safety, and specifically as it applies to correct administration of prophylactic antibiotics.

Delegate Vote: Agree: 97%, Disagree: 1%, Abstain: 2% (Strong Consensus)

Justification: Checklists seem to improve inter-professional communication in the OR. High-quality evidence exists supporting the beneficial effect of surgical safety checklists and time-outs for reduction of SSI and other major postoperative complications by assuring timely administration of preoperative antibiotic prophylaxis. However, evidence shows that many elements of adapted checklists are not adequately performed. There is no evidence regarding the influence of implementing a mandatory surgical checklist on appropriate application of evidence-based measures for SSI in TJA. Existing evidence shows the beneficial effect of mandatory safety checklists on infectious complications for other simpler procedures.

One study showed that implementation of an inter-professional preoperative checklist in the OR was associated with a decline in communication failures (mean number of communication failures per procedure decreased from 3.95 to 1.31; the number of communication failures associated with visible negative consequences decreased by 64%).[225]

A relationship appears to exist between the adoption of a routine preoperative checklist by the surgical team and improvement in the timing of antibiotic prophylaxis.[226-228] In a prospective study of 8 diverse hospitals around the world (including high- and low-income locations), substantial decreases in major surgical complications and mortality during the early postoperative period was observed after implementation of a World Health Organization checklist in the OR. The adherence rate to appropriate preoperative antibiotic administration increased from 5% to 83% and the incidence of SSI significantly decreased from 6.2% to 3.4% ($p<0.001$). The improvement in quality of care was observed even with incomplete compliance of the checklist.[229] In another study performed in hospitals with a high standard of care in the Netherlands, performing the surgical patient safety system checklist, which includes pre-, intra-, and postoperative elements, also reduced the incidence of SSI (from 3.8% to 2.7%, $p=0.006$) as well as other major postoperative complications. Compliance was associated with greater improvements in quality of care.[226]

In a prospective study, it was observed that many evidence-based measures for SSI reduction (prophylactic antibiotic timing, maintaining normothermia during surgery, appropriate urinary tract catheterization, and hand hygiene) were not applied adequately for arthroplasty procedures and the situation was even worse for fracture surgeries.[230] There is no evidence regarding the influence of a mandatory checklist on appropriate application of its components. However, there are prospective studies demonstrating that implementing mandatory checklists resulted in decrease in the incidence of central line associated bloodstream infections in intensive care unit patients.[231, 232]

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Workgroup 5: Blood Conservation

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Question 1: Is blood transfusion associated with an increased risk of surgical site infection (SSI)/periprosthetic joint infection (PJI)?

Consensus: Yes. Allogeneic blood transfusions is associated with an increased risk of SSI/PJI. The role of autologous transfusion in the risk of SSI/PJI remains inconclusive.

Delegate Vote: Agree: 91%, Disagree: 5%, Abstain: 4% (Strong Consensus)

Justification: Based on the Centers for Disease Control and Prevention (CDC) guideline, perioperative allogeneic blood transfusion in arthroplasty increases the risk of SSI/PJI. The association between autologous blood transfusion and the risk of SSI/PJI is less clear.

According to high-quality evidence from two randomized controlled trials (RCTs) and 4 observational studies, there is an increased risk of SSI with any blood transfusion (allogeneic, autologous, and autologous plus allogeneic blood transfusion data combined) as compared to no transfusion. This is further supported by both a meta-analysis of 6 studies (n=8,493) [odds ratio (OR): 1.56; 95% confidence interval (CI): 1.18–2.06; p=0.002] and a meta-analysis (n=7,484) of 4 observational studies (OR 1.59; 95% CI: 1.15–2.18; p=0.004).[1]

Data from a meta-analysis (n=970) of 2 RCTs in hip arthroplasty suggests that autologous blood transfusion is not associated with an increased risk of SSI when compared to no blood transfusion (OR: 1.15, 95% CI: 0.43–3.13; p=0.78).[1]
Low-quality evidence from a meta-analysis (n=5,737) of 4 observational studies indicates that allogeneic blood transfusion is associated with an increased risk of SSI (non-adjusted OR: 1.46, 95% CI: 1.09-1.95, p=0.01).[1]
Evidence from a meta-analysis (n=2,592) of three observational studies shows that transfusion with allogeneic blood increases the risk of SSI as compared to transfusion with autologous blood (OR: 4.57, 95% CI: 2.39–8.73, p<0.0001).[1] The study by Innerhofer et al.[2] demonstrated a clear increased risk for allogeneic blood over autogenous blood (high overall infection risk in this study). White cell depletion does not appear to affect the infection rate with autologous blood in hip surgery.[3]
Evidence from one RCT and two observational studies indicates no increased risk of SSI in patients who receive both autologous and allogeneic blood transfusions).[1]

Question 2: What are the predictors of the need for allogeneic blood transfusion in patients undergoing surgery for TJA?

Consensus: A lower preoperative hemoglobin level is the strongest predictor for the potential need for allogeneic transfusion after TJA. The use of general anesthesia, higher Charlson comorbidity index, female gender, and longer duration of surgery are predictors of the potential need for allogeneic blood transfusion in patients undergoing total joint arthroplasty (TJA).

Delegate Vote: Agree: 90%, Disagree: 4%, Abstain: 6% (Strong Consensus)

Justification: The above-mentioned factors have been described as predictors of allogeneic blood transfusion in patients undergoing primary TJA. However, in these studies various transfusion triggers have been utilized, with a lower transfusion rate seen when a lower predefined Hgb level is used (currently 7-8 g/dL). Currently the most optimal hemoglobin threshold for transfusion remains unknown. The only prospective randomized controlled trial in orthopaedics is the FOCUS trial,[4] which found no outcome differences with transfusing above or below 8 gm/dL. The results of this trial were similar to those found in the TRICC trial.[5] There are also many studies emphasizing the effect of operative time on perioperative blood loss and transfusion rate.[6-17]

In a single-institute study of 11,373 TJAs, including 4,769 total knee arthroplastyies (TKAs) and 6,604 total hip arthroplasties (THAs), multivariate analysis indicated that male gender (263.59 mL and 233.60 mL in hips and knees), Charlson comorbidity index of >3 (293.99 mL and 167.96 mL in hips and knees respectively), and preoperative autologous blood donation (593.51 mL in hips and 592.30 in knees) increase the amount of blood loss.[18] Regional anesthesia compared to general anesthesia reduced the amount of blood loss. Amount of blood loss in both THA (OR: 1.43, 95% CI: 1.40-1.46) and TKA (OR: 1.47, 95% CI: 1.42-1.51) and Charlson comorbidity index-only in TKA patients (OR: 3.2, 95% CI: 1.99-5.15) increased risk of allogeneic blood transfusion. Preoperative autologous blood donation (OR: 0.01, 95% CI: 0.01-0.02 in hips and 0.02, 95% CI: 0.01-0.03 in knees) decreased the risk of allogeneic blood transfusion.

In a study by Faris et al.[19] the predictive power of 7 preoperative variables (hemoglobin concentration, age, erythropoietin level, ferritin concentration, serum iron, total iron-binding capacity, and predicted blood volume) on the risk of transfusion in orthopaedic patients was tested in 276 surgical cases. The authors found that baseline hemoglobin concentration and predicted blood volume were significant predicators of transfusion risk. They also found an inverse correlation between hemoglobin concentration and transfusion risk. Placebo-treated patients with hemoglobin > 10 to ≤ 13 g/dL had an approximately two times greater risk of transfusion than patients with hemoglobin > 13 g/dL.

The study by Prazoo et al.[20] also confirmed that the preoperative hemoglobin level was a strong predictor of need for blood transfusion following TJA. They assessed the association between preoperative autologous blood donation and risk of transfusion in 600 TJA patients, including 312 THAs and 288 TKAs. The authors suggested that a pre-operative autologous donation may not be necessary. Their data also suggested that the use of a cell salvage system may be effective in reducing the blood transfusion rate.

The study by Hamaji et al. indicated that pre-operative fluid loading can reduce the transfusion requirement and possibly infection rate; however, it was a small study with a high infection rate.[21] Colloid may be preferable over crystalloid[22] and neither method has a significant effect on clotting *in vitro*.[23]

Question 3A: What is the role of the type of anesthesia in minimizing blood loss and allogeneic blood transfusion during arthroplasty surgery for PJI?

Consensus: Compared to general anesthesia, neuraxial anesthesia reduces the amount of blood loss during TKA or THA.

Delegate Vote: Agree: 77%, Disagree: 11%, Abstain: 12% (Strong Consensus)

Question 3B: Is there evidence against neuraxial blockade in PJI cases (due to probable risk of spreading infection)?

Consensus: No. The decision to use neuraxial versus general anesthesia in patients with PJI lies with the anesthesia team and needs to take into account the numerous benefits of neuraxial anesthesia versus the potential for development of infectious central nervous system complications (arachnoiditis, meningitis, and abscess) with the use of anesthesia.

Delegate Vote: Agree: 83%, Disagree: 6%, Abstain: 11% (Strong Consensus)

Justification: Several systematic reviews and meta-analyses[24-28] compared neuraxial with general anesthesia regarding the amount of blood loss and blood transfusion during TJA. All these reviews support the role of neuraxial anesthesia in reducing amount of blood loss and transfusion requirements.

A meta-analysis by Hu et al.[25] of 21 RCTs published from 1966 to April 2008 was performed to study the relationship between type of anesthesia and transfusion requirement. Pooled results from these trials showed that neuraxial anesthesia reduces the operating time (OR: −0.19; 95% CI: −0.33 to −0.05) and transfusion requirement (OR 0.45; 95% CI: 0.22 to 0.94) compared with general anesthesia. Furthermore, a systematic review of 18 studies published from January 1990 to October 2008 involving 1,239 THA patients showed that blood loss may be reduced in patients receiving neuraxial anesthesia compared to general anesthesia.[26] Another systematic review of articles published up until 2004 showed that neuraxial anesthesia reduced the number of transfused THA patients (p=0.0009).[24] The authors concluded that neuraxial blocks have a clear and definite effect on surgical blood loss and result in a reduction in the number of transfused patients. A meta-analysis of 10 clinical trials whose results were published up until August 2005, including 330 THA patients under general anesthesia and 348 patients under neuraxial block, indicated that neuraxial block decreases total operative time by 7.1 min/case (95% CI: 2.3-11.9 min) and intraoperative blood loss by 275 mL/case (95% CI: 180-371 mL).[28] Another study by Stundner et al.[29] demonstrated that neuraxial anesthesia versus general anesthesia significantly reduced overall complications, including the transfusion requirement. Lastly, using a large database, Memtsoudis et al.[30] demonstrated that the need for blood transfusion was reduced with neuraxial versus general anesthesia.

On the contrary, a systematic review of 28 studies published from January 1990 to October 2008 involving 1,538 TKA patients failed to find any evidence supporting a lower amount of blood loss or blood transfusion for patients receiving regional compared to general anesthesia.[27]

A meta-analysis of 17 RCTs about various orthopaedic surgeries including TJA indicated that induced hypotension can reduce blood loss by approximately 287 mL of [95% CI: -447 to -127] during the orthopaedic surgeries.[31] Moreover, a statistically significant reduction in the transfusion rate was also observed in the same cohort (-667 mL of blood transfused; 95% CI: -963 to -370). No statistically significant differences were found regarding operative time and improve surgical condition.

There is ample evidence to suggest that regional anesthesia can be performed safely if antibiotic treatment of the infection has started prior to the placement of the regional block.[32] It appears that serious central nervous system infections such as arachnoiditis, meningitis, and abscess are rare after neuroaxial anesthesia. Thus, an individualized decision must be made for performing neuroaxial block in cases with infection. The anesthetic alternatives, advantages of neuroaxial block, and risk of central nervous system infection, which theoretically may develop in the case of bacteremia, should be taken into account in making this decision. There is a paucity of literature that studies the risk of epidural abscess in patients undergoing surgery for PJI under regional anesthesia. In a recent study, Gritsenko et al.[33] suggested that the risk of the central nervous system after neuraxial block during the removal of infected hip/knee implants is very small and that neuraxial anesthetics be used more liberally in this setting if there are no systemic signs of infection. They also recommended that no epidural catheters remain in place after the procedure. It appears that multiple neuroaxial blocks within a short time period may be a risk factor for development of epidural abscess in patients with underlying PJI.

If neuroaxial anesthesia is employed in patients undergoing treatment for PJI, every effort should be made to remove the epidural catheter soon after surgery. If a central nervous system infection occurs, prompt diagnosis and treatment of infection must be performed to avoid neurologic sequelae.

The study by Chang et al.[34] found that the infection risk was 2.2 times lower with spinal anesthesia versus general anesthesia.

Question 4A: What is the role for adjuvant technologies including cell salvage systems, reinfusion drains, bipolar sealers, and hemodilution for minimizing blood loss during surgery for PJI?

Consensus: There is no defined benefit for the use of cell salvage systems, reinfusion drains, biopolar sealers, and hemodilution for management of PJI.

Delegate Vote: Agree: 85%, Disagree: 8%, Abstain: 7% (Strong Consensus)

Question 4B: What is the role for adjuvant technologies including cell salvage systems, reinfusion drains, bipolar sealers, and hemodilution for minimizing blood loss during TJA?

Consensus: There is no defined benefit for the use of cell salvage systems, reinfusion drains, biopolar sealers, and hemodilution during primary, unilateral TJA.

Delegate Vote: Agree: 80%, Disagree: 11%, Abstain: 9% (Strong Consensus)

Justification: The role of cell salvage in reducing transfusion rates is unclear; however, it appears that cell salvage can be used in infected cases. Leukocyte depletion filters can be used to filter any salvaged blood. These filters are effective at removing white blood cell counts (WBCs) and bacterial loads up to 10^4 CFU/mL. Any residual bacteria would be treated by perioperative antibiotics in the same way as any bacteremia that occurs during the surgery.[35] The use of bipolar sealers has been associated with mixed results in primary TJA. In a double-blind RCT, 71 and 69 THA patients were assigned to either a bipolar sealer or a control arm group (conventional electrocautery), respectively.[36] The authors did not find any significant differences between the two groups regarding either the amount of blood loss or transfusion rate. Based on these findings, the authors discontinued the use of bipolar sealer for THA patients. In another prospective RCT of 105 patients undergoing primary THA, Zeh et al.[37] found that there was no statistically significant difference between total intraoperative and postoperative blood loss between the bipolar sealer and conventional electrocautery group.

On the contrary, a case-matched study showed that use of bipolar sealer may be effective in reducing the amount of blood loss and hemoglobin drop in patients undergoing revision THA for infection.[38] In a case-matched study of 76 consecutive revision THAs for infection, a bipolar sealing group was compared with conventional electrocautery.[38] The results of this study showed that total blood loss, intraoperative blood loss, and perioperative hemoglobin drop were

significantly less in the bipolar sealer group. Furthermore, in a prospective, blinded, randomized study, 50 primary THA were assigned to two groups: bipolar sealer and standard electrocautery.[39] The results of this study revealed that the total blood loss in the bipolar sealer group decreased by 40% and the transfusion rate was reduced by 73%. There was a significant reduction in intra- and postoperative blood loss. Similarly, Marulanda et al.[40] showed that the bipolar sealer can reduce the amount of blood loss in TKA.

Question 5A: Does the use of a drain(s) influence the incidence of SSI/PJI?

Consensus: No. There is no evidence to demonstrate that the use of closed drains increases the risk of SSI/PJI following TJA.

Delegate Vote: Agree: 88%, Disagree: 8%, Abstain: 4% (Strong Consensus)

Question 5B: When should drain(s) be removed?

Consensus: There is no conclusive evidence for the optimal timing of drain removal.

Delegate Vote: Agree: 68%, Disagree: 22%, Abstain: 10% (Strong Consensus)

Justification: Based on a systematic review and a meta-analysis,[41,42] the use of a drain following TJA increases the transfusion rate but there is no increased risk for developing SSI. Studies have indicated that about 90% of postoperative bleeding is collected by the drain within the first 24 postoperative hours. By considering the probable increase in the risk of bacterial colonization due to the drain after 24 hours,[43] it is recommended that drains be removed within 24 hours after routine elective arthroplasty. In select circumstances, the treating surgeon may decide to retain the drain in the operated joint for a longer period of time.

In a Cochrane systematic review, all randomized or quasi-RCTs comparing the use of closed suction drainage systems with no drainage systems for all types of elective and emergency

orthopaedic surgery were evaluated.[41] Thirty-six studies involving 5,464 participants with 5,697 surgical wounds were included. Various types of orthopaedic surgeries, including THA and TKA, were evaluated in this systematic review. Pooling the results of these trials indicated no statistically significant difference in the incidence of wound infection, hematoma, dehiscence, or re-operations between patients in whom a drain was inserted and those without a drain. Blood transfusion was required more frequently in those with drains. The need for reinforcement of wound dressings and the occurrence of bruising were more common in the group without drains. The Cochrane study thus concluded that there is insufficient evidence to support the routine use of closed suction drainage in orthopaedic surgery.

In a meta-analysis by Parker et al.[42] 18 studies on elective THA and TKA including 3,495 patients with 3,689 wounds were evaluated. The results of this systematic review indicated that closed suction drainage increases the transfusion requirements after elective THA and TKA and has no major benefits.

Question 6A: What is the role for tranexamic acid (TA) for minimizing blood loss during surgery for treatment of PJI?

Consensus: Administration of both intravenous and topical TA reduces the amount of blood loss and allogeneic blood transfusion in TJA.

Delegate Vote: Agree: 82%, Disagree: 5%, Abstain: 13% (Strong Consensus)

Question 6B: Does administration of topical TA have an advantage over intravenous (IV) administration?

Consensus: Topical TA does not have any obvious advantage over IV administration of the drug and both are safe. However, topical TA may be used in certain group of patients in whom IV TA is considered to be inappropriate.

Delegate Vote: Agree: 76%, Disagree: 4%, Abstain: 20% (Strong Consensus)

Justification: Based on 7 available systematic reviews and meta-analyses,[44-50] administration of TA reduces the amount of blood loss and blood transfusion in THA and TKA patients. It can be concluded that administration of TA is safe and effective in reducing the amount of blood loss and allogeneic blood transfusion in revision TJA, including surgeries for treatment of PJI. There has been no study to demonstrate that use of either topical or intravenous TA results in a higher incidence of thromboembolic episodes. In fact the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage trial (CRASH) found that TA may be protective against thrombotic complications.[51-53]

A systematic review and meta-analysis by Alshryda et al.[44] evaluated 19 placebo-controlled RCTs. Eighteen of these studied the IV administration of TA, one study evaluated oral administration,[54] another examined topical application of TA,[55] and one compared TA with normovolemic hemodilution.[56] Three RCTs evaluated the effect of high doses (>4 grams) of TA[54,57,58] and others evaluated the effect of low-dose TA.[59-65] The systematic review and meta-analysis found that TA causes a significant reduction in the rate of blood transfusion (risk ratio (RR): 2.56, 95% CI: 2.1 to 3.1, p<0.001; heterogeneity I^2=75%) and total blood loss by a mean of 591 ml (95% CI: 536 to 647, p<0.001; I^2=78%). A subgroup analysis of high-dose TA indicated a reduction in blood transfusion (RR 5.33; 95% CI: 2.44 to 11.65, p<0.001; I^2=0%). This systematic review and meta-analysis did not find any evidence that supported an increase in the risk of either deep-vein thrombosis or pulmonary embolism following administration of TA in TKA patients.

A systematic review and meta-analysis by Sukeik et al.[49] evaluated the effect of administration of TA in THA patients. Eleven RCTs [66-76] were included in the meta-analysis. The authors showed that use of TA reduces intraoperative blood loss by a mean of 104 ml (95% CI: −164 to −44, p=0.0006, I^2:0%), postoperative blood loss by a mean of 172 ml (95% CI: −263 to −81, p=0.0002, I^2:63%), and total blood loss by a mean of 289 ml (95% CI: −440 to −138, p<0.0002, I^2:54%). TA resulted in a significant reduction in the allogeneic blood transfusion rate (risk difference: −0.20, 95% CI: −0.29 to −0.11, p<0.00001, I^2:15%). No significant differences were observed in the rate of deep vein thrombosis, pulmonary embolism, infection rates, or other complications among the study groups.

Administration of TA is effective to further reduce the amount of perioperative blood loss following TKA. In an RCT of 151 patients, Lin et al.[77] randomly assigned patients who

underwent unilateral TKA to one of 3 groups: 1) a placebo group (50 patients); 2) a one-dose TA group (52 patients), who received one injection of TA (10 mg/kg) intra-operatively on deflation of the tourniquet; and 3) a two-dose TA group (49 patients), who received two injections of TA (10 mg/kg) given pre-operatively and intra-operatively. They demonstrated that one intra-operative dose of TA was as effective as two doses for blood conservation during TKA.

In a study by Aguilera et al.[78] the effect of TA in reducing blood loss and blood transfusion in revision TKA was evaluated. In this study, patients who received TA had a significantly lower amount of blood loss (p=0.015); however, the rate of transfusion was not statistically lower in the TA group (p=0.057). No adverse events were observed in the studied patients.

In an RCT of 98 adult patients undergoing THA or TKA, Oremus et al.[79] showed that adding TA to a restrictive transfusion protocol in patients undergoing TJA makes the use of a postoperative blood salvage system unnecessary.

Question 7: What is the role for other agents such as platelet-rich plasma (PRP), fibrin glue for minimizing blood loss?

Consensus: The routine use of PRP is not recommended. There is some evidence that fibrin products may reduce blood loss.

Delegate Vote: Agree: 91%, Disagree: 1%, Abstain: 8% (Strong Consensus)

Justification: There are several RCTs supporting the efficacy of fibrin products in reducing the amount of blood loss and transfusion requirements in TJA patients. However, the results of studies on PRP are mixed and it is difficult to draw a definite conclusion.

In the study by Diiorio et al.[80] 134 TKA patients who received PRP were retrospectively evaluated. The authors failed to show a statistically significant difference regarding the amount of blood loss between patients who received PRP and those who did not.

In a retrospective study of 98 unilateral TKAs (61 received platelet gel intraoperatively), Gardner et al.[81] found that patients who received platelet gel had less difference in preoperative and postoperative hemoglobin levels on day 3 (2.7 vs 3.2 g/dl; p=0.026), which was considered as an indicator of blood loss.

In a retrospective study, Berghoff et al.[82] found that administration of platelet-rich and platelet-poor plasma during wound closure is associated with a better hemoglobin profile and a lower rate of transfusion.

In an RCT, 66 THA patients were randomized to 1 of the 3 following groups 1) a 10 mg/kg bolus of TA before operation; 2) 10 mL of fibrin spray during the operation, or 3) a control (neither TA nor fibrin spray administered).[83] The authors suggested that topical fibrin spray and IV TA both reduce the amount of blood loss significantly compared to the controls. There was no statistically significant difference between the fibrin spray and TA groups regarding the amount of blood loss.

In an RCT of 100 THA, patients were assigned to the study group (receiving autologous fibrin tissue adhesive) or control (no fibrin tissue adhesive) group.[84] The results of this RCT showed a significantly lower amount of blood loss in the fibrin tissue adhesive at 580±240 ml compared to the controls at 810±341 ml.

In an RCT, 81 patients who underwent THA were assigned to receive standard of care plus fibrin sealant (10 mL total) or standard of care without fibrin sealant. In the fibrin sealant group, the amount of blood loss decreased significantly by 23.5%.[81]

The results of two RCTs showed that the administration of fibrin products is associated with reduced blood drainage from the wound and blood loss as well as blood transfusion in TKA patients.[85-87]

Question 8: What is the role for blood salvage (intraoperative and postoperative) during the second stage of two-stage exchange arthroplasty for treatment of PJI?

Consensus: The role of blood salvage (intraoperative and postoperative) during the second stage exchange arthroplasty is inconclusive. Blood salvage should be utilized with caution.

Delegate Vote: Agree: 80%, Disagree: 11%, Abstain: 9% (Strong Consensus)

Justification: The efficacy of a cell salvage system has been shown in orthopaedic surgeries.[88] Although there is no strong evidence regarding the contraindication of cell salvage in PJI cases, traditionally the presence of infection is considered as a contraindication for use of this type of system.[89] However, some authors have suggested that cell salvage can be used in infected cases. Leukocyte depletion filters can be used to filter any salvaged blood. These filters are effective at removing WBC counts and bacterial loads up to 10^4 CFU/mL. Any residual bacteria would be treated by perioperative antibiotics in the same way they would for any bacteremia that occurs during the surgery.[35]

In a Cochrane systematic review, RCTs in which adult patients undergoing elective surgeries were randomized to either a cell salvage group or a control group (no intervention), were evaluated.[88] The results of this systematic review indicated that in orthopaedic procedures the relative risk of exposure to red blood cell transfusion in patients receiving cell salvage systems drops to 0.46 (95% CI: 0.37 to 0.57) and the use of cell salvage systems was not associated with any adverse events.

Question 9: What is the role of administration of erythropoietin, hematinics, or other agents between the two stages of exchange arthroplasty for the treatment of PJI?

Consensus: Treatment of preoperative anemia with iron, with or without erythropoietin, will reduce the risk of transfusion in patients undergoing TJA.

Delegate Vote: Agree: 78%, Disagree: 9%, Abstain: 13% (Strong Consensus)

Justification: There is evidence to suggest that treatment of preoperative anemia with iron, with or without erythropoietin, will reduce the risk of transfusion in patients undergoing TJA. [90] However, some authors suggest that for patients undergoing TJA, anemia should be investigated rather than treated empirically as the risk of gastrointestinal malignancy and/or gastrointestinal bleeding is present.

A systematic review by Spahn[90] indicated that treatment of preoperative anemia with iron, with or without erythropoietin, will reduce the risk of transfusion in patients undergoing TJA.

A double-blind, multicenter RCT compared two regimens of Epoetin-α in reducing the need for allogeneic blood transfusion in patients undergoing THA. Patients were assigned to receive 4 weekly doses of Epoetin-α, 40,000 units (high-dose; n=44) or 20,000 units (low-dose; n=79), or placebo (n=78), starting 4 weeks before surgery. Oral iron supplementation (450 mg/d) for 42 or more days before surgery was administered in all cases. The results of this RCT revealed that both regimens were effective in reducing the need for allogeneic blood transfusion. Patients who received a high-dose regimen had the lowest rate of transfusion.[91]

In two studies by Delasotta et al.[92,93] the authors showed that in mildly anemic patients who undergo revision TKA or THA, administration of Epoetin-α decreases the rate of transfusion.

Question 10: Are self-contained suction suction devices a source of contamination?

Consensus: There is evidence indicating that the tip of surgical suction drains can be a source of contamination.

Delegate Vote: Agree: 70%, Disagree: 9%, Abstain: 21% (Strong Consensus)

Justification: A few studies indicate that microorganisms can be obtained from a considerable number of cultures from the tip of surgical suctions. However, there is no evidence indicating that there is a correlation between the tip of suction contamination and subsequent SSI/PJI.

Robinson et al.[94] assessed the colonization of the suction tip in an ultraclean-air operating theater in 39 patients and found evidence of bacterial contamination in 41% of them. Similarly, Strange-Vognsen and Klareskov obtained positive cultures from 12 out of 22 suction tips used in THA.[95]

Question 11: What is the role of preoperative autologous blood donation between the two stages of exchange arthroplasty for PJI?

Consensus: There is no role for autologous blood donation between the two stages of exchange arthroplasty for PJI.

Delegate Vote: Agree: 83%, Disagree: 7%, Abstain: 10% (Strong Consensus)

Justification: To the best of our knowledge, there is no single study about the role of autologous blood donation between the two stages of exchange arthroplasty. However, due to the theoretical risk of spreading infection, blood banks refuse to accept blood donation from patients with infection or those suspected of having an infection.

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Workgroup 6: Prosthesis Selection

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Question 1: Does the type of prosthesis influence the incidence of surgical site infection (SSI) or periprosthetic joint infection (PJI)?

Consensus: The type of prosthesis (cemented versus uncemented) or coating with hydroxyapatite does not influence the incidence of SSI or PJI.

Delegate Vote: Agree: 92%, Disagree: 4%, Abstain: 4% (Strong Consensus)

Justification: Based on the available literature there is no difference in the incidence of SSI or PJI following the use of cemented (without antibiotics) versus uncemented arthroplasty components. Some registry data support the finding that in total hip arthroplasty (THA) the risk of revision due to infection is equivalent between uncemented and cemented arthroplasty with antibiotic-loaded cement, but higher for cemented arthroplasty without antibiotic cement.

Cemented versus uncemented THA: Although various randomized controlled trials (RCTs) and systematic reviews comparing the survival of cemented versus uncemented components for THA were found,[1,2] none had PJI as the primary endpoint.

Excluding hybrid configurations from the analysis, the Swedish hip arthroplasty registry (SHAR) showed that in 145,339 patients who underwent 170,413 THAs between 1992 and 2007 the rate of deep infection was 0.5%. The main indication for THA was primary osteoarthritis (OA), but cases of fractures, inflammatory arthropathy, and others accounted for 24%. Uncemented THA did not present a higher risk of revision due to infection compared to cemented THA (risk ratio (RR)=0.9, confidence interval (CI): 0.6–1.3). Although a differential analysis comparing antibiotic-laden cement versus cement alone is not presented, the authors stated that in the SHAR, more than 90% of the cases used antibiotic-laden cement. The authors concluded that "it appears that the risk of revision due to infection should be about equal if uncemented fixation is compared with cemented fixation, provided that the cement is antibiotic-laden."[3]

Data from the Norwegian registry showed that in over 97,344 primary THAs performed in 79,820 patients from 1987 to 2007, the 5-year survival was 99.46% when revision due to deep infection was considered as the endpoint.[4] The RR for the first revision due to infection was lower in the group of patients receiving a prosthesis fixed with antibiotic-laden cement. When

compared to antibiotic-laden cemented fixation, uncemented fixation had a higher risk of revision due to infection (RR: 1.4, CI: 1.0–1.8, p=0.03). The use of cement without antibiotics also had a higher RR when compared to antibiotic-laden cemented fixation (RR: 1.9, CI: 1.5–2.3, p<0.001). The higher risk of PJI presented by cement without antibiotics was described in a previous study from the same registry lead by Engesaeter et al.,[5] who found that the risk of revision due to infection was the same for uncemented and for cemented arthroplasties with antibiotic-loaded cement, but higher for cemented arthroplasties without antibiotic cement.

A prospective study from 3 Norwegian health registries comprising the period 2005 to 2009[6] evaluated the rate of SSI and revisions due to infections in THA. The rate of SSI was 3% (167/5,540) and was not influenced by the type of fixation (cemented, uncemented, or hybrid). The rate of revision due to infection was 0.8% (236/31,086) and was influenced by the type of fixation. Compared to cemented hips, uncemented hips had a higher adjusted risk of revision due to infection (RR: 1.5, CI: 1.0–2.2, p=0.03). The rate of revision due to infection presented by hybrid fixation was not different when compared to cemented fixation (RR: 1.1, CI: 1.6-0.7, p=0.7).

In a study demonstrating the increasing risk of PJI conducted by the Nordic Arthroplasty Register Association (Denmark, Finland, Norway, and Sweden), the use of cement without antibiotics and hybrid configurations were found to be risk factors for infection.[7]

Arthroplasty due to hip fractures: A Cochrane review from 2010 compared cemented and uncemented hemiarthroplasties for proximal femur fractures in adults. With regards to the rate of superficial wound infection, the review found no differences between the groups (test for overall effect: Z=0.16, p=0.88). With respect to deep infections, again no differences among the studied groups were found (test for overall effect: Z=0.46, p=0.64).[8]

A recently published RCT comparing 80 cemented hemiarthroplasties and 80 uncemented hemiarthroplasties for displaced femoral neck fractures in the elderly found that the rate of infections was similar in both groups: 5% (CI: 2.0-12.2) in the cemented group versus 6.3% (CI: 2.7-13.8) in the uncemented group.[9] Unfortunately, the use of antibiotic-laden cement was not clarified by the authors.

Arthroplasty due to osteonecrosis: A recent case series from a single surgeon did not find a difference in the rate of infections between cemented and uncemented stems employed in the

treatment of end-stage OA secondary to osteonecrosis of the femoral head. It is important to disclose that cemented stems were used in the context of a hybrid construct.[10]

Revision arthroplasty: In the setting of revision arthroplasty, a study from the Swedish registry compared the survival between an uncemented stem and a cemented stem. No difference in the rate of failure due to infection was observed.[11]

Cemented versus uncemented total knee arthroplasty (TKA): Although various RCTs and systematic reviews comparing the survival of cemented versus uncemented components for TKA were found, none presented with PJI as the primary endpoint.

A recent review from the Cochrane group comparing the performance of cemented versus uncemented components in TKAs did not include a formal comparison regarding SSI/PJI as a relevant outcome.[12]

A recently published RCT evaluated the performance of cemented and uncemented knees in the same patient (bilateral TKA in 50 patients). No difference was found in terms of the infection rate.[13]

An RCT compared the performance of cemented TKA (277 replacements) versus non-cemented press-fit condylar implants (224 replacements) in a 10-year survival analysis. A greater number of cemented implants (5 cemented, 1 cementless) were revised for infection. Using revision for infection as the endpoint, the 10-year survival rates were 98.1% (95% CI 94.1-99.4) in the cemented group and 99.5% (95% CI 95.3-99.9) in the cementless group. The difference was not statistically significant (hazard ratio 4.31, 95% CI 0.50-37.14, p=0.18).[14] The analysis at 15 years showed that in the cemented group components were revised for infection in 7 patients (2.5%). In the cementless group, components were revised for infection in 4 patients (1.8%), showing no significant difference.[15]

Role of hydroxyapatite (HA): A Cochrane review studied hemiarthroplasty versus HA-coated hemiarthroplasty for proximal femur bone fractures in adults. No difference in the rate of superficial or deep infections was found.[8]

An RCT compared HA-coated tibial implants with cemented tibial fixation in primary TKA. No difference in the rate of infection was found (3 cases of cellulitis/41 cemented TKA versus 3 cases of cellulitis/40 HA-coated TKA.[16]

An RCT compared HA-coated (29 knees) with cemented (28 knees) tibial components. Two infections were found in the group of HA knees versus none in the cemented group, with no statistical difference.[17]

Question 2A: Does antibiotic-impregnated cement reduce the incidence of PJI following elective primary total joint arthroplasty (TJA)?

Consensus: Yes. Antibiotic-impregnated polymethylmethacrylate cement (ABX-PMMA) reduces the incidence of PJI following TJA and should be used in patients at high risk for PJI following elective arthroplasty.

Delegate Vote: Agree: 90%, Disagree: 9%, Abstain: 1% (Strong Consensus)

Question 2B: Does antibiotic-impregnated cement reduce the incidence of PJI following elective revision joint arthroplasty?

Consensus: Yes. Antibiotic should be added to cement in all patients undergoing cemented or hybrid fixation as part of revision arthroplasty.

Delegate Vote: Agree: 88%, Disagree: 9%, Abstain: 3% (Strong Consensus)

Justification: There is evidence that the addition of antibiotics to PMMA cement leads to a reduction in the incidence of PJI and all-time failure of the prostheses after elective arthroplasty.[18-21] A number of studies have shown that the addition of antibiotic powder to cement, particularly during revision arthroplasty, leads to a dramatic reduction in the incidence of later failure due to infection.[21,22] Thus, we feel it is justified to state that antibiotics (dose and type are at the discretion of the surgeon) should be added to cement during revision arthroplasty, particularly revision performed for infection.

The use of ABX-PMMA during primary arthroplasty is not as clear-cut. The main concerns and unresolved issues that are related to the routine use of ABX-PMMA cement during primary arthroplasty are: a) the type and dose of antibiotic, b) cost, c) possible emergence of resistant organisms, d) mechanical weakening of the PMMA cement and possible increase in subsequent failure of the prosthesis, and e) off-label use.

It is difficult to determine from the literature which antibiotic and what dose should be added to cement and if there is a difference between various cement formulations with regard to their ability to prevent infection. What is known is that there is a clear difference in the elution profile of antibiotics from PMMA cement that is affected by the type of antibiotic, dose of antibiotic, and the type of PMMA. High viscosity cements containing MA-MMA copolymers, such as Cobalt G-HV, Palacos R+G, Refobacin, and SmartSet GHV, have been shown to have better antibiotic elution profiles than other PMMA formulations.[23-28]

What remains unknown at the present time is whether the use of antibiotic-impregnated cement products during elective primary arthroplasty is cost effective.[29] One of the reasons for the lack of conclusive findings regarding the economic aspect of this practice relates to the inability to determine the exact cost of treatment of PJI. All available costs for treatment of PJI are estimates and vary widely. However, one known fact is that the cost of treatment of PJI caused by methicillin-resistant organisms is drastically higher.[30] Thus, in geographic areas of the world where the incidence of methicillin-resistant *Staphylococcus aureus* PJI is high, the cost of routine use of antibiotic-impregnated cement may be justified. Due to the cost,[29] we feel that the routine use of ABX-PMMA during elective primary arthroplasty should be limited to patients at high risk of PJI (such as those with diabetes or immunosuppressive conditions).

The concern that remains is whether hand-mixing of antibiotic to cement (at the low-dose quantity) can lead to a significant reduction in the mechanical properties of cement and subsequent failure of the prostheses.[31,32] Because of the latter issue, we recommend that either pre-mixed ABX-PMMA should be used (if the cost can be justified) or if hand-mixing of cement is being considered, the dose of antibiotic added to cement should remain around 1-1.5g per 40g pack of cement.

Different antibiotics can be mixed with PMMA, such as gentamicin, tobramycin, cefuroxime,[18] vancomycin, piperacillin/tazobactam,[33] and clindamycin.[34] Potentially, other antibiotics can be added to PMMA, including cefazolin, ciprofloxacin, gatifloxacin, levofloxacin, linezolid, and rifampin. [35] A recent publication by Han et al.[36] showed that bone cement polymerization was

delayed to a mean of 122.5 minutes when rifampin was added to the matrix. The authors conclude that rifampin is unsuitable for antibiotic-loaded bone cement.

An animal model compared different combinations: cefazolin (Ancef; 4.5g/40g cement powder), ciprofloxacin (Cipro; 6g/40g powder), clindamycin (Cleocin; 6g/40 g powder), ticarcillin (Ticar; 12g/40g powder), tobramycin (Nebcin; 9.8g/40g powder), and vancomycin (Vancocin; 4g/40g powder).[37] Clindamycin, vancomycin, and tobramycin demonstrated the best elution into bone and granulation tissue.

In addition, the Australian Orthopaedic Association's National Joint Replacement Registry has shown that THA done with ABX cement resulted in a lower rate of failure secondary to infection and aseptic reasons.[38]

Question 3: Does the type of bearing surface in THA influence the incidence of SSI/PJI?

Consensus: Observational data suggest that metal-on-metal bearing may be associated with a higher risk of PJI.

Delegate Vote: Agree: 78%, Disagree: 15%, Abstain: 7% (Strong Consensus)

Justification: Different studies evaluated the performance of different bearing surfaces in THA. Milošev et al.[39] compared the 10-year survivorship of hip prostheses with use of conventional polyethylene, metal-on-metal, or ceramic-on-ceramic bearings and found no differences in the rate of PJI. Nikolaou et al.[40] in a RCT compared cobalt–chrome on ultra-high-molecular-weight polyethylene, cobalt–chrome on highly cross-linked polyethylene, or a ceramic-on-ceramic bearing. Again, no differences in terms of PJI were found. Using Medicare data, Bozic et al.[41] found that metal-on-metal bearings were associated with a higher risk of PJI (hazard ratio: 3.03; CI: 1.02-9.09) when compared with ceramic-on-ceramic bearings (0.59% versus 0.32%, respectively). In a more recent study from the same group,[42] this observation was confirmed. After adjusting for patient and hospital factors, metal-on-metal bearings were associated with

higher risk of PJI (p=0.001) than metal-on-polyethylene and higher risk of PJI (p=0.014) than ceramic-on-ceramic bearings.

Question 4: Does the size of prosthesis (volume of foreign material) influence the incidence of SSI following TJA?

Consensus: Yes. The incidence of infection is higher following the use of mega-prostheses.

Delegate Vote: Agree: 85%, Disagree: 11%, Abstain: 4% (Strong Consensus)

Justification: Although it is known that the incidence of infection following the use of megaprostheses for reconstruction (both for neoplastic and non-neoplastic conditions) is higher than for routine arthroplasty,[43] there is no clear evidence that this relates to the size or volume of the prosthesis used. Patients receiving megaprostheses are placed at a higher risk of infection due to the extent of soft tissue dissection, larger amounts of blood loss, subsequent need for transfusion, underlying diagnosis of cancer for some patients, immunocompromised status, older age (for patients with non-neoplastic failure), and poor local condition of the soft tissues.[44] There is no focused study that has evaluated the influence of the size and volume of the prosthesis in the incidence of PJI.

Question 5: Is there a difference between various types of cement with regard to the incidence of SSI/PJI after TJA?

Consensus: There is no clear difference in the incidence of SSI/PJI following joint arthroplasty when different PMMA cement formulations are used.

Delegate Vote: Agree: 92%, Disagree: 3%, Abstain: 5% (Strong Consensus)

Justification: Although there are some *in vitro* studies comparing the elution profiles of different commercial brands of PMMA,[24,28,45] we found no clinical studies supporting that the use of one or another PMMA formulation is superior in terms of incidence of PJI.

Question 6: Is there a difference between various types of cement with regard to antibiotic elution?

Consensus: There is a clear difference in the elution profile of antibiotics from PMMA cement that is determined by the type of cement, type, and dose of antibiotic.

Delegate Vote: Agree: 96%, Disagree: 0%, Abstain: 4% (Strong Consensus)

Justification: There are a number of studies that have evaluated the elution of antibiotics from PMMA cement. The majority of these studies are *in vitro* studies and do not capture the clinical setting. High-viscosity cements containing MA-MMA copolymers, such as Cobalt G-HV, Palacos R+G, Refobacin, and SmartSet GHV have been shown to have higher cumulative delivery of antibiotic than other PMMA formulations.[23-28,45]

Meyer et al. compared the antibiotic elution of Cemex Genta (1.0g gentamicin), Cobalt G-HV (0.5g gentamicin), Palacos R+G (0.5g gentamicin), Simplex P (1.0g tobramycin), SmartSet GMV (1.0g gentamicin), and VersaBond AB (1.0g gentamicin). Cobalt G-HV and Palacos R+G produced similar 5-day cumulative antimicrobial activity under both vacuum and atmospheric mixing regimes. These two cements produced cumulative antimicrobial activities that were statistically greater than all of other cements tested when vacuum-mixed and all of the cements except Cemex Genta when mixed under atmospheric conditions, despite containing only half of the antibiotic dose found in the other cements.[25]

Squire et al. compared the antibiotic efficacy of Cemex Genta (1.0g gentamicin), Cobalt G-HV (0.5g gentamicin), Palacos R+G (0.5g gentamicin), Simplex P (1.0g tobramycin), SmartSet GMV (1.0g gentamicin), SmartSet GHV (1.0g gentamicin), and VersaBond AB (1.0g gentamicin). Generally, the low- and medium-viscosity cements showed the highest antimicrobial efficacy after one day, but on days 2 to 7, higher viscosity cements demonstrated

greater bacterial growth inhibition. No significant differences between Palacos R+G, Cobalt G-HV, and SmartSet GHV were noted at any of the time points. Again, Palacos R+G and Cobalt G-HV performance in this study was achieved with only half of the antibiotic dose found in the other cement formulations.[27]

These two studies[25,27] suggest that antibiotic elution and activity from Palacos and Cobalt HV bone cement formulations is very similar (no statistically significant differences noted for any comparisons in the two studies) and that their elution characteristics are generally superior those of other PMMA bone cements.

Dall et al. compared the gentamicin elution of Palacos R+G to Refobacin Bone Cement R.[23] No statistically significant differences for the gentamicin elution were noted at 1 hour or at 72 hours. Neut et al. also compared the gentamicin release and antibacterial efficacy of Palacos R+G to Refobacin Bone Cement R.[26] There were no statistically significant differences between Refobacin Bone Cement R and Palacos R+G for bulk gentamicin release or antimicrobial efficacy of the gentamicin elution.

The cement-specific mechanisms governing the elution of antibiotic are not perfectly clear, but it is known that the hydrophilicity of different types of acrylic polymers vary, with MMA-MA copolymers being more hydrophilic than pure PMMA, and PMMA being more hydrophilic than MMA-styrene copolymers.[46] Cements comprised of more hydrophilic polymers will exchange water more readily with their environment and release water soluble antibiotics more freely. Cement viscosity and resulting cement mass morphology (eg porosity profile) may also influence antibiotic elution.[25]

Question 7: Is there a difference in the incidence of SSI/PJI with the use of different uncemented prostheses?

Consensus: The incidence of SSI/PJI may be lower with the use of porous metal (tantalum) implants during revision arthroplasty compared to titanium.

Delegate Vote: Agree: 44%, Disagree: 33%, Abstain: 23% (No Consensus)

Justification: There is no study that demonstrates with certainty that there may be a clear difference in the incidence of SSI/PJI following primary TJA using different uncemented components. There is evidence in the literature[47-51] in addition to a recent unpublished study showing the incidence of infection to be lower with the use of tantalum prostheses (Tokarski et al., publication pending). The latter was particularly true when tantalum components were used in revisions performed for the treatment of infection. Thus, the incidence of recurrence or reinfection following reimplantation surgery for PJI was much lower in patients receiving tantalum compared to titanium.

The scientific rationale for this observation may relate to the higher osseointegration potential of tantalum compared to titanium implants. The race to the surface may be accomplished earlier and better when porous implants are used during challenging reconstructive surgeries, particularly those performed for infection. An additional factor that has been proposed as a possible protective factor for PJI with tantalum may relate to the three-dimensional structure and pore size of tantalum prosthesis, which prohibits bacterial growth and the formation of biofilm.

Question 8: Is there a role for the use of antibiotic powder (such as vancomycin) in the wound during TJA?

Consensus: No. There is no literature to suggest that the use of vancomycin powder poured into the wound or placed in the vicinity of an implant reduces the incidence of PJI. A few studies have shown that the use of vancomycin powder reduces the incidence of SSI following non-arthroplasty procedures. Future studies are needed.

Delegate Vote: Agree: 91%, Disagree: 5%, Abstain: 4% (Strong Consensus)

Justification: There are no studies that have evaluated the role of adding vancomycin powder to the incision during TJA. There are a number of studies that showed a reduced incidence of SSI following spine procedures when vancomycin powder was placed in the incision.[50,52,53] There is a clear need for a randomized, prospective study to evaluate this issue.

Question 9: Is there a difference in the incidence of SSI/PJI with the use of metal augments compared to allograft to reconstruct bone deficiency in the setting of infection?

Consensus: There is no difference in the incidence of SSI/PJI following the use of metal augments or allograft bone for reconstruction of bone defects.

Delegate Vote: Agree: 80%, Disagree: 7%, Abstain: 13% (Strong Consensus)

Justification: There is no study in the orthopaedic literature that has evaluated this particular issue. Although one may be tempted to assume that the use of bone allograft, especially when combined with antibiotics, should lead to a lower incidence of infection, there is no clear evidence for such an assumption. We believe that the incidence of infection following complex revisions with extensive bone loss that necessitates the use of metal augment and/or bone graft is naturally higher than primary or simple revision arthroplasty. However, the increase in these patients cannot be attributed to the use of augment or bone graft.

Question 10: Is there a role for modification of the prosthesis surface that may minimize PJI?

Consensus: There is a real need for surface modifications of implants that can help reduce bacterial colonization and subsequent SSI/PJI.

Delegate Vote: Agree: 76%, Disagree: 15%, Abstain: 9% (Strong Consensus)

Justification: Modification of the prosthesis surface to reduce bacterial colonization and subsequent infection appears to be promising in the field of TJA. At the present, a variety of surface modification employing antibiotics,[54-57] silver,[58,59] copper,[60,61] and others[62,63] have proven to be successful in preclinical models. One experience with the use of copper in a spacer in the clinical setting appears favorable.[64] Further investigations are required to make stronger

conclusions regarding the applicability, biosafety, and cost-effectiveness of these technologies. In emerging clinical studies the use of implants coated with silver or iodine-supported titanium implants used during reconstruction of joints in immunocompromised patients has lead to a substantial reduction in the incidence of SSI/PJI (see question 18, Workgroup 8).

Question 11: Are there any novel developments for the prevention of SSI/PJI?

Consensus: The orthopaedic community needs to explore the potential for surface modifications of the prosthesis in an effort to reduce the incidence of SSI/PJI.

Delegate Vote: Agree: 84%, Disagree: 10%, Abstain: 6% (Strong Consensus)

Justification: PJI has emerged as one of the most important issues in the field of TJA and will continue to grow over the coming decades. Utilizing developed risk indices to stratify and medically optimize patients, modifying implants to incorporate antimicrobial and anti-biofilm properties, and developing clinically applicable vaccines and biofilm inhibiting enzymes will address current struggles in preventing PJI. The success of future treatment strategies will hinge on refining the indications and techniques of current surgical procedures as well as the rational use of biofilm-disrupting technologies and photodynamic therapy. Finally, the field of metabolomics, though still relatively in its infancy, likely holds the key to a novel diagnostic and treatment approach to infection and a more profound understanding of the pathophysiology of PJI in the human body.[65]

New Methods for the Detection and Prevention of Orthopaedic Biofilm Infections.
The limited activity of conventional antimicrobials against biofilm-centered device infections requires new strategies for 1) detection of biofilm on indwelling implants, 2) treatment options of infected implants, and 3) conferring protection onto implants against *a priori* bacterial colonization and resulting biofilm formation. Ehrlich et al. argued that the detection of biofilm infections is negatively impacted by the fact that biofilm cultures fail to recover and grow under current culture protocols.[66] This compromises clinical decision making due to the lack of a

causative pathogen aiding in the selection of an efficacious antimicrobial regimen.[67] The consensus to improved diagnoses and biofilm detection is being addressed by workgroup 7. Novel engineering approaches to the control of orthopaedic biofilm infections have been discussed by Ehrlich et al. whereas microelectromechanical-systems-based biosensors monitor bacterial biofilm dynamics such as quorum sensing, with the goal to release a drug payload that will effectively eradicate both biofilm and planktonic bacteria.[66] While the development and validation process for smart sensing implants is still in the benchtop phase, other strategies addressing implant surface modifications have advanced through rigorous preclinical testing, with some awaiting or entering early human clinical trials. These technologies are largely based on either releasing a timed payload of an antimicrobial to achieve high local tissue concentrations from a carrier coating such as a hydrogel, sol-gel, or other thin layer coating methodologies.[68] Variable release kinetics associated with drug eluting technologies often heighten the concerns for bacterial resistance, an area that continues to draw attention both from a clinical and regulatory perspective. Other surface derivatization strategies achieve a deadly topography killing bacteria on contact, such as covalent tethering of antimicrobial peptides or the binding of charged molecules to the substrate surface.[56,69] While some of these covalently-attached coatings aim to confer long-term protection to the implant, the longevity of these bactericidal coatings has not been established beyond short-term efficacy in an *in vivo* setting. The field of biomimetics is rapidly gaining mainstream interest in many engineering and material science disciplines. Hierarchical structures with dimensions of features ranging from the macroscale to the nanoscale are extremely common in nature to provide intriguing properties of interest. This field allows one to emulate biology or nature to develop nanomaterials, nanodevices, and processes which could provide desirable surface topographies in the battle against bacterial colonization of implants. The growing literature reports on a large number of objects including aquatic animals, insects, plants, and bacteria with surface properties of commercial interest.[70] Although there are many appealing technologies addressing biofilm mitigation for implant-associated infections, considerable challenges remain. Challenges along the pivotal path of translation include successful development of concepts for the transfer of lab-type processes to mass production (eg surface synthesis) in a cost-effective manner, designing refined preclinical *in vivo* studies to address pertinent regulatory metrics for both safety and efficacy (eg local and systemic effects of chronic antimicrobial exposure, efficacy in the context of polymicrobial exposure.).

As our understanding of biofilm physiology, immune modulation, and systemic and local host interactions increases, so will our repertoire of anti-biofilm strategies. With continued

interdisciplinary collaborative efforts between clinicians, academia, and the industry, new and effective interventions will follow. A critical cornerstone in the equation of successful periprosthetic infection control is a constructive educational dialogue with the various regulatory bodies. This effort is paramount to support the successful translation of innovative technologies from bench to bedside.

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Workgroup 7: Diagnosis of Periprosthetic Joint Infection

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Question 1A: What is the definition of periprosthetic joint infection (PJI)?

Consensus: PJI is defined as:

* Two positive periprosthetic cultures with phenotypically identical organisms, or
* A sinus tract communicating with the joint, or
* Having three of the following minor criteria:
    - Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR)
    - Elevated synovial fluid white blood cell (WBC) count OR ++change on leukocyte esterase test strip
    - Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)
    - Positive histological analysis of periprosthetic tissue
    - A single positive culture

Delegate Vote: Agree: 85%, Disagree: 13%, Abstain: 2% (Strong Consensus)

Question 1B: What are some considerations for the definition of PJI?

Consensus: Clinically, PJI may be present without meeting these criteria, specifically in the case of less virulent organisms (eg P. acnes). Synovial leukocyte esterase can be performed as a rapid office or intraoperative point of care test using urinalysis strips. In the case of a bloody aspiration, centrifugation has been shown to preserve the accuracy of the colorimetric test for leukocyte esterase

Delegate Vote: Agree: 76%, Disagree: 14%, Abstain: 10% (Strong Consensus)

Justification: This is an adaptation of the Musculoskeletal Infection Society's (MSIS) definition of PJI.[1] A sinus tract communicating with the prosthetic joint or two positive cultures with

phenotypically identical organisms can be considered pathognomonic for PJI and therefore either of these items alone defines it.

The minor criteria are traditional tests utilized in the work-up of PJI that have a proven, reproducible accuracy in diagnosis yet are not independently pathognomonic for joint infection. Serum ESR and CRP are known sensitive markers of PJI with relatively poor specificity and can be influenced by other infectious and non-infectious inflammatory diseases, including extra-articular infection.[2-6] The combination of an elevated ESR and CRP with traditional thresholds has been shown to be a more accurate predictor of PJI than isolated elevations of the ESR or CRP alone.[4,5,7]

Synovial fluid WBC count and PMN% are well established as markers of PJI.[3,8-12] They are accurate predictors of PJI that can occasionally be elevated in an aseptic joint pain.

Despite significant variability between institutions, multiple authors—including those of a rigorous meta-analysis[13]—have shown the utility of histologic analysis of periprosthetic tissue to diagnose PJI.[13-20] Although the appropriate thresholds for diagnosing PJI in histologic analysis is controversial, a maximum tissue concentration between 5 and 10 PMN/HPF in each of 5 or more HPF seems to carry the best diagnostic performance. The criterion of a total of 23 PMNs in 10 HPF[17] is thought to lead to the same final diagnosis as the criteria listed above in most cases. Neutrophils entrapped in superficial fibrin are not predictive of infection and submitting samples obtained by sharp dissection instead of cautery will help limit false positive diagnoses due to thermal artifacts.

Recent analyses have shown that application of synovial fluid to a simple urine test strip and attention to leukocyte esterase results can be an accurate marker of PJI (sensitivity=81%-93% specificity=87%-100%) with instantaneous results.[21,22] One study found that one-third of synovial aspirates were unable to be tested with colorimetric reagent strips.[22] However, recent work suggests that centrifugation of the synovial sample at 6,600 revolutions per minute for 2-3 minutes will help separate out the red blood cells and allowing for colorimetric testing to be performed accurately.[23]

A single positive culture, while suggestive of PJI, can represent a false positive[24-26] and is therefore a minor criterion and must be weighed in light of other diagnostic tests.

Gram stain[24,27-32] and serum white blood cell count and differential[12,33,34] have been shown to be poor markers of PJI and have therefore not been included in this definition.

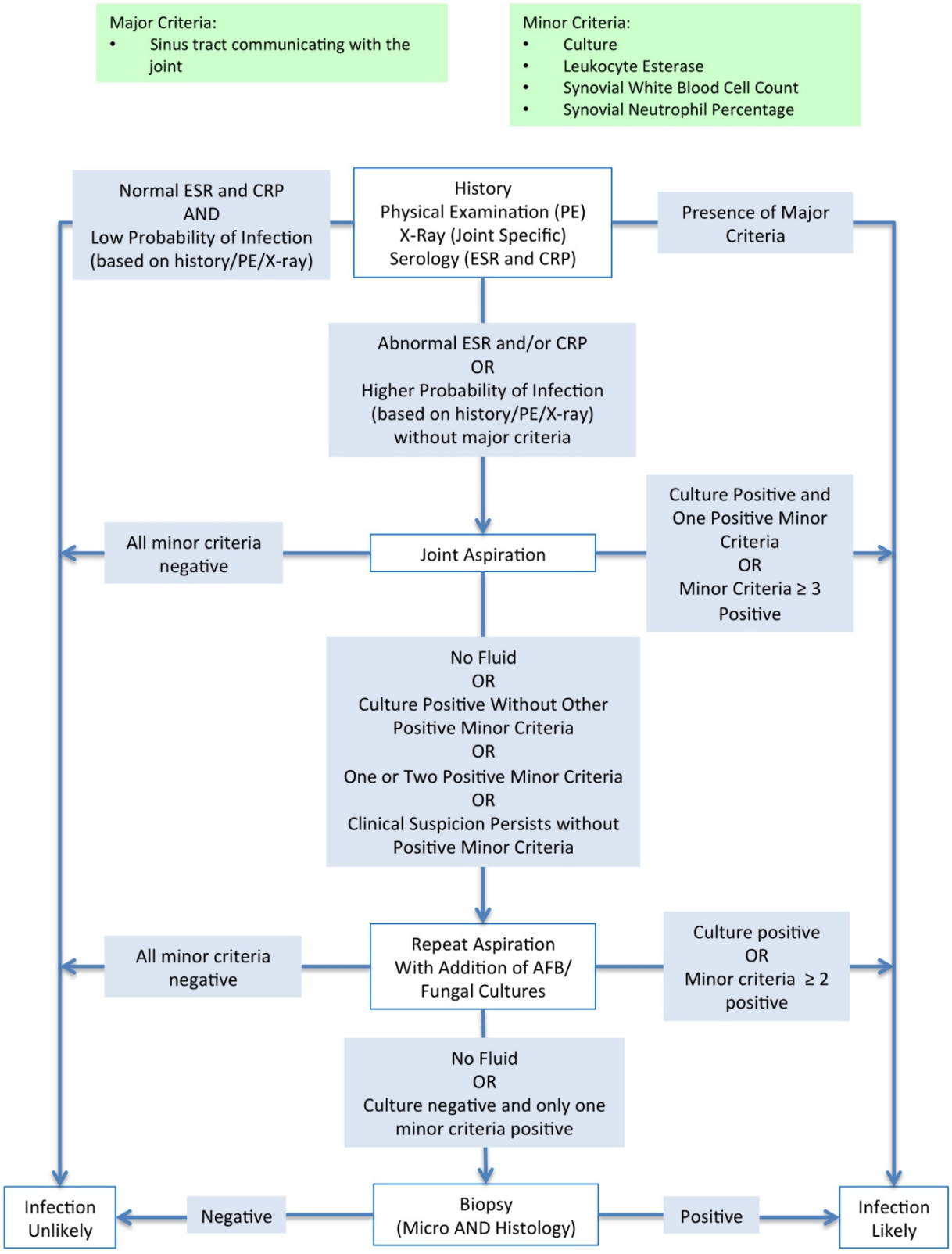
Intra-articular purulence, a former minor criterion of the MSIS,[1] has often been considered

pathognomonic for PJI. However, purulence has also recently been found in cases of adverse local tissue reaction to metal-on-metal hip implants and corrosion reactions associated with a modular metal-on-metal junction.[35-37] Furthermore, determining the presence of purulence is subjective. As a consequence purulence has now been removed as a minor criterion from definition of PJI.

Question 2: Do you agree with the American Academy of Orthopaedic Surgeons's (AAOS) algorithm for diagnosis of PJI?

Consensus: The following is an adaptation of the AAOS's algorithm for the diagnosis of PJI. This algorithm should be applied to patients who present with a painful or failed arthroplasty.

Delegate Vote: Agree: 91%, Disagree: 0%, Abstain: 9% (Strong Consensus)


Major Criteria:
• Sinus tract communicating with the joint
Minor Criteria:
• Culture
• Leukocyte Esterase
• Synovial White Blood Cell Count
• Synovial Neutrophil Percentage
Normal ESR and CRP AND Low Probability of Infection (based on history/PE/X-ray)
History
Physical Examination (PE)
X-Ray (Joint Specific)
Serology (ESR and CRP)
Presence of Major Criteria
Abnormal ESR and/or CRP OR Higher Probability of Infection (based on history/PE/X-ray) without major criteria
All minor criteria negative
Joint Aspiration
Culture Positive and One Positive Minor Criteria OR Minor Criteria ≥ 3 Positive
No Fluid OR Culture Positive Without Other Positive Minor Criteria OR One or Two Positive Minor Criteria OR Clinical Suspicion Persists without Positive Minor Criteria
All minor criteria negative
Repeat Aspiration With Addition of AFB/ Fungal Cultures
Culture positive OR Minor criteria ≥ 2 positive
No Fluid OR Culture negative and only one minor criteria positive
Infection Unlikely
Negative
Biopsy (Micro AND Histology)
Positive
Infection Likely

Considerations:

Clinical judgment should not be outweighed by use of the diagnostic algorithm or any one individual test. A preoperative aseptic diagnosis using this algorithm should not eliminate suspicion for PJI. Patients should be considered to have a higher probability of infection if they have a history of persistent pain or stiffness and any of the following:

- Recent bacteremia,
- Multiple surgeries on the same joint,
- History of periprosthetic joint infection,
- Comorbidities predisposing patients to an immunocompromised state, eg diabetes mellitus, inflammatory arthropathy, or malnourishment,
- Factors that increase risk of skin barrier penetration, eg intravenous drug use, poor wound conditions, psoriasis, chronic venous stasis, or skin ulceration,
- Superficial surgical site infection related to the joint.

Physical exam findings suggestive of PJI:

- Wound dehiscence, or
- Joint warmth, redness, or swelling

Plain radiographic signs suggestive of PJI:

- Signs of loosening of previously well-fixed components (particularly loosening seen within the first 5 years postoperatively),
- Osteolysis or bone resorption around the prosthetic components should not be considered to be related to wear of the bearing surface, particularly if seen at less than 5 years post-operatively,
- Subperiosteal elevation, or
- Transcortical sinus tracts.

It is important to note that plain radiographs are generally normal in the setting of PJI.

Justification: In data analysis performed by this workgroup's members, the use of serology screening followed by joint aspiration with fluid cell count analysis has an estimated accuracy of 90% for diagnosing PJI in the preoperative setting when compared to the definition of PJI provided above. A separate multi-criteria decision analysis by workgroup members exhibited that ESR and CRP screening with subsequent joint aspiration is the most cost-effective method for diagnosing PJI.[38]

This algorithm is an adaptation of the AAOS algorithm,[39] incorporating the components of the definition provided above. As discussed above, these individual components are accurate markers of PJI.

Biopsy of the joint has an established accuracy in diagnosing PJI.[40-46] Due to the invasive nature of this tool and the theoretical risk of contaminating a previously aseptic joint, pre-operative biopsy should be limited to those cases with a high probability of PJI with inconclusive aspirate results. Intraoperative frozen sections, however, may help distinguish infection from aseptic failure with less potential morbidity than pre-operative biopsy.

The presence of well-established risk factors for PJI should raise the suspicion of septic failure. Risk factors include those that increase pathogen exposure to the joint or impair the body's ability to eradicate pathogens.[47-50]

A sinus tract communicating with the joint is considered a pathognomonic physical examination finding for PJI. Other findings, such as wound dehiscence, joint tenderness, or joint swelling, are not specific for PJI, but should increase the suspicion.

Question 3A: What should the threshold be for ESR, serum CRP, PMN%, and WBC count for *ACUTE* PJI?

Consensus: The approximate cutoffs listed below apply to tests obtained fewer than 6 weeks from the most recent surgery:

-No threshold for ESR could be determined as it is not useful in diagnosis of acute PJI.

-CRP > 100 mg/L (knee and hip),

- Synovial WBC count > 10,000 cells/μL, and

- Synovial PMN% > 90%.

Delegate Vote: Agree: 81%, Disagree: 12%, Abstain: 7% (Strong Consensus)

Question 3B: What should the threshold be for ESR, serum CRP, PMN%, and WBC count

for *CHRONIC* PJI?

Consensus: The approximate cutoffs listed below apply to tests obtained more than 6 weeks from the most recent surgery:

-ESR > 30 mm/hr,

-CRP > 10 mg/L,

-Synovial WBC count > 3,000 cells per μL, and

-Synovial PMN% > 80%.

Delegate Vote: Agree: 81%, Disagree: 14%, Abstain: 5% (Strong Consensus)

Question 3C: What should the threshold be for ESR, serum CRP, PMN%, and WBC count for PJI in inflammatory arthropathies?

Consensus: Based upon very limited evidence, we recommend no change from the above thresholds for ESR, serum CRP, PMN%, and WBC count for PJI diagnosis in patients who have underlying inflammatory arthopathies. However, further research is needed to confirm this statement.

Delegate Vote: Agree: 87%, Disagree: 9%, Abstain: 4% (Strong Consensus)

Justification:

Serology

ESR and CRP are traditionally utilized as screening tests for the detection of PJI. As such, it is imperative that these tests have a high sensitivity, possibly compromising specificity.

These serology thresholds have been established and confirmed by a multitude of studies with limited variability. ESR and CRP have both been shown to be elevated in the acute

postoperative time period (6 weeks) regardless of infection status. ESR has been shown to have limited diagnostic utility in this setting.[8] In the acute postoperative setting CRP has been shown in published and workgroup research to have accuracy in diagnosing PJI.[8] The existing literature used 6 weeks as their definition of the acute postoperative time period. However, ESR and CRP are likely still elevated up to 90 days following surgery.

Limited evidence suggests that no difference exists in the thresholds of ESR, CRP, or synovial fluid WBC count and differential to diagnose PJI in patients with and without inflammatory arthropathies.[3]

Synovial fluid

These thresholds are based upon extensive data analysis from members of this workgroup. Evidence for synovial fluid thresholds to diagnose PJI varies significantly.[7, 9-12,51-53] It is believed that these variations are due to the different definitions of PJI utilized in these studies and variances in laboratory results.[54,55] The thresholds reported here were calculated with the aforementioned definition of PJI and similar laboratory techniques when available.

Evidence, both published and analyzed by this workgroup, has shown that synovial WBC count and PMN% remain highly valuable in the diagnosis of infection in the acute postoperative period, despite having a baseline elevation due to the insult of surgery.[8] As discussed above, while these thresholds are likely still valid within 90 days, evidence is only available for the first 6 postoperative weeks.

Evidence has indicated that the presence of inflammatory arthropathies does not impact synovial WBC count and PMN% thresholds for the diagnosis of PJI.[3]

Early data suggest that the synovial fluid WBC count may be unreliable and prone to falsely positive results in the setting of a failed metal-on-metal bearing or corrosion reaction. These results should be considered carefully in this setting. A manual synovial fluid WBC count is recommended in this setting and if a differential cannot be performed on the sample, the results should be suspect.

Failed metal-on-metal bearings or corrosion reactions may result in a marked variability of the synovial fluid WBC count and differential.[56] Monocytes with phagocytosed metal particles seem to be interpreted as polymorphonuclear leukocytes (neutrophils) by some automated hematology instruments leading to false positive PMN interpretations. Therefore, synovial WBC analysis in patients with metal-on-metal bearings and corrosion reactions should be counted manually, especially when discordance between PMN% and WBC count elevation is noted.

Question 4: In analyzing synovial fluid cell count, what are important techniques to minimize variation?

Consensus: To accurately analyze synovial fluid cell count we recommend that (1) synovial fluid WBC count results be transformed using the synovial red blood cell (RBC), serum RBC, and serum WBC concentrations to adjust for traumatic aspirations and (2) in joints with metal-on-metal components a manual WBC analysis should be performed.

Delegate Vote: Agree: 92%, Disagree: 1%, Abstain: 7%.

Justification: Numerous studies, despite having varying definitions of PJI, have identified similar thresholds for ESR and serum CRP in diagnosing PJI.[3-5,57,58]

Reported variations between laboratories for synovial fluid analysis[55] may be the cause for heterogeneity in thresholds of synovial WBC count and PMN% to diagnose PJI, specifically in the hip versus knee versus shoulder. Such differences may be accounted for in part by:

- Traumatic aspirations.
- Presence of metal-on-metal bearing surfaces or corrosion reactions.

Using a validated technique, the true level of synovial leukocytosis can be determined by adjusting for the synovial RBC, serum RBC, and serum WBC counts.[59]
Metal-on-metal bearings and corrosion reactions may result in a significant variability of the synovial fluid WBC count and differential.[56] Therefore, synovial WBC analysis in patients with metal-on-metal bearings and corrosion reactions should be counted manually, especially when discordance between PMN% and WBC count elevation is noted.

Question 5: How long should routine cultures be kept?

Consensus: We recommend that routine cultures should be maintained between 5 and 14 days. In cases of suspected PJI with low virulence organisms or if preoperative cultures have failed to show bacterial growth and the clinical picture is consistent with PJI (suspected culture-negative PJI) the cultures should be maintained for 14 days or longer.

Delegate Vote: Agree: 93%, Disagree: 5%, Abstain: 2%.

Justification: Evidence has shown that extending periprosthetic cultures to 2 weeks in attempts to diagnose PJI significantly increases the culture sensitivity while not increasing the risk of contaminants.[60-63] While there is no evidence to determine the cost-effectiveness of 2-week versus 1-week cultures in presumed aseptic cases, the incidence of clinically significant positive results is not insignificant. Therefore, adequate culture duration for all potential pathogens is recommended in presumed aseptic cases.[64,65] It is also believed that the majority of common infecting organisms can be isolated within a few days of conventional cultures. There is no reason to extend the duration of culture in patients in whom the infecting organism has been isolated preoperatively. For patients with suspected PJI, culture negative cases, and patients who may be infected with low virulence organisms, the culture should be maintained for a prolonged period (14 days and perhaps longer).

Question 6A: Is there a role for routine acid-fast bacillus (AFB) and fungal testing in suspected PJI?

Consensus: In proven or suspected PJI, AFB and fungal cultures should be limited to those patients at risk for such infections or when other traditional pathogens have not been identified and clinical suspicion persists.

Delegate Vote: Agree: 92%, Disagree: 6%, Abstain: 1% (Strong Consensus)

Question 6B: Is there a role for routine AFB and fungal testing in suspected aseptic failure?

Consensus: No. AFB and fungal cultures do not play a role in presumed aseptic cases (eg cases where a synovial fluid WBC count and differential performed preoperatively were not suggestive of infection).

Delegate Vote: Agree: 91%, Disagree: 7%, Abstain: 2% (Strong Consensus)

Justification: Mycobacteria and fungi are rare causes of PJI.[66-68] Therefore, even in cases of proven or suspected PJI, costly and time-consuming investigation is likely not warranted in patients without risk or suspicion for atypical infections.

Evidence has shown that routine AFB and fungal testing in presumed aseptic cases does not yield clinically important findings, nor is it cost-effective.[69]

Question 7A: How many intraoperative tissue samples should be sent for culture in suspected PJI cases and cases of suspected aseptic failure?

Consensus: In most revision procedures, more than 3 but not more than 6 distinct intraoperative tissue samples should be sent for aerobic and anaerobic culture.

Delegate Vote: Agree: 88%, Disagree: 10%, Abstain: 2% (Strong Consensus)

Question 7B: How should culture samples be obtained?

Consensus: Tissue or fluid samples from representative area should be taken, preferably from the interface, each sample taken with an unused instrument. We strongly recommend against swab cultures from wound or periarticular tissues.

Delegate Vote: Agree: 97%, Disagree: 2%, Abstain: 1% (Strong Consensus)

Question 7C: Should antibiotic be withheld prior to obtaining samples for culture in all cases?

Consensus: No. Perioperative prophylactic antibiotics should be withheld only in cases with a high suspicion for PJI in which an infecting organism has not been isolated.

Delegate Vote: Agree: 87%, Disagree: 12%, Abstain: 1% (Strong Consensus)

Justification: Protocols for periprosthetic tissue collection have historically been established with a target of 5 samples.[25,63,70]

In the only known quantitative analysis, it was found that sensitivity and specificity are maximized with 5 or 6 periprosthetic samples being collected.[24]
It has been suggested that for less virulent organisms or in patients with recent antibiotic use, up to 10 periprosthetic samples should be routinely collected.[71] However, it is believed that poor sensitivity due to recent antibiotic use or less virulent organisms can be overcome by other techniques (eg increased incubation time, molecular techniques, or explant sonication).[63,72-74]
As such, culture specificity should not be compromised by taking more than 5 samples.
In an analysis of 117 revision cases (30 with PJI) with 3 periprosthetic tissue and 3 periprosthetic swab cultures, it was shown that swab cultures have a sensitivity (70% vs 93%) and specificity (89% vs 98%) inferior to tissue culture.[75] This is in support of an earlier study with similar findings with a less stringent definition of PJI.[76]
Two prospective (one randomized) studies have demonstrated that prophylactic preoperative antibiotics do not impair the sensitivity of traditional intraoperative cultures.[77,78] As such, it is suggested that mandatory withholding of prophylactic antibiotics is not justified in cases in which a pathogen has already been identified. In cases in which PJI is diagnosed or suspected and a pathogen has yet to be identified, the use of prophylactic antibiotics is dependent upon clinical judgment.

Question 8: Is there a role for routine sonication of the prosthesis? If so, in which group of patients should this be done?

Consensus: No. We do not recommend routine sonication of explants. Its use should be limited to cases of suspected or proven PJI (based upon presentation and other testing) in which preoperative aspiration does not yield positive culture and antibiotics have been administered within the previous 2 weeks.

Delegate Vote: Agree: 84%, Disagree: 9%, Abstain: 7% (Strong Consensus)

Justification: Explant sonication during revision arthroplasty of the hip, knee, and shoulder has been shown to increase the likelihood of isolating pathogens without increasing the rate of

contaminants.[73,74,79-83]

Sonication of explants is a time- and resource-intensive procedure that is likely not justified in presumed aseptic cases. Further, the equipment to perform sonication is not widely available. In a large prospective analysis of 331 cases, the greatest advantage of explant sonication over standard tissue culture was appreciated when antibiotics were provided within 2 weeks of surgery.[74] Sonication likely has this advantage because the process removes biofilm from the explant, allowing for sampling and culture. Planktonic bacteria typically captured by standard periprosthetic sampling are more susceptible to antibiotic therapy than sessile organisms.

Question 9: Is there a role for molecular techniques such as polymerase chain reaction (PCR) for diagnosis of PJI? If so, in which group of patients should this be done?

Consensus: Nucleic acid based testing is not currently a recommended routine diagnostic test for PJI. In cases with high clinical suspicion of infection but negative cultures or other diagnostic tests, molecular techniques with or without sonication may help identify the unknown pathogens or antibiotic sensitivity for targeting antimicrobial therapies.

Delegate Vote: Agree: 96%, Disagree: 3%, Abstain: 1% (Strong Consensus)

Justification: PCR techniques have been shown to be significantly more sensitive than standard tissue culture for detecting pathogens.[72,79,84-92] However, despite multiple modified techniques, the number of false-positive results precludes screening with the types of molecular techniques currently most commonly available.The specificity of PCR techniques has a wide reported range between 0%-100%.[72,86-89,93]

An advantage of molecular techniques is that it can be used in the detection of organisms, even with recent antibiotic use.[79,93]
Improved detection is observed in PCR of sonication fluid from explants with and without standard tissue culture.[79,85,90,93,94] This additive effect is likely observed due to the introduction of sessile bacteria into the tested sample.
While molecular techniques have shown some promise in identifying genes associated with antibiotic resistance,[72,81,94] they do not yet match the clinical applicability of testing the antibiotic susceptibility of organisms grown in culture. The cost and availability of this technology limit its

broad application and therefore is not considered a standard tool in the work-up of PJI.

Question 10: Is there a role for imaging modalities in the diagnosis of PJI?

Consensus: Plain radiographs should be performed in all cases of suspected PJI. Magnetic resonance imaging (MRI), computed tomography (CT), and nuclear imaging currently DO NOT have a direct role in the diagnosis of PJI but may be helpful in the identification of other causes of joint pain/failure.

Delegate Vote: Agree: 93%, Disagree: 7%, Abstain: 0% (Strong Consensus)

Justification: Plain radiographs are not accurate markers of PJ I.[95] Despite this, other etiologies of joint failure are well apparent on plain radiographs. Plain film may show subperiosteal bone growth, loosening, transcortical sinus tracts, or normal findings in the setting of PJI.

There is a paucity of data regarding the diagnostic value of MRI. However, the artifact caused by the presence of the prosthetic implant is well known and suggests that evaluation of the periprosthetic region for infection may not be possible.[96]

One analysis is known to have investigated the diagnostic utility of CT imaging for periprosthetic hip infection.[97] That study reported that soft-tissue findings such as joint distention and periprosthetic fluid collections were accurate (94% and 89%, respectively) markers of PJI. However, these findings cannot be generalized to other joints and have not been confirmed in subsequent studies. Therefore, it is not currently recommended to utilize CT to evaluate for PJI when other imaging and non-invasive tests have proven efficacy.

There is substantial evidence regarding the effectiveness of nuclear imaging in diagnosing PJI.[94,98-108] While many different nuclear imaging techniques have been tested and proven for PJI diagnosis, the most accurate and cost-effective technique has yet to be elucidated. Furthermore, with the high cost of performing and analyzing nuclear imaging, its role in the work-up for PJI should be limited. As such, there is rare utility for nuclear imaging with the multitude of more cost-effective measures. Furthermore, plans to return the patient to the operating room will allow for joint visualization, periprosthetic tissue culture, and possible

explant sonication.

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Workgroup 8: Wound Management

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Question 1A: What is the optimal dressing for a wound after total joint arthroplasty (TJA)?

Consensus: We recommend the use of occlusive dressings with alginated hydrofiber, when available.

Delegate Vote: Agree: 63%, Disagree: 25%, Abstain: 12% (Weak Consensus)

Justification: An occlusive dressing (Aquacel) secured with hydrocolloid was found to have a lower blister rate postoperatively when compared to Mepore (Molnlycke,GA).[1-4] and Cutiplast (Smith and Nephew, Memphis, LA)[5] and had a lower rate of dressing changes. A clinical audit comparing Mepore to Aquacel found that Aquacel had a lower rate of surgical site infection (SSI) (3 in the Mepore group and 1 in the Aquacel group).[1] A prospective, randomized controlled trial (RCT) comparing Mepore and Aquacel showed similar wound inflammation and infection rates in the two groups.[2] In one RCT, wound healing was delayed in the occlusive group (eg, foams, alginates, hydrogels, hydrocolloids, hydrofibers, or films) compared to gauze-based dressings, with an increase in accrued cost.[6] There are also inconsistent data comparing hydrofiber and alginate dressings.[7,8]

One study aimed to compare the performance of a hydrofiber (Aquacel) and an alginate (Sorbsan) dressing on acute surgical wounds (pilonidal, breast, axilla, groin, and wound abscess) left to heal by secondary intention. A total of 100 patients were prospectively randomized pre-operatively to receive either the hydrofiber or alginate dressing. Dressing performance was measured at operation and postoperatively at 24 hours and 7 days. Parameters measured included ease of application and removal of the first dressing, re-application on the first postoperative day, and removal and re-application one week postoperatively. The hydrofiber dressing received higher scores for all of these categories. Patients in this group also experienced less pain (mild or none) on removal of the first dressing and at one week. However, these results did not achieve statistical significance and should be seen as a trend. Nevertheless, the authors recommend the use of hydrofiber dressings on open acute surgical wounds.[7]

A comparative evaluation was conducted involving 428 patients undergoing primary elective total hip arthroplasty (THA) or total knee arthroplasty (TKA) in a single hospital between January

and April 2006. Patients received either the traditional postoperative dressing (adhesive dressing with an integral absorbent pad, Mepore) or the new dressing regimen (Aquacel secured with hydrocolloid dressing, Duoderm), as well as liquid film-forming acrylate. Patients under the age of 50 and/or with a condition or comorbidity that could compromise wound healing were excluded. A protocol was developed for dressing changes based on the extent of strikethrough. Outcome measures were blister rate, wear time, number of dressing changes, SSI rate, and delayed patient discharge.[1]

Patients treated with the new dressing design had a lower blister rate, lower incidence of delayed discharge, longer wear time, fewer dressing changes, and a lower SSI rate. Only 4 cases of SSIs requiring washout were reported in both groups (one for the new dressing design and 3 for the traditional dressing) and the rest were successfully treated with antibiotics. To date there have been no revisions for deep infection in either group.

One hundred twenty-four patients (62 THAs and 62 TKAs) were randomly selected to have either a standard adhesive dressing (Mepore) or jubilee method dressing (Aquacel with hydrocolloid layer, Duoderm). The number of dressing changes, incidence of blistering, leakage, subjective assessment of wound inflammation, infection rate, and the average hospital stay was recorded. The Jubilee dressing significantly reduced the rate of blistering, leakage, and number of dressing changes when compared to a traditional adhesive dressing ($p<0.05$). The rate of inflammation and average length of stay in the hospital was not significantly different between the two groups. There were no cases of periprosthetic joint infection (PJI) reported.[2]

Cutiplast (absorbent perforated dressing with adhesive border; Smith & Nephew) is commonly used following orthopaedic operations, but complications with its use have been reported. A prospective RCT was performed to compare the efficacy of Cutiplast versus an Aquacel (hydrofiber dressing; ConvaTec) covered with Tegaderm (vapour-permeable dressing; 3M). Two hundred patients were randomized to receive one of the two dressings following elective and non-elective surgery of the hip and the knee. The authors were able to study 183 patients. The condition of the wound and any complications such as skin blistering or signs of infection were noted, as was the frequency of dressing changes. The Aquacel and Tegaderm dressing was 5.8 times more likely to result in a wound with no complications (as compared to a Cutiplast dressing (odds ratio, 5.8; 95% confidence interval (CI) 2.8–12.5; $p<0.00001$).

Taking blisters alone as a complication, in the Cutiplast group 22.5% of patients had wounds with blisters compared to only 2.4% of the group dressed with Aquacel/Tegaderm. The patients

receiving Aquacel covered by Tegaderm had statistically fewer wound dressing changes. Taking the group as a whole, the dressing pain score was statistically lower for the patients receiving the Aquacel/Tegaderm dressing ($p<0.001$).[5]

Two prospective clinical audits were performed over a 6-month period and involved 100 patients undergoing THA or TKA. Fifty consecutive patients with traditional dressings (Mepore) were evaluated prior to a change in practice to a modern dressing (Aquacel). Fifty consecutive patients were then evaluated with the new dressing to complete the audit cycle. Clinical outcome measures were wear time, number of changes, blister rate, and length of hospital stay. Wear time for the traditional dressing (2 days) was significantly shorter than for the modern dressing (7 days; $p<0.001$), and required more changes (0 vs 3; $p<0.001$). Blisters developed in 20% of the patients with the traditional dressing compared with 4% in the modern dressing group ($p=0.028$). The median length of stay was the same for the modern dressing (4 days) compared with the traditional dressing (also 4 days). In the modern dressing group, 75% of patients were discharged by day 4, whereas in the traditional group this took until day 6.[3]

Abuzakuk et al. reported the results of a prospective RCT comparing a hydrofiber (Aquacel) and central pad (Mepore) dressing in the management of acute wounds following primary THA or TKA left to heal by primary intention. Dressing performance was measured in 61 patients receiving THA or TKA. There was a significant reduction in the requirement for dressing changes before 5 postoperative days in the hydrofiber group (43% compared with 77% in the central pad group) and there were fewer blisters among patients in the hydrofiber group (13% compared with 26% in the central pad group).[4]

Ubbink et al. compared the effectiveness and costs of gauze-based vs occlusive, moist-environment dressings in 205 hospitalized surgical patients with open wounds. Patients received occlusive (ie, foams, alginates, hydrogels, hydrocolloids, hydrofibers, or films) or gauze-based dressings until their wounds were completely healed. No significant differences in wound healing were observed in chronic wounds (ie, vascular insufficiency, diabetes, or pressure sores), traumatic wounds, or wounds included in the first vs the second half of the trial (to detect a learning curve effect, if any). However, in postoperative wounds, 62% of all wounds in this trial, wound healing in the occlusive group took significantly ($p=.02$) longer (median, 72 days; inter-quartile range, 36 to 132 days) than in the gauze group (median, 45 days; interquartile range, 22 to 93 days). The total cost for local wound care per patient per day during

hospitalization was €7.48 (US $11.74) in the occlusive group and €3.98 (US $6.25) in the gauze-based group (p=.002).[6]

Ravnskog et al. compared the performance of hydrofiber and alginate dressings used in the treatment of primary THA wounds. Patients were randomized into one of two groups, receiving either a hydrofiber or an alginate dressing. Outcome measures included skin damage (erythema, blisters, and skin injuries) and the dressing's ability to handle exudates. Photos of the dressing and the skin area around the wounds were taken. Patients noted skin problems, discomfort at mobilization, and pain at dressing removal. In the alginate group, there were fewer blisters in the wound area compared with the hydrofiber group (7% vs 18%, p=0.03). During dressing removal, fewer patients in the alginate group reported pain than patients in the hydrofiber group (2.1% vs 15%, p=0.01).[8]

Question 1B: Does the use of silver-impregnated dressings reduce SSI /PJI?

Consensus: Silver-impregnated dressings have not been conclusively shown to reduce SSI/PJI.

Delegate Vote: Agree: 87%, Disagree: 5%, Abstain: 7% (Strong Consensus)

Justification: Three prospective RCTs compared silver-impregnated colloid dressings (Aquacel, Alginate) to non-silver dressings in treatment of a variety of wound types including acute surgical wounds, infected and non-infected diabetic foot ulcers, and traumatic wounds, failed to show any difference in terms of outcome in wound/ulcer healing and local infection rates.[9-11] One prospective RCT, comparing silver-impregnated alginate dressings to non-silver dressings in the treatment of chronic venous ulcers, found significant improvement in silver dressings in preventing wounds from progressing to infection, as well as a greater rate of wound healing.[12] A Cochrane meta-analysis that compared the effect of silver-impregnated dressings to non-silver dressings in infected acute or chronic wounds found no significant difference in wound healing rates, antibiotic use, pain, patient satisfaction, length of hospital stay, and costs.[13] Another Cochrane meta-analysis assessing burn wounds and a mixture of non-infected

wound types found that the addition of silver to the dressings did not promote wound healing or prevent wound infections.[14]

Beele et al. observed both the clinical signs and symptoms of wounds at risk of infection; that is, critically-colonized (biofilm infected) wounds. They studied the antimicrobial performance of an ionic silver alginate/carboxymethylcellulose (SACMC) dressing in comparison with a non-silver calcium alginate fiber (AF) dressing, on chronic venous leg and pressure ulcers. Thirty-six patients with venous or pressure ulcers, considered clinically to be critically colonized (biofilm infected), were randomly chosen to receive either an SACMC dressing or a non-silver calcium AF dressing. The efficacy of each wound dressing was evaluated over a 4-week period. The primary study endpoints were prevention of infection and progression to wound healing. The SACMC group showed a statistically significant ($p=0.017$) improvement in healing, indicated by a reduction in the surface area of the wound over the 4-week study period compared with the AF control group. The SACMC dressing showed a greater ability to prevent wounds progressing to infection when compared with the AF control dressing. The results of this study also showed an improvement in wound healing for SACMC when compared with a non-silver dressing.[12]

Trial et al. compared the efficacy and tolerability of a new ionic silver alginate matrix (Askina Calgitrol Ag) with that of a standard silver-free alginate dressing (Algosteril). Patients with locally-infected chronic wounds (pressure ulcers, venous or mixed etiology leg ulcers, or diabetic foot ulcers) or acute wounds were eligible for this prospective, open-label RCT. Patients were randomized to receive one of the two dressings for a two-week period. The criteria for efficacy were based on the evolution from day 1 to day 15 of local signs of infection using a clinical score ranging from 0 to 18 and the evolution of the bacteriological status for each wound. The latter was determined by (blind) bacteriological examinations of results obtained from two biopsies performed at days 1 and 15. A 3-point scale (deterioration, unchanged, and improvement) was also used. Acceptability, usefulness, and tolerance were also assessed.

Forty-two patients (20 women and 22 men aged 68.9±18.8 and 66.5±15.7 respectively) were randomly assigned to receive either Askina Calgitrol Ag (n=20) or Algosteril (n=22). Most had chronic wounds such as pressure ulcers (57%) or venous or mixed-etiology leg ulcers and diabetic foot ulcers (29%), with a few having acute wounds (14%). Clinical scores of infection were comparable in both groups at inclusion, 8.9±2.4 and 8.6±3.2 in the Askina Calgitrol Ag group and the Algosteril group respectively (not significant), but decreased significantly in both groups at day 15, 3.8±2.9 in the Askina Calgitrol Ag group ($p=0.001$) and 3.8±3.4 in the

Algosteril group (p=0.007). There was no significant difference between the two groups at day 15. Although there was also no significant difference in bacteriological status between the treatment groups, a trend in favor of Askina Calgitrol Ag was found for the relative risk of improvement, especially in patients who were not treated with antibiotics either at the beginning of or during the study. No differences between groups were observed regarding local tolerance, acceptability, and usefulness of the dressings.[9]

In a retrospective study, Saba et al. compared Aquacel Ag Hydrofiber dressing (Aquacel Ag) to a standard dressing for the treatment of partial thickness burns in children. The authors used the St. Christopher's Hospital burn center registry to identify 20 pediatric patients who had sustained partial-thickness burns over a 10-month period. Ten of these patients had been treated with Aquacel Ag Hydrofiber dressing and 10 were treated with conventional Xeroflo gauze with Bacitracin Zinc ointment, the institutional standard of care for nonoperative partial-thickness burn wounds. Outcomes measured for the Aquacel Ag versus the Xeroflo gauze with Bacitracin Zinc ointment group included hospital length of stay (2.4 vs 9.6 days), total number of in-house dressing changes (2.7 vs 17.1), pain on a 10-point scale associated with dressing changes (6.4 vs 8.2), total number of intravenous narcotic administrations (2.3 vs 14.4), nursing time adjusted for percentage total body surface area (1.9 vs 3.5 min), time to wound reepithelialization (10.3 vs 16.3 days), and patient primary caregiver satisfaction score using a 4-point scale, with 4 delineating maximum satisfaction (3.8 vs 1.8). All variables were significant ($p<0.001$).[15]

Storm-Versloot et al. searched the Cochrane Wounds Group Specialized Register (6 2009), The Cochrane Central Register of Controlled Trials (CENTRAL) (2009 Issue 2), Ovid MEDLINE (1950 to April Week 4 2009), Ovid EMBASE (1980 to 2009 Week 18), EBSCO CINAHL (1982 to April Week 4 2009), and Digital Dissertations (to 2009) for relevant RCTs comparing silver-containing wound dressings and topical agents with non silver-containing versions on uninfected wounds. This review identified 26 trials involving 2,066 participants that compared silver-containing dressings or creams against dressings or creams that did not contain silver. Twenty of the trials were on burn wounds, while the others were on a mixture of wound types. Most studies were small and of poor quality. The authors concluded that there is not enough evidence to support the use of silver-containing dressings or creams, as generally these treatments did not promote wound healing or prevent wound infections. Some evidence from a number of small, poor-quality studies suggested that one silver-containing compound (silver sulphadiazine) has no effect on infection and slows down healing in patients with partial-thickness burns.[14]

In a prospective, multicenter study, Jude et al. compared the clinical efficacy and safety of Aquacel hydrofiber dressings containing ionic silver (AQAg) with those of Algosteril calcium alginate (CA) dressings in managing outpatients with type 1 or 2 diabetes mellitus and non-ischaemic Wagner Grade 1 or 2 diabetic foot ulcers. Patients stratified by antibiotic use on enrolment were randomly assigned to similar protocols, including off-loading, AQAg (n=67), or CA (n=67) primary dressings and secondary foam dressings for 8 weeks or until healing. The mean time to healing was 53 days for AQAg ulcers and 58 days for CA ulcers (p=0.34). AQAg-treated ulcers reduced in depth nearly twice as much as CA-treated ulcers (0.25 cm vs 0.13 cm; p=0.04). During the study, the incidence of clinical infection adverse events in the study ulcer group was comparable, with 11 AQAg subjects (16%) and 8 CA subjects (12%) reporting infection as adverse events in the study ulcer group. The median time for clinical infection to resolve without recurrence during the study was comparable for AQAg and CA subjects: 9 days for the 8 (88.9%) AQAg-resolved infections and 15 days (p=0.35) for the 10 (76.9%; p=0.48) CA-resolved infections.[10]

A prospective RCT by Jurczak et al. compared pain, comfort, exudate management, and wound healing and safety with hydrofiber dressing with ionic silver (hydrofiber Ag dressing) and with povidone–iodine gauze for the treatment of open surgical and traumatic wounds. Patients were treated with hydrofiber Ag dressing or povidone–iodine gauze for up to 2 weeks. Pain severity was measured with a 10 centimeter visual analogue scale (VAS). Other parameters were assessed clinically with various scales. Pain VAS scores decreased during dressing removal in both groups and decreased while the dressing was in place in the hydrofiber Ag dressing group (n=35) but not in the povidone–iodine gauze group (n=32). Pain VAS scores were similar between treatment groups. At final evaluation, hydrofiber Ag dressing was significantly better than povidone–iodine gauze for overall ability to manage pain (p<0.001), overall comfort (p<0.001), wound trauma on dressing removal (p=0.0001), exudate handling (p<0.001), and ease of use (p<0.001). Rates of complete healing at study completion were 23% for Hydrofiber Ag dressing and 9% for povidone–iodine gauze (not significant). No adverse events were reported with hydrofiber Ag dressing and one subject discontinued povidone–iodine gauze due to an adverse skin reaction. During study treatment, 4 (11.4%) subjects in the hydrofiber Ag dressing group and 4 (12.5%) subjects in the povidone–iodine gauze group had infected wounds (not significant).[11]

In another meta-analysis, Vermuelen et al. evaluated the effects of topical silver and silver dressings on wound healing in the treatment of contaminated and infected acute or chronic

wounds. They searched for relevant trials from the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Wounds Group Specialized Register in March 2006, and in MEDLINE, EMBASE, CINAHL, and Digital Dissertations databases up to September 2006. In addition, the authors contacted companies, manufacturers, and distributors for information to identify relevant trials, seeking RCTs that assessed the effectiveness of topical silver in the treatment of contaminated and infected acute or chronic wounds. Three RCTs were identified, comprising a total of 847 participants. One trial compared silver-containing foam (Contreet) with hydrocellular foam (Allevyn) in patients with leg ulcers. The second trial compared a silver-containing alginate (Silvercel) with an alginate alone (Algosteril). The third trial compared a silver-containing foam dressing (Contreet) with best local practice in patients with chronic wounds. The data from these trials show that silver-containing foam dressings did not significantly increase complete ulcer healing as compared with standard foam dressings or best local practice after up to 4 weeks of follow-up, although a greater reduction of ulcer size was observed with the silver-containing foam. The use of antibiotics was assessed in two trials, but no significant differences were found. Data on pain, patient satisfaction, length of hospital stay, and costs were limited and showed no differences. In one trial, leakage occurred significantly less frequently in patients with leg ulcers and chronic wounds treated with a silver dressing than with a standard foam dressing or best local practice. There is insufficient evidence to recommend the use of silver-containing dressings or topical agents for the treatment of infected or contaminated chronic wounds.[13]

However, evidence in emerging that appears to endorse the role of occlusive, silver impregnated dressing in reducing incidence of SSI/PJI. In a recent single institution retrospective study, the incidence of acute PJI (occurring within 3 months) was compared between 903 consecutive patients undergoing total joint arthroplasty who received the Aquacel surgical dressing and 875 consecutive patients who received standard gauze dressing. (Cai et al.; publication pending). After performing a multivariate analysis, the investigators found that Aquacel dressing was an independent factor for reduction of acute PJI with an acute PJI incidence of 0.44% for patients who received the Aquacel dressing compared to 1.7% of patients who received the standard gauze dressing ($p=0.005$).
In another recently completed Level I prospective randomized study of 300 patients Aquacel Ag dressing compared to standard surgical dressing showed statistically significant reductions in wound complications, blisters, number of dressing changes, and overall patient satisfaction with the Aquacel Ag surgical dressing.[16]

Question 2: What is considered to be persistent drainage from a wound after TJA?

Consensus: Persistent wound drainage after TJA is defined as continued drainage from the operative incision site for greater than 72 hours.

Delegate Vote: Agree: 80%, Disagree: 15%, Abstain: 5% (Strong Consensus)

Justification: Studies in the literature have a wide range of definitions for persistent wound drainage (48 hours to 1 week). However, limiting wound drainage to 72 hours postoperatively allows for earlier intervention and may limit the adverse consequences of persistent drainage.

Persistent wound drainage after TJA is defined by time, type of secretion (hematogenous or clear), site (wound secretion, secretion after removal of suction drains), and microbial content. The timing of drainage is defined in multiple ways:

- Forty-eight hours[17]
- Postoperative day 3 or 4.[18]
- Beyond postoperative day 4.[19]
- Several days after surgery.[20]
- Two days postoperative for non-infected cases, 5.5 days postoperative for infected cases.[21]
- Limited amount of time.[22]
- One week.[23]

The amount of drainage is alternately defined as:

- Drainage has soaked through the postoperative dressings.[17,18]
- Greater than 2cm x 2cm area of drainage covering gauze.[24]
- Discharge from the wound.
- Microorganism cultured from drainage.[25]

This workgroup believe that substantial drainage (>2x2 cm area of gauze) from a wound beyond 72 hours should be considered abnormal. We strongly recommend against performing culture of the draining wound.

Question 3A: What are non-surgical strategies to address a draining wound after TJA?

Consensus: Persistent wound drainage for greater than 72 hours after TJA should be managed by wound care.

Delegate Vote: Agree: 65%, Disagree: 26%, Abstain: 9% (Weak Consensus)

Justification: Various studies recommend using medical management to attempt wound drainage control prior to surgical intervention. Other interventions, such as antibiotics, are discouraged because they can mask an underlying infection. Observation alone is highly discouraged, given the fact that persistent wound drainage is correlated with PJI.[17,21,24,26] The risk of infection increases by 29% after TKA and by 42% after THA with each day of persistent wound drainage.[24]

Studies have recommended various interventions to reduce the amount of wound drainage after TJA. One prospective RCT evaluated negative pressure wound therapy (NPWT) in patients with large surgical wounds after THA and found that NPWT decreased the size of postoperative seromas.[27] A pilot study of patients undergoing THA who developed postoperative drainage treated with NPWT that was applied for an average of 2 days (range, 1-10 days) found that 76% of the patients did not require further intervention while 24% had subsequent surgery.[18]

However, a prospective RCT comparing NPWT to standard dry dressings on surgical incisions (primary closure or delayed primary closure of the lower extremity or abdominal wounds) found no significance in dehiscence rates, mean time to dehiscence, wound infection, and reoperation rates between the NPWT and dry dressing groups.[28] A Cochrane meta-analysis included trials that compared NPWT with other types of wound dressings or compared one type of NPWT with a different type of NPWT for persistently draining wounds in skin graft patients, orthopaedic patients undergoing arthroplasty, and general and trauma surgery. The authors concluded that

there is no evidence for the effectiveness of NPWT on the complete healing of wounds expected to heal by primary intention.[29]

A retrospective review of 300 patients who developed persistent (greater than 48 hours postoperatively) wound drainage revealed that drainage stopped spontaneously between 2 and 4 days of drainage in 72% of the patients treated with local wound care and oral antibiotics. It is discouraged to use greater than 24 hours of postoperative antibiotics to treat persistent wound drainage after TJA because there is no evidence supporting the statement that it decreases PJI.[18,20] Additionally, administering antibiotics in light of a persistently draining wound may confound the culture findings if an arthrocentesis is performed to determine if any organisms are present within the synovial fluid. This workgroup discourages the use of oral antibiotic for management of wound drainage.

Question 3B: What are surgical strategies to address a draining wound after TJA?

Consensus: Surgical management consisting of opening the fascia, performing a thorough irrigation and debridement (I&D) with exchange of modular components should be considered if wound drainage has persisted for 5 to 7 days after the index procedure.

Delegate Vote: Agree: 77%, Disagree: 16%, Abstain: 7% (Strong Consensus)

Justification: After 5 days of persistent wound drainage, surgical intervention should be carried out to reduce the likelihood of developing a PJI. Surgery should consist of opening the fascia, performing a thorough I&D with exchange of modular components, and performing a meticulous fascia and wound reclosure. In case meticulous reconstruction of the fascia and skin is not possible, NPWT might be a viable option, followed by coverage of the wound by a plastic surgeon after cultures and other data exclude early PJI. Deep cultures should be taken at the time of reoperation and antibiotics should be administered according to the sensitivity of the organism. We recommend against taking wound swab cultures.

An older retrospective study by Weiss and Krackow encouraged surgical intervention in TJA patients with persistent wound drainage, including I&D, polyethylene exchange, and parenteral

antibiotics.[26] However, this was performed at 12.5 days postoperatively, which would have allowed more bacteria colonization on polyethylene. A study by Jaberi et al. demonstrated that patients who failed medical management of persistent wound drainage after postoperative day 4 and subsequently underwent a single-stage I&D had a cessation of drainage in 76% of patients.[17] However, despite this early intervention, 24% of patients underwent subsequent treatment, including long-term antibiotics, resection arthroplasty, or repeat debridement. A review paper supported reoperation for exploration, deep culture, irrigation, and meticulous wound reclosure.[20] If the deep cultures were positive, then the authors encouraged parenteral antibiotic therapy for 6 weeks. To ensure adequate debridement of the affected area, a study by Kelm et al. injected methylene blue dye into the fistula, performed a debridement with acetabular polyethylene and femoral head exchange, and closed the wound using a vacuum-assisted closure.[30] Persistent drainage that is more concerning should be treated as an infected TJA[22] with a low threshold for performing I&D or exchange arthroplasty.[31] Open debridement with polyethylene exchange has variable results. There is a high failure rate associated with polyethylene exchange and may lead to future resection arthroplasty.[32]

Question 3C: Should oral or intravenous antibiotics be administered to patients with persistent wound drainage?

Consensus: We recommend against administration of oral or intravenous antibiotics to patients with persistent wound drainage.

Delegate Vote: Agree: 80%, Disagree: 17%, Abstain: 3% (Strong Consensus)

Justification: Currently there is little to no evidence to support administration of antibiotics to patients with draining wound. Although the rationale for this practice appears logical, in that one is attempting to prevent ingress of infecting organisms through the draining wound, the issue of emergence of antibiotic resistance and adverse effects associated with administration of antibiotics cannot be overlooked. In addition, administration of an antibiotic is likely to mask the underlying infection or make diagnosis of PJI difficult by influencing the culture results. Thus, the

consensus workgroup feels that this is an area in need of future study and does not endorse administration of antibiotics to patients with persistent wound drainage.

Question 4: What are the indications for reoperation for a persistently draining wound after TJA?

Consensus: A wound that has been persistently draining for greater than 5 to 7 days from the time of diagnosis should be reoperated on without delay.

Delegate Vote: Agree: 77%, Disagree: 19%, Abstain: 4% (Strong Consensus)

Justification: Studies have shown that the risk of infection increases after 5 days of wound drainage. Thus, performing surgical intervention after 5 days is the most appropriate for preventing PJIs.

The number of postoperative drainage days at which I&D was performed for persistently draining wounds varied from 5 to 12.5 days.[17,21,26] Two studies found that patients with 5 days or more of persistent drainage or greater were more likely to become infected later on and require further surgical intervention than patients with less drainage time.[17,21] Specifically, the study by Saleh et.al. demonstrated that patients who had an average of 5.5 days of drainage were 12.7 times more likely to be infected than those with less wound drainage time.[21] Another study found that each day of prolonged wound drainage increased the risk of wound infection by 42% following a THA and by 29% following a TKA.[24] However, waiting 5 days for the wound to dry may be secondary to anticoagulation use; therefore, holding off on surgical management until postoperative day 5 is reasonable. In another study, wound drainage was examined after 5 days of NPWT. [27] There was a reduction in persistent wound drainage with the use of NPWT and further surgical intervention could then be conducted after medical intervention was performed. A registry-based study found that patients with TKA who undergo early surgical treatment (within 30 days) for wound complications have a two-year cumulative probability of major subsequent surgery (component resection, muscle flap coverage, or amputation) and deep infection rates of 5.3% and 6.0%, respectively.[33]

Question 5: How can we optimize patient status prior to reoperation to minimize SSI?

Consensus: We recommend that patients should be optimized prior to undergoing reoperation. Correction of malnutrition, anticoagulation, anemia, and diabetes should be reasonably pursued.

Delegate Vote: Agree: 95%, Disagree: 3%, Abstain: 2% (Strong Consensus)

Justification: Preoperative malnutrition has been associated with delayed wound healing,[34] longer length of stay (LOS) and anesthesia/surgical times,[35] and failure of treatment of persistently draining wounds inevitably leading to deep infection.[17] The measures of malnutrition have varied and include transferrin, total lymphocyte count (TLC), total albumin, and prealbumin.

Malnutrition: Gherini et al. assessed 103 THA pre-and postoperatively to determine nutritional status and correlation with delayed wound healing. Parameters indicative of nutritional status included serum albumin, transferrin levels and total lymphocyte count. Delayed wound healing complicated 33% of the THAs**.** Only preoperative serum transferrin levels showed a significant value in predicting which patients had delayed wound healing.[34]

Lavernia et al. evaluated 119 patients in whom standard preoperative laboratory tests were performed. Patients with albumin levels less than 34 g/L had 32.7% higher charges ($p<0.006$), higher medical severity of illness ($p<0.03$), and longer LOS ($p<001$). Patients with a total lymphocyte count less than 1,200 cells/mL had higher charges ($p<004$) and longer LOS ($p<0.004$), anesthesia ($p=0.002$), and surgical times ($p=0.002$) when compared with patients with TLC higher than 1,200 cells/mL.[35]

Diabetes: Diabetes mellitus has been implicated in early wound complications after TJA[33] and PJI[36] with the capacity to double this risk independent of diabetes.[37] Perioperative glycemic control was found to predispose cardiac surgery patients to infection.[38] In a review of 3,468 patients who underwent 4,241 primary or revision THA or TKA at one institution, HbA1C was not found to be a reliable marker of predicting joint infection. Hemoglobin A1c levels were examined to evaluate if there was a correlation between the control of HbA1c and infection after

TJA. There were 46 infections (28 deep and 18 superficial [9 cellulitis and 9 operative abscesses]). Twelve (3.43%) occurred in diabetic patients (n=350; 8.3%) and 34 (0.87%) in nondiabetic patients (n=3891; 91.7%) (p<0.001). There were 9 deep (2.6%) infections in diabetic patients and 19 (0.49%) in nondiabetic patients. In noninfected diabetic patients, HbA1c level ranged from 4.7 to 15.1% (mean, 6.92%). In infected diabetic patients, HbA1c level ranged from 5.1 to 11.7% (mean, 7.2%) (p=0.445). The average HbA1c level in patients with diabetes was 6.93%. Diabetic patients have a significantly higher risk for infection after TJA. Hemoglobin A1c level was not found to be reliable for predicting the risk of infection after TJA.[39] Similarly, in another study, patients undergoing TKA with controlled and uncontrolled diabetes were compared with patients without diabetes. No association was found between controlled and uncontrolled diabetes and the risk for requiring a revision or developing deep infection when using HbA1C as a marker for diabetic control.[40]

Jamsen et al. analyzed the one-year incidence of PJI in a single-center series of 7,181 primary THA and TKA (unilateral and simultaneous bilateral) performed between 2002 and 2008 to treat osteoarthritis. The data regarding PJI (defined according to Centers for Disease Control and Prevention criteria) were collected from the hospital infection register and were based on prospective, active surveillance. Diabetes more than doubled the PJI risk independent of obesity (adjusted OR, 2.3; 95% CI, 1.1 to 4.7). In patients without a diagnosis of diabetes at the time of the surgery, there was a trend toward a higher infection rate in association with a preoperative glucose level of >6.9 mmol/L (124 mg/dL) compared with <6.9 mmol/L.[37]

Pedersen et al. evaluated the extent to which diabetes affects the revision rate following THA. Through the Danish Hip Arthroplasty Registry the authors identified all patients undergoing a primary THA (n=57,575) between January 1996 and December 2005, of whom 3,278 had diabetes. The presence of diabetes among these patients was identified through the Danish National Registry of Patients and the Danish National Drug Prescription Database. They estimated the risk ratio (RR) for revision and the 95% CIs for patients with diabetes compared to those without, adjusting for confounding factors. Diabetes is associated with an increased risk of revision due to deep infection (RR=1.45 (95% CI 1.00 to 2.09), particularly in those with type 2 diabetes (RR=1.49 (95% CI 1.02 to 2.18)), those with diabetes for less than 5 years prior to THA (RR=1.69 (95% CI 1.24 to 2.32)), those with complications due to diabetes (RR=2.11 (95% CI 1.41 to 3.17)), and those with cardiovascular comorbidities prior to surgery (RR=2.35 (95% CI 1.39 to 3.98)).[36]

Golden et al. performed a prospective cohort study based on chart review of a total of 411 adults with diabetes who underwent coronary artery surgery from 1990 to 1995 in the cardiac surgery service of an urban university hospital. Perioperative glycemic control was characterized by the mean of 6 capillary glucose measurements taken during the 3 hour interval following surgery. After simultaneous adjustment for age, sex, race, underlying comorbidity, acute severity of illness, and LOS in the surgical intensive care unit, patients with higher mean capillary glucose readings were at increased risk of developing infections. Compared with people in the lowest quartile of postoperative glucose, those in quartiles 2 (relative odds of infection, 95% CI=1.17 [0.57–2.40]), 3 (1.86 [0.94–3.68]), and 4 (1.78 [0.86–3.47]) were at progressively higher risk for infection (p=0.05).[38]

Adams et al. conducted a retrospective cohort study in 5 regions of a large integrated healthcare organization. Eligible subjects, identified from the Kaiser Permanente Total Joint Replacement Registry, underwent an elective primary TKA between 2001 and 2009. Data on demographics, diabetes status, preoperative hemoglobin A1c (HbA1c) level, and comorbid conditions were obtained from electronic medical records. Subjects were classified as nondiabetic, diabetic with HbA1c<7% (controlled diabetes), or diabetic with HbA1c > 7% (uncontrolled diabetes). Outcomes were deep venous thrombosis or pulmonary embolism within 90 days after surgery and revision surgery, deep infection, incident of myocardial infarction, and all-cause rehospitalization within one year after surgery. Patients without diabetes were the reference group in all analyses. All models were adjusted for age, sex, body mass index, and Charlson comorbidity index. Of 40,491 patients who underwent TKA, 7,567 (18.7%) had diabetes, 464 (1.1%) underwent revision arthroplasty, and 287 (0.7%) developed a deep infection. Compared with patients without diabetes, no association between controlled diabetes (HbA1c < 7%) and the risk of revision (OR, 1.32; 95% CI, 0.99 to 1.76), risk of deep infection (OR, 1.31; 95% CI, 0.92 to 1.86), or risk of deep venous thrombosis or pulmonary embolism (OR, 0.84; 95% CI, 0.60 to 1.17) was observed. Similarly, compared with patients without diabetes, no association between uncontrolled diabetes (HbA1c > 7%) and the risk of revision (OR, 1.03; 95% CI, 0.68 to 1.54), risk of deep infection (OR, 0.55; 95% CI 0.29 to 1.06), or risk of deep venous thrombosis or pulmonary embolism (OR, 0.70; 95% CI, 0.43 to 1.13) was observed.[40]

Anticoagulation: Well-designed studies evaluating the effects of anticoagulation on wound complication and hematoma formation in patients who have undergone reoperation for wound-related problems are lacking. However, the effects of aggressive or excessive anticoagulation

have been studied extensively in patients undergoing primary or revision TKA and THA. One case control study found that patients with a postoperative INR>1.5 were more likely to develop hematomas and wound drainage after joint replacement and subsequent infection.[41] Another retrospective observational study found that patients who received low-molecular-weight heparin for prophylaxis had a longer time until the postoperative wound was dry than did those treated with aspirin and mechanical foot compression or those who received Coumadin (warfarin) until the eighth postoperative day. Each day of prolonged wound drainage increased the risk of wound infection by 42% following a THA and by 29% following a TKA.[24] Recently, a case control study by Mortazavi et al. identified 38 patients requiring reoperation due to hematoma following THA between 2000 and 2007. The 38 patients were matched with 117 patients without hematoma. The mean follow-up was 4.1 years (range, 2.1–9.6). Multivariate regression showed that blood loss, administration of fresh frozen plasma and vitamin K, perioperative anticoagulation, and hormonal therapy were independent predictors for hematoma formation. Chronic anticoagulation and autologous blood transfusion were independent risk factors for mortality. Hematoma itself was found to be an independent risk factor for adverse outcomes, increasing morbidity and mortality despite adequate treatment.[42]
Although persistent drainage and hematoma formation are recognized risk factors for the development of PJI, it is not known if excess anticoagulation is a predisposing factor. Parvizi et al. conducted a 2 to 1 case control study with 78 cases that underwent revision for septic failure. The controls underwent the same index procedure but did not develop consequent infection. Patient comorbidities, medications, and intraoperative and postoperative factors were compared. Postoperative wound complications including development of hematoma and wound drainage were significant risk factors for PJI. A mean INR of greater than 1.5 was found to be more prevalent in patients who developed postoperative wound complications and subsequent PJI. Cautious anticoagulation to prevent hematoma formation and/or wound drainage is critical to prevent PJI and its undesirable consequences.[41]

Anemia: Preoperative anemia prior to TJA has been associated with a prolonged LOS, greater 90-day readmission rates, and higher allogenic blood transfusion requirements.[43,44] Therefore, all possible means must be undertaken to improve hemoglobin levels prior to TJA. However, both preoperative anemia and allogenic transfusions have been associated with higher rates of PJI.[44] Hence, blood conservation protcols were devised to decrease the need for postoperative transfusions in anemic patients. A systematic approach to optimizing hemoglobin levels preoperatively that implements oral and possibly intravenous iron, folic acid supplements, and

erythropoietin while minimizing blood loss intraoperatively using tranexamic acid, cell salvage, and induced hypotension has been shown to diminish allogenic transfusion requirements.[43] Although such protocols and studies are lacking in patients with TJA undergoing reoperation for SSI, these preoperative and intraoperative measures can be easily implemented during the initial procedure and prior to the I&D.

Question 6: Should intraoperative cultures be taken when performing I&D for a persistently draining wound after TJA?

Consensus: Yes. Intraoperative cultures (minimum of 3) should be taken when performing I&D reoperation for a persistently draining wound.

Delegate Vote: Agree: 98%, Disagree: 1%, Abstain: 1% (Strong Consensus)

Justification: In a retrospective study performed by Jaberi et al., positive bacterial cultures from deep periprosthetic tissue were present in 34% of cases (28/83) of persistently draining wounds that underwent I&D.[17] Positive bacterial cultures obtained from deep (periprosthetic) tissue were more common in the failure group (17 of 20 [85%]) than in the success group (11 of 63 [17%]). In another retrospective study of 8 TKAs with persistent drainage, 25% (2/8) proved to have a positive joint culture at the time of I&D.[26] Atkins et al. recommended taking a minimum of 3 samples after they found that the isolation of an indistinguishable microorganism from 3 or more independent specimens was highly predictive of infection. Their prospective study was performed to establish criteria for the microbiological diagnosis of PJI at elective revision arthroplasty. Revisions on 334 patients were performed over a 17-month period, of which 297 procedures were evaluable. There were 41 infections, with only 65% of all samples sent from infected patients being culture positive, suggesting low numbers of bacteria in the samples taken. The isolation of an indistinguishable microorganism from 3 or more independent specimens was highly predictive of infection (sensitivity, 65%; specificity, 99.6%; LR, 168.6).[45]

Question 7: Should perioperative antibiotics be withheld prior to skin incision for I&D of TJA?

Consensus: No. Perioperative antibiotics given within one hour prior to I&D reoperation should not be withheld prior to skin incision.

Delegate Vote: Agree: 82%, Disagree: 14%, Abstain: 4% (Strong Consensus)

Justification: Ghanem et al. retrospectively reviewed 171 patients undergoing TKA, diagnosed with PJI from 2000 to 2005, who had a positive preoperative aspiration culture. The details of any antibiotics given to the patients preoperatively were documented. Seventy-two of 171 patients received preoperative antibiotics before surgery. Intraoperative culture was negative in 9, with a false-negative rate of 12.5%. An organism could not be isolated from intraoperative samples in 8 of the 99 patients who did not receive preoperative antibiotics, with a false-negative rate of 8%. We observed no difference in the incidence of false-negative cultures between the two groups. Administration of preoperative antibiotics to patients with a positive preoperative joint aspiration did not interfere with isolation of the infecting organism from intraoperative culture samples more than when antibiotics were withheld. Two prospective studies reached the same conclusion that preoperative prophylactic antibiotics had no significant effect on cultures obtained intraoperatively.[46,47]

Burnett et al. undertook a prospective study to determine whether prophylactic preoperative intravenous antibiotics would affect the results of cultures obtained intraoperatively. They enrolled 25 patients with 26 infected TKAs, a known preoperative infecting organism, and no recent antibiotic therapy. Reaspiration of the infected TKA was performed after anesthesia and sterile preparation. Intravenous antibiotic prophylaxis was then administered and the tourniquet inflated. Intraoperative culture swabs and tissue were obtained at arthrotomy. The timing of events was recorded. Pre- and postantibiotic culture data were analyzed to determine the effect of intravenous preoperative prophylactic antibiotics on cultures obtained intraoperatively. In all 26 knees the organism(s) cultured on the preoperative aspiration and from the operating room cultures before antibiotic infusion were the same organism(s) cultured at the time of arthrotomy despite the routine infusion of antibiotics.[46]

Tetreault et al. randomized 65 patients with known PJI after 37 TKAs and 28 THAs at 3 centers. Patients were included in the trial if they had a culture-positive aspiration and had not taken antibiotics within 2 weeks of the procedure. Patients were randomized to receive prophylactic antibiotics either before the skin incision or after a minimum of 3 sets of intraoperative cultures were obtained. Preoperative and intraoperative cultures were then compared. Results between patients who did and did not receive antibiotics were compared using an equivalence test for proportion differences (two one-sided t-tests [TOST]) with a 0.2 margin. Intraoperative cultures yielded the same organisms as preoperative cultures in 28 of 34 patients (82%) randomized to receive antibiotics before the skin incision compared to 25 of 31 patients (81%) randomized to receive antibiotics after obtaining operative cultures (statistically equivalent by TOST estimate: p=0.0290).[47]

Question 8: What is the optimal method for wound closure after TJA to minimize the risk of SSI and PJI?

Consensus: Despite the lack of evidence supporting the superiority of one technique of skin closure over others (staples, suture, adhesive, or tapes), we recommend the use of monofilament suture for wound closure in patients who undergo reoperation for wound-related problems during the early postoperative period after index arthroplasty.

Delegate Vote: Agree: 75%, Disagree: 15%, Abstain: 10% (Strong Consensus)

Justification: A prospective RCT comparing skin adhesives, subcuticular closure, and skin staples for closure of TKA and THA revealed no significant difference in early and late complications, wound cosmesis, or patient satisfaction.[48] Another prospective RCT compared TKA tissue adhesives, stapling, and suturing as wound closure techniques and found no significant differences in infection, dehiscence, cosmesis, or functional outcomes.[49] A similar prospective RCT comparing skin adhesive and staples for skin closure in THA found no significant difference between groups in the cosmetic appearance of scars at 3 months (p=0.172), the occurrence of complications (p=0.3), or patient satisfaction (p=0.42).[50] A meta-analysis was conducted to compare the clinical outcomes of staples vs sutures in wound

closure after orthopaedic surgery. The study found no significant difference between sutures and staples in the development of inflammation, discharge, dehiscence, necrosis, and allergic reaction; but the risk of developing a superficial wound was over 3 times greater after staple closure than suture closure ($p=0.01$).[51] However, the authors stated that the included studies had several major methodological limitations, including the recruitment of small, underpowered cohorts, poor randomization of patients, and not blinding assessors to the allocated methods of wound closure. A Cochrane meta-analysis determined the relative effects of various tissue adhesives and conventional skin closure techniques (staples, sutures, and tapes) on the healing of surgical wounds.[52] The authors concluded that there is insufficient evidence either to support or refute the idea that using tissue adhesive leads to lower or higher levels of dehiscence, satisfaction with cosmetic appearance when assessed by patients or surgeons, patients' and surgeons' general satisfaction, or infection.

Khan et al. carried out a blinded prospective RCT comparing 2-octylcyanoacrylate (OCA), subcuticular suture (monocryl) and skin staples for skin closure following THA and TKA. They included 102 THA and 85 TKA. OCA was associated with less wound discharge in the first 24 hours for both the hip and the knee. However, with TKA there was a trend for a more prolonged wound discharge with OCA. With THA there was no significant difference between the groups for either early or late complications. Closure of the wound with skin staples was significantly faster than with OCA or suture. There was no significant difference in the LOS, Hollander wound evaluation score (cosmesis), or patient satisfaction between the groups at 6 weeks for either hips or knees.[48]

Eggers et al. compared 4 wound closure techniques for TKA in a RCT with 75 subjects. The study compared tissue adhesives, stapling, and suturing with respect to procedure time and cost, together with functional and clinical outcome. TKA closure time (capsule to cutaneous) favored staples at 26 s/cm, followed by adhesives (45 and 37 s/cm for 2-octyl and n-butyl-2, respectively), and finally subcuticular suturing at 54 s/cm ($p<0.0007$). Reduced procedure time translated into intraoperative cost reduction where closure cost per centimeter was $70, $62, $57, and $75 for 2-octyl, n-butyl-2, staples, and sutures, respectively. No significant differences in infection, dehiscence, cosmesis, general health (SF-12v2; QualityMetric Inc., Lincoln, Rhode Island), and functional and clinical assessments (range of motion, Knee Society score, and pain) were observed.[49]

Livesey et al. undertook a RCT to compare the outcomes of skin adhesive and staples for skin closure in THA. The primary outcome was the cosmetic appearance of the scar at 3 months using a surgeon-rated VAS. In all, 90 patients were randomized to skin closure using either skin adhesive (n=45) or staples (n=45). Data on demographics, surgical details, infection, and oozing were collected during the in-patient stay. Further data on complications, patient satisfaction, and evaluation of cosmesis were collected at 3 months follow-up and a photograph of the scar was taken. An orthopaedic and a plastic surgeon independently evaluated the cosmetic appearance of the scars from the photographs. No significant difference was found between groups in the cosmetic appearance of scars at 3 months (p=0.172), the occurrence of complications (p=0.3), or patient satisfaction (p=0.42). Staples were quicker and easier to use than skin adhesive and less expensive. Skin adhesive and surgical staples are both effective skin closure methods in THA.[50]

Smith et al. conducted a meta-analysis to compare the clinical outcomes of staples versus sutures in wound closure after orthopaedic surgery. Medline, CINAHL, AMED, Embase, Scopus, and the Cochrane Library databases were searched, in addition to the grey literature published in all languages from 1950 to September 2009. Two authors independently assessed papers for eligibility. RCTs and non-RCTs that compared the use of staples with suture material for wound closure after orthopaedic surgery procedures were included. Publications were not excluded because of poor methodological quality. The primary outcome measure was the assessment of superficial wound infection after wound closure with staples compared with sutures. Six papers, which included 683 wounds, were identified; 332 patients underwent suture closure and 351 underwent staple closure. The risk of developing a superficial wound infection after orthopaedic procedures was over 3 times greater after staple closure than suture closure (RR 3.83, 95% CI 1.38 to 10.68; p=0.01). On subgroup analysis of hip surgery alone, the risk of developing a wound infection was 4 times greater after staple closure than suture closure (4.79, 1.24 to 18.47; p=0.02). There was no significant difference between sutures and staples in the development of inflammation, discharge, dehiscence, necrosis, and allergic reaction. The included studies had several major methodological limitations, including the recruitment of small, underpowered cohorts, poor randomization of patients, and not blinding assessors to the allocated methods of wound closure.[51]

Coulthard et al. conducted a meta-analysis to determine the relative effects of various tissue adhesives and conventional skin closure techniques (staples, sutures, and tapes) on the healing of surgical wounds. Screening of eligible studies and data extraction were conducted

independently and in triplicate while assessment of the methodological quality of the trials was conducted independently and in duplicate. Results were expressed as random effects models using the mean difference for continuous outcomes and RR with 95% CIs for dichotomous outcomes. Heterogeneity was investigated including both clinical and methodological factors. For this update the following databases were searched: the Cochrane Wounds Group Specialized Register (search conducted 11/17/09), The Cochrane Central Register of Controlled Trials (CENTRAL)--The Cochrane Library Issue 4 2009, Ovid MEDLINE-1950 to November Week 1 2009, Ovid EMBASE--1980 to 2009 Week 46, and EBSCO CINAHL--1982 to 17 November 2009.

For adhesive compared with sutures, there was an overall favoring of sutures for dehiscence. However, sutures were significantly faster to use than tissue adhesives. For adhesives compared with tapes, there was a significant difference in time taken for closure, which favored the control (tapes). The surgeon's opinion of the cosmetic outcome was better in the tape group. For adhesives compared with staples, there was a significant difference in time taken for closure, favoring the staples group. For adhesives compared with other techniques, when assessing operator and patient satisfaction there was a statistical difference favoring the control group over adhesives. In this same analysis there was a statistical difference favoring the adhesive for time taken to closure. For all other analyses there was insufficient evidence either to support or refute the idea that using tissue adhesive led to lower or higher levels of dehiscence, satisfaction with cosmetic appearance when assessed by patients or surgeons, patients' and surgeons' general satisfaction, or infection, when used in comparison with sutures, adhesive tape, staples, or an adhesive with a lower viscosity.[52]

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Workgroup 9: Spacers

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Question 1: Is there a functional difference in the use of non-articulating or articulating spacers for the treatment of periprosthetic joint infection (PJI) in the knee, between two-stage exchange arthroplasty?

Consensus: Articulating spacers provide better function than non-articulating spacers for the patient in between the stages of total knee arthroplasty (TKA). An articulating spacer is especially preferred for patients who are likely to have a spacer in place for longer than 3 months.

Delegate Vote: Agree: 89%, Disagree: 6%, Abstain: 5% (Strong Consensus)

Justification: The current available peer-reviewed literature reveals an overall of 46 original articles (excluding case reports, review articles, and technical reports) including 4 level 2, 8 level 3, and 34 level 4 studies related to the use of spacers.

The majority of these studies have evaluated the mid-term functional outcome of patients after reimplantation and compared articulating with non-articulating spacers. A few studies that evaluated patient function between the stages for resection arthroplasty and reimplantation detected a superior outcome for patients receiving articulating spacers compared to those with non-articulating spacers.[1-46]

Question 2: Is there a functional difference in the use of non-articulating or articulating spacers for treatment of PJI in the knee at minimum two years after reimplantation?

Consensus: There is a non-significant trend in range of motion improvement with articulating compared to non-articulating spacers, but the panel believes that this is still of value to the patient

Delegate Vote: Agree: 82%, Disagree: 12%, Abstain: 6% (Strong Consensus)

Justification: A review of the current available peer-reviewed literature reveals an overall number of 46 original articles (excluding case reports, review articles, and technical reports) including 4 level 2, 8 level 3, and 34 level 4 studies related to the use of spacers.[1-46]

The majority of these studies have evaluated the mid-term functional outcome of patients after reimplantation and compared articulating with non-articulating spacers. The majority of studies have demonstrated a higher range of motion at mid-term follow-up for patients receiving articulating spacers compared to patients with non-articulating spacers. The average reported flexion angle for all reported patients receiving articulating spacers (1,195 cases) after an average follow-up of 44.3 months was 96.4˚ (range 63˚ to 115˚; standard deviation (SD)=10.8), whereas in all reported patients of the non-articulating group (474 cases) an average flexion angle of 91.2˚ (range 73.8˚ to 106˚; SD=8.7) was reported after an average follow-up of 52 months.

Question 3: Is there a functional difference in the use of non-articulating or articulating spacers for the treatment of PJI in the hip between the stages of two-stage exchange arthroplasty?

Consensus: A well performing articulating spacer provides better function for the patient in between the stages of total hip arthroplasty (THA). These are especially preferred for patients who are likely to have a spacer in place for longer than 3 months.

Delegate Vote: Agree: 89%, Disagree: 7%, Abstain: 4% (Strong Consensus)

Justification: There are 26 original articles (excluding case reports, review articles, and technical reports) analyzing the functional outcomes of patients who have undergone two-stage exchange for PJI of the hip. Most of the available studies report functional outcome according to the Harris Hip Score (HHS). We found one level 1 study, 2 level 2 studies, 2 level 3 studies, and 21 level 4 studies.

A few studies that evaluated patient function between stages for resection arthroplasty and reimplantation detected a superior outcome for patients receiving articulating spacers compared to those with non-articulating spacers.[42,47-71]

Question 4: Is there a functional difference in the use of non-articulating or articulating spacers for the treatment of PJI in the hip, at a minimum of two years after reimplantation?

Consensus: There is a non-significant trend in functional improvement with articulating compared to non-articulating spacers, but the panel believes that this is still of value to the patient.

Delegate Vote: Agree: 81%, Disagree: 12%, Abstain: 7% (Strong Consensus)

Justification: There are 26 original articles (excluding case reports, review articles, and technical reports) analyzing the functional outcomes of patients who have undergone two-stage exchange for PJI of the hip. Most of the available studies report functional outcome according to the HHS. We found one level 1 study, 2 level 2 studies, 2 level 3 studies, and 21 level 4 studies. The majority of the reports comparing the mid-term outcome of surgical treatment for PJI revealed a better functional outcome (as measured by the HHS) for patients who received articulating spacers compared to non-articulating spacers. The average reported HHS for all patients receiving articulating spacers (898 cases) after an average follow-up of 50 months was 83 (range 68 to 98 points; SD=8.2), compared to the HHS of 81 points (range, 78 to 83 points; SD=2.3) for those receiving non-articulating spacers (63 patients) after an average follow up of 61 months.[42,47-71]

Question 5: Is there a difference in reimplantation (surgical ease) with the use of non-articulating or articulating spacers for the treatment of PJI in the knee and hip?

Consensus: Yes. Reimplantation surgery is easier overall in patients receiving articulating spacers compared to non-articulating spacers.

Delegate Vote: Agree: 81%, Disagree: 8%, Abstain: 11% (Strong Consensus)

Justification: As far as we could find there were no studies that directly compared the ease of reimplantation of spacers between patients receiving non-articulating or articulating spacers. However, based on anecdotal reports it appears that the use of articulating spacers facilitates reimplantation surgery. Better soft tissue tension, improved ability of the patient to move the joint in the interim between resection and reimplantation, and better restoration of anatomy may all be reasons for this difference.

Question 6: Is there a difference with regards to control of infection with the use of articulating or non-articulating spacers in the knee?

Consensus: No. The type of spacer does not influence the rate of infection eradication in two-stage exchange arthroplasty of the knee.

Delegate Vote: Agree: 89%, Disagree: 6%, Abstain: 5% (Strong Consensus)

Justification: Evaluation of the peer-reviewed literature revealed 59 original articles (excluding case reports, review articles, and technical reports) related to this subject. There were no level 1 studies that examined the success of surgical treatment with regard to infection control. There were 5 level 2 studies, 11 level 3 studies, and 43 level 4 studies.[1-59]

Eleven studies compared the eradication of infection rates through the use of articulating or non-articulating spacers. We analyzed all available literature, including 1,557 cases treated with articulating spacers and 601 cases treated with non-articulating spacers. The eradication rate of 91.5% (132 cases of reinfection) was higher with the use of an articulating spacer at latest mean follow-up of 42 months. The eradication rate was 87.0% (78 cases of reinfection) using a non-articulating spacer at 56 months follow-up. It is possible that the longer follow-up for the non-

articulating spacer cohort may explain the slight difference in infection control between the non-articulating and articulating spacer cohort. A further limiting factor for comparison of both groups might relate to the differences in organism profile (low vs high virulence), patient age, and comorbidities. None of the studies performed a multivariate analysis to isolate the use of spacer as an independent factor influencing the outcome of surgical treatment with regard to infection control.[1-6,8-27,29-46,72-85]

Question 7: Is there a difference with regards to control of infection with the use of articulating or non-articulating spacers in the hip?

Consensus: No. The type of spacer does not influence the rate of infection eradication in two-stage exchange arthroplasty of the hip.

Delegate Vote: Agree: 95%, Disagree: 3%, Abstain: 2% (Strong Consensus)

Justification: An evaluation of the peer-reviewed literature revealed 65 original articles (excluding case reports, review articles, and technical reports) related to this matter. Most (55) of the available studies are level 4 studies, followed by 5 level 3 studies and 4 level 2 studies. Only one level 1 study was available.[9,42,47-72,74,78,86-120]

Based on the available literature, we found 2,063 infected THA cases treated with articulating and 354 infected THA cases treated with non-articulating spacers. The eradication rate was slightly higher with the use of an articulating spacer with 92.5% (154 cases of reinfection) at latest follow-up of 43.4 months. The eradication rate was 90.7% (33 cases of reinfection) at latest follow-up of 49.6 months using a non-articulating spacer. Again, the confounding variables here may be the differences in follow-up, organism profile, patient age, patient comorbidities, and numerous other factors that influence the outcome of surgical intervention for PJI. None of the studies performed a multivariate analysis to isolate the type of spacer as an independent factor influencing control of infection.

Question 8: Is there a difference with regards to control of infection between different types of articulating spacers used in the knee?

Consensus: Control of the infection is no different between different types of articulating spacers in the treatment of infected TKA.

Delegate Vote: Agree: 90%, Disagree: 5%, Abstain: 5% (Strong Consensus)

Justification: Evaluation of the available peer-reviewed literature revealed 45 original articles (excluding case reports, review articles, and technical reports). There were no level 1 studies. There were 5 level 2 studies, 11 level 3 studies, and 29 level 4 studies.[1,3-6,8-10,12-14,16-18,21-25,27,29,30,32,33,35-38,40-45,51,72,73,77,79-82,85]

We evaluated the outcome of combined cohorts, which included 1,492 infected TKA cases treated with different articulating spacers (PROSTALAC, Depuy, Warsaw, IN, n=314 cases; Hoffmann technique, n=410; cemented molds, n=716; and Spacer K, n=52 cases). The eradication rate was higher with the use of a Spacer K with 94.2% (3 cases of reinfection) followed by the Hoffmann technique with 93.7% (26 cases of reinfection), and cemented molds with 91.6% (60 cases of reinfection) in the treatment of infected TKA. The eradication rate with the use of the PROSTALAC spacer was 91.1% (28 cases of reinfection).

Question 9: Are there contraindications for the use of non-articulating and/or articulating spacers?

Consensus: There are no clear contraindications for the use of non-articulating or articulating spacers, other than the technical feasibility of the procedure. In patients with massive bone loss and/or lack of integrity of soft tissues or ligamentous restraint, strong consideration should be given to the use of non-articulating spacers.

Delegate Vote: Agree: 92%, Disagree: 3%, Abstain: 5% (Strong Consensus)

Justification: Based on available evidence, it is difficult to determine if there are any contraindications for the use of either spacers in the knee or the hip. However, expert surgeons who treat patients with PJI of the hip and knee on a frequent basis feel that the use of articulating spacers in patients with massive bone loss or lack of soft tissue or ligamentous integrity may lead to dislocation of the spacer. In addition, some surgeons prefer to use non-articulating spacers in patients with compromised soft tissue around the joint in order to prevent motion and allow better soft tissue healing. However, this practice has not been evaluated scientifically. We also analyzed the spacer complication rate using articulating and non-articulating hip spacers. The overall complication rate was 11.6% using articulating spacers and 6.9% using non-articulating spacers.[9,47-72,74,78,86-120] The higher complication rate for articulating spacers should be noted.

Question 10: Are there any differences in functional outcome between manufactured spacers versus surgeon-made dynamic spacers used in the knee?

Consensus: There is no difference in functional outcome between manufactured spacers versus surgeon-made articulating spacers used in the knee. However, issues of cost, ease of use, and antibiotic delivery should be considered.

Delegate Vote: Agree: 89%, Disagree: 5%, Abstain: 6% (Strong Consensus)

Justification: Evaluation of the available peer-reviewed literature revealed 50 original articles (excluding case reports, review articles, and technical reports). None of the studies were level 1. There were 6 level 2 studies, 11 level 3 studies, and 33 level 4 studies.[1-50]

We analyzed 1,525 infected TKA cases treated with either a handmade spacer (n=1074) or manufactured spacers (n=451). The mean flexion at latest follow-up was tendentially higher with a mean of 101.9° (range 77°to 115°; SD=8.3) using a handmade spacer compared to a mean of

90.2° (range 63°to 106°; SD=12.3) with a manufactured spacer.[1,3-10,12-14,16-19,22-25,27-29,31-45,72,73,75,77,79-82,84,85,108]

Question 11: Are there any differences in the rate of infection control between manufactured spacers versus surgeon-made articulating spacers used in the knee?

Consensus: There are no differences in the rate of infection control between manufactured spacers and surgeon-made articulating spacers used in the knee. However, issues of cost, ease of use, and antibiotic delivery should be considered.

Delegate Vote: Agree: 93%, Disagree: 2%, Abstain: 5% (Strong Consensus)

Justification: Evaluation of the available peer-reviewed literature revealed 50 original articles (excluding case reports, review articles, and technical reports). None of the studies were level 1. There were 6 level 2 studies, 11 level 3 studies, and 33 level 4 studies.[1-50]

We analyzed 1,525 infected TKA cases treated with either a handmade spacer (n=1,074) or manufactured spacers (n=451). The eradication rate was comparable with the use of a handmade spacer with 92.2% (84 reinfections) compared to the use of an industry-made spacer with 90.5% (43 reinfections).[1,3-10,12-14,16-19,22-25,27-29,31-45,72,73,75,77,79-82,84,85,108]

Question 12: Are there any differences in functional outcome between manufactured spacers versus surgeon-made dynamic spacers used in the hip?

Consensus: There is no difference in functional outcome between manufactured spacers versus surgeon-made articulating spacers used in the hip. However, issues of cost, ease of use, and antibiotic delivery should be considered.

Delegate Vote: Agree: 89%, Disagree: 7%, Abstain: 4% (Strong Consensus)

Justification: Evaluation of the available peer-reviewed literature revealed 55 original articles (excluding case reports, review articles, and technical reports). There were one level 1 study, 4 level 2 studies, 4 level 3 studies, and 46 level 4 studies.[9,47-54,56-59,61-63,72,74,78,86-88,90-98,100-108,110-113,123,64-67,70,71,115,117,119,120]

We analyzed 1,925 infected THA cases treated with either a handmade spacer (n=1,011) or manufactured spacer (n=914). The mean HHS at latest follow-up was also comparable using a handmade spacer (mean 84.9; range 68 to 97.8; SD=8.7) or manufactured spacer (mean HHS=82.3; range 70 to 93 points; SD=8.0).

Question 13: Are there any differences in the rate of infection control between manufactured spacers versus surgeon-made dynamic spacers used in the hip?

Consensus: There is no difference in the rate of infection control between manufactured spacers versus surgeon-made articulating spacers used in the hip. However, issues of cost, ease of use, and antibiotic delivery should be considered.

Delegate Vote: Agree: 94%, Disagree: 3%, Abstain: 3% (Strong Consensus)

Justification: Evaluation of the available peer-reviewed literature revealed 55 original articles (excluding case reports, review articles, and technical reports). There were one level 1 study, 4 level 2 studies, 4 level 3 studies, and 46 level 4 studies.[9,47-54,56-59,61-63,72,74,78,86-88,90-98,100-108,110-113,123,64-67,70,71,115,117,119,120]

We analyzed 1,925 infected THA cases treated with either a handmade spacer (n=1,011) or manufactured spacer (n=914). The infection control rate with the use of a handmade spacer was 94.0% (61 reinfections) which was similar to the use of a manufactured spacer with 93.5% (59 reinfections).

Question 14: Which antibiotic should be used and how much of it should be added to cement spacers?

Consensus: The type of antibiotic and the dose needs to be individualized for each patient based on the organism profile and antibiogram (if available) as well as the patient's renal function and allergy profile. However, most infections can be treated with a spacer with Vancomycin (1 to 4 g per 40 g package of cement) and gentamicin or tobramycin (2.4 to 4.8 g per 40 g package of cement). We provide a list of all available antibiotics and the range of doses to be used against common infecting organisms.

Delegate Vote: Agree: 89%, Disagree: 7%, Abstain: 4% (Strong Consensus)

Antibiotic Group	**Type of Antibiotic**	**Activity Against**	**Dose per 40 g cement (in grams)**
Aminoglycoside	Tobramycin	Gram-negative bacteria such as *Pseudomonas*	1 to 4.8
Aminoglycoside	Gentamicin	Gram-negative bacteria-*Escherichia coli, Klebsiella* and particularly *Pseudomonas aeroginosa*. Also aerobic bacteria (not obligate/facultative anaerobes)	0.25 to 4.8
Cephalosporin , 1st gen	Cefazolin	Gram-positive infections, limited Gram negative coverage	1 to 2
Cephalosporin, 2nd gen	Cefuroxime	Reduced gram-positive coverage, improved gram-negative coverage	1.5 to 2
Cephalosporin, 3rd gen	Ceftazidime	Gram-negative bacteria, particularly *Pseudomonas*	2
Cephalosporin, 4th gen	Cefotaxime	Gram-negative bacteria, no activity against *Pseudomonas*	2
Cephalosporin, 5th gen	Ceftaroilne	Gram-negative bacteria, no activity against *Pseudomonas*	2 to 4

Fluoroquinolone	Ciprofloxacin	Gram-negative organisms including activity against *Enterobacteriaciae*	0.2 to 3
Glycopeptide	Vancomycin	Gram-positive bacteria, including methicillin-resistant organisms	0.5 to 4
Lincosamide	Clindamycin	Gram-positive cocci, anaerobes	1 to 2
Macrolide	Erythromycin	Aerobic gram-positive cocci and bacilli	0.5 to 1
Polymyxin	Colistin	Gram-negative	0.24
ß-lactam	Piperacillin-not available Pip-tzobactam	Gram-negative bacteria (particularly *Pseudomonas*), Enterobacteria and anaerobes	4 to 8
ß-lactam	Aztreonam	Only gram-negative bacteria	4
β-lactamase inhibitor	Tazobactam	Gram-negative bacteria (particularly *Pseudomonas*), Enterobacteria, and anaerobes in combination with Piperacillin	0.5
Oxazolidinones	Linezolid	Multidrug-resistant gram-positive cocci such as MRSA	1.2
Carbapenem	Meropenem	Gram-positive and gram-negative bacteria, anaerobes, *Pseudomonas*	0.5 to 4
Lipopeptide	Daptomycin	Only gram-positive organisms	2
Antifungals	Amphotericin	Most Fungi	200
Antifungal	Voricanazole	Most fungi	300-600 mg

AVAILABLE ANTIBIOTICS AND ANTI-FUNGALS WHICH CAN BE USED IN SPACERS. The dose ranges reveal only the reported doses in the analyzed studies and are not recommendations.[1-134] Again, the type of antibiotic and the dose needs to be individualized for

each patient based on the organism profile and antibiogram (if available) as well as the patient's renal function and allergy profile.

Justification: Some antibiotics become deactivated during the exothermic setting of polymethylmethacrylate (PMMA) cement and hence cannot be used in spacers. A list of all available antibiotics and the organisms against which they are active is provided (**Table 1**).

Although there are some studies claiming that the addition of high doses of antibiotic to PMMA cement is possible and does not carry the risk of systemic toxicity, the majority of surgeons have had experience with patients who developed renal toxicity following the use of an antibiotic-impregnated cement spacer. There are 3 main factors that influence the elution of antibiotic from PMMA spacers and the potential for renal toxicity. This includes the type of PMMA cement used (with high-viscosity cements containing MA-MMA copolymers having better antibiotic elution profiles than other acrylic bone cement formulations), renal function of the patient, and the manner in which the spacer is made and positioned in the infected joint. The larger the surface area of the spacer, the higher the antibiotic elution will be from the given spacer. Some surgeons place a ball of cement spacer in the joint, whereas others may place numerous PMMA beads in the soft tissue or the intramedullary canal. The treating surgeon needs to consider both of these options when operating on a patient with an infected joint.

We did not find any evidence in favor of or against any of the commercially-available PMMA cements that may be used in fashioning a spacer. Two of the most commonly used PMMA cements, namely Palacos and Simplex cement, were compared. We analyzed the available data with regard to infection control rates between these two cement types. Overall, 1,160 infected TKA cases were included. In 811 out of 1,160 cases Palacos cement (69.9%) was used and in the remaining 349 cases Simplex cement was used (30.1%). The eradication rate was similar with a 91.6% rate of eradication (68 cases of reinfection) using Palacos cement compared to Simplex cement with an eradication rate of 89.4% (37 cases of reinfection).[1-4,7-10,12-14,17,18,28-30,32,33,36,38,40,41,43,72,73,76-78,80-84,108]

We also analyzed the available data for infected THA cases. We included 1,454 cases (Palacos, n=1,201; and Simplex, n=253). The infection control rate was similar in both groups with a rate of 93.7% (16 cases of reinfection) for Simplex and 93.8% (74 cases of reinfection) for Palacos cement.[3,9,47,48,50-54,56,60-66,70,72,73,78,87,90-92,94,95,98,100,102,104,105,108,110,113,115,117,119,123]

Question 15: What is the optimal technique for preparing a high-dose antibiotic cement spacer (mixing, when and how to add antibiotics, and porosity)?

Consensus: There is no consensus on the best method of preparation of high-dose antibiotic cement spacers.

Delegate Vote: Agree: 93%, Disagree: 3%, Abstain: 4% (Strong Consensus)

Justification: The pharmacokinetics of antibiotic release from the matrix is influenced by numerous factors, including the porosity of the cement (high viscosity cement containing MA-MMA copolymers have been shown to have better antibiotic elution profiles than other acrylic bone cement formulations) dose and type of antibiotics added to PMMA, and the shape and surface area of the spacer.

One of the basic principles of spacer preparation is recognition that local antibiotic concentration must be clearly above the minimal inhibitory concentration and have minimal bactericidal concentrations of the infecting organism.[124] In general, the spacers should generate high local concentrations of antibiotic without associated systemic toxicity. Elution of antibiotics from the cement has been shown to be highest in the first 24 to 72 hours after surgery.[125] It seems that the initial high elution from the cement is a result of mechanical erosion of the spacer surface. The prolonged release over weeks relates to the antibiotic-loaded bone cement itself.[126]

Another factor influencing the efficacy of antibiotic release from spacers includes the combination of antibiotics used, fatigue life of PMMA, and mixing technique. Antibiotic combinations can alter the elution characteristic of each agent; therefore, as one antibiotic dissolves, porosity increases and changes the surface, which allows for increased elution of other antibiotics. For instance, it has been shown that there was a statistically significant increase in the elution of vancomycin when the dose of tobramycin was increased from 2.4g to at least 3.6g in the mixture.[108]

General principles of mixing antibiotics to cement:

Antibiotic needs to be bactericidal, in powder form to allow better integration with cement,[127] sterile, heat/thermo stable, and soluble in water.

The technical aspects of preparing a spacer include:

For preparation of antibiotic-loaded cement for the spacer, some technical aspects apply. As the dosage of antibiotics increases, the difficulty of incorporating the antibiotics into the cement during the mixing process increases. In these situations, mixing the cement powder and monomer for 30 seconds,[134] followed by the addition of the antibiotic powder in multiple small doses, will facilitate incorporation. It is also advisable to crush clumps of antibiotic, although some irregularity in the antibiotics is acceptable, and may be preferable for early elution of active antibiotics. Hand mixing in a bowl without vacuum is recommended as bubbles facilitate elution of the antibtioics.[130] Addition of fillers such as Xyletol or Ancef may improve the elution of active antibiotics.[122,131-133] The addition of a high amount of antibiotic to cement will decrease the fatigue strength and increase the fracture risk. The addition of more than 4.5g of powder substantially weakens the cement. For most antibiotic spacers, elution of antibiotics is a primary concern over the mechanical property, but the surgeon must keep this in mind for structural spacers.

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Workgroup 10: Irrigation and Debridement

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Question 1A: When can irrigation and debridement (I&D) be considered?

Consensus: I&D may be performed for early postoperative infections that occur within 3 months of index primary arthroplasty with less than 3 weeks of symptoms.

Delegate Vote: Agree: 84%, Disagree: 13%, Abstain: 3% (Strong Consensus)

Question 1B: Can I&D be considered for late hematogenous infections?

Consensus: I&D may be performed for patients with late hematogenous infection that occurred within 3 weeks of an inciting event or with symptoms not longer than 3 weeks.

Delegate Vote: Agree: 88%, Disagree: 9%, Abstain: 3% (Strong Consensus)

Justification: I&D is a viable option to consider for patients with early postoperative or late hematogenous infections.[1] The rate of success of I&D has been stated to be between 0 to 89%.[2] What is known is that this procedure has a higher success rate in healthier patients, infections with low virulence organisms, and in patients with short period of symptoms.[1,3-25] If I&D is to be attempted, it is imperative to ensure that the prostheses are well-fixed and well-positioned and there is a good soft tissue envelope to cover the prosthesis.

Question 2: What are the contraindications for I&D?

Consensus: The inability to close a wound or the presence of a sinus tract are absolute contraindications to performing an I&D and retention of the prosthesis. Another absolute contraindication is the presence of a loose prosthesis.

Delegate Vote: Agree: 95%, Disagree: 4%, Abstain: 1% (Strong Consensus)

Justification: The inability to close a wound is an absolute contraindication for retention of the prosthesis. An open wound allows for contamination and colonization of the prosthesis and will

result in a chronic infection. Other relative contraindications include infection with highly virulent organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA)[25,26] or polymicrobial infections[27] (often as a result of the presence of a sinus) and in patients with extensive comorbidities, in particular those with immunocompromised status.[13,28] Marculescu et al. found that the presence of a sinus tract leads to an odds ratio of 2.84 for failure of I&D.[29]

Question 3A: When performing an I&D for hematoma after total knee arthroplasty (TKA), should the deep fascia be opened?

Consensus: The fascia/arthrotomy should always be opened in patients with TKA and hematoma formation.

Delegate Vote: Agree: 87%, Disagree: 8%, Abstain: 5% (Strong Consensus)

Question 3B: When performing an I&D for hematoma after total hip arthroplasty (THA), should the deep fascia be opened?

Consensus: Aspiration of the joint, either prior to surgery or at the time of I&D, should be performed. For patients with a clear fascial defect or hematoma/fluid deep to the fascia confirmed by aspiration, the fascia should be opened.

Delegate Vote: Agree: 87%, Disagree: 9%, Abstain: 4% (Strong Consensus)

Justification: There is little to no guidance in the literature about what should be done when a surgeon encounters a draining wound and/or hematoma formation.[18,30] Although superficial hematoma formation is not infrequent, the consequences of missing a deep hematoma or infection in a patient with a prosthesis can be dire.[15] Thus, it is the opinion of this consensus group that appropriate investigations should be performed to evaluate whether a presenting hematoma is superficial or if it extends to deeper layers. The fascia should be opened and the deeper hematoma evacuated in patients in whom there is a blood or fluid collection deeper in the fascia. I&D is a different procedure compared to reoperation done for evacuation of a hematoma.

Question 4: How should I&D be performed for periprosthetic joint infection (PJI)?

Consensus: An I&D of a prosthetic joint needs to be performed meticulously and according to the detailed protocol provided. Briefly this includes:

- Preoperative optimization of the patient
- Good visualization and thorough debridement
- Obtaining multiple culture samples
- Copious irrigation (6 to 9 L) of the joint
- Explantation of the prosthesis if indicated.

Delegate Vote: Agree: 90%, Disagree: 6%, Abstain: 4% (Strong Consensus)

Justification: The joint should be opened via the previously mentioned access under aseptic conditions.[30] Brush and wash all surfaces with an antiseptic solution. Copious irrigation using low-pressure pulse lavage or bulb irrigation should be performed. Reports in trauma surgery have raised concern regarding the use of high pressure lavage, which may spread the infection deeper.[31,32]

Question 5: Should the modular part always be exchanged during I&D?

Consensus: Yes. All modular components should be removed and exchanged, if possible, during I&D.

Delegate Vote: Agree: 92%, Disagree: 8%, Abstain: 0% (Strong Consensus)

Justification: There is little evidence in the literature regarding the role of exchanging modular components. Although this practice results in added expenses, prolongs the surgery, and could potentially result in increased morbidity, in our opinion it is necessary in order to allow access to parts of the joint that otherwise could not be accessed without removing the modular

components. The latter is particularly true for TKA. Access to the posterior capsule to perform extensive debridement is not possible without removal of the tibial polyethylene. In addition, removal of the modular components allows for removal of slime from the undersurface of such components, leading to better reduction of biodurden. We therefore believe it is advisable to remove and exchange modular components (if possible) in all patients undergoing I&D.[1,6,7,11,13,17,25,26,30,33,34]

Although removal of polyethylene is absolutely necessary for through debridement, reinsertion of a sterilized component may also be reasonable. In a study by Laffer et al.[35] the polyethylene modular component was removed and washed with antiseptic during I&D of TKA. The authors suggest that this may be a reasonable option to exchange of components, which carries additional cost.

Question 6: Do useful classification systems (such as the Tsukayama classification) exist that may guide a surgeon in deciding on the appropriateness of an I&D?

Consensus: The available classification system is inadequate in guiding a surgeon in selecting the appropriate surgical intervention for management of early PJI. There is a need for further studies to identify risk factors for failure of I&D in patients with acute PJI.

Delegate Vote: Agree: 84%, Disagree: 5%, Abstain: 11% (Strong Consensus)

Justification: There are numerous classification systems for PJI. The Tsukayama classification has been used as a rough guide and basis for selection of surgical treatment.[17,36] It defines an early infection as one that occurs within one month of index arthroplasty and any infection beyond this point as late. Acute hematogenous infection is also included in this classification system. The Zimmerli/Trampuz classification defines an early infection as one that occurs within 3 months of index surgery. Infections with onset between 3 to 24 months are delayed infections and those occurring >24 months after index arthroplasty are classified as late.[23] These classification systems are useful in that they provide a description for pathogenesis, with the theory being that early infections may be the result of seeding during surgery, whereas late infections are likely acquired by hematogenous spread. Another classification proposed by Senneville et al. relies mostly on the duration of symptoms and places less emphasis on the timing of index arthroplasty. Based on this classification, acute infection is one with less than

one month of symptoms and any infection with greater than one month of symptoms is considered late.[37] Less than 4 weeks of symptoms is quite common according to Garvin et al.[17,38,39] The classification proposed by McPherson considers criteria other than timing, such as host factors and micro-organism factors, and looks at periods of less than 3 weeks.[40] Recent data suggest that the success of prosthesis retention depends on many factors other than the time at which infection occurs.[41,42] Thus, the decision to perform an I&D for a patient with infection must take into account many other parameters including the host type, the virulence of the infecting organism, and status of the soft tissues. Biofilm is the key factor for success or failure using irrigation and debridment.[30,43] Only with further research may we be able to identify factors that influence the outcome of surgical intervention for PJI in general and I&D in particular.

Question 7: Is I&D an emergency procedure or can the patient be optimized prior to the procedure?

Consensus: No. I&D is not an emergency procedure in a patient without generalized sepsis. All efforts should be made to optimize the patients prior to surgical intervention.

Delegate Vote: Agree: 92%, Disagree: 6%, Abstain: 2% (Strong Consensus)

Justification: Although many believe that a patient presenting with an acute infection should undergo surgery as soon as possible, there is no evidence to suggest that any delay in surgical intervention adversely affects the outcome. What is known is that patients with medical comorbidities that are not controlled may be at risk for medical complications, some of which could prove to be fatal. In addition, subjecting a patient to I&D without addressing an underlying coagulopathy that could be the result of administration of anticoagulants can result in the development of a further hematoma with all its adverse effects. Thus, it is critical that conditions such as uncontrolled hyperglycemia (>180 mg/ml), severe anemia (Hb<10 mg/dL), coagulopathy, and other reversible conditions are addressed prior to subjecting a patient to I&D. The nutritional status of any patient undergoing reoperation should also be checked and provisions implemented to reverse malnutrition, if present.

Question 8: Does arthroscopy have a role in I&D?

Consensus: Arthroscopy has no role in I&D of an infected prosthetic joint.

Delegate Vote: Agree: 91%, Disagree: 7%, Abstain: 2% (Strong Consensus)

Justification: There are some published studies demonstrating that the outcome of I&D is markedly worse when debridement was performed using arthroscopy.[6,35,44] As mentioned above, one of the main factors determining the success of surgical intervention for treatment of PJI is the ability to perform through debridement and reduce bioburden. Using arthroscopy the surgeon is not able to access all compartments and parts of the joint; therefore, thorough debridement is unlikely to be performed. However, there may be a diagnostic role for arthroscopy in knee arthroplasty.

Question 9: How many I&Ds are reasonable before implant removal is considered?

Consensus: Following the failure of one I&D, the surgeon should give consideration to implant removal.

Delegate Vote: Agree: 94%, Disagree: 6%, Abstain: 0% (Strong Consensus)

Justification: Although surgical intervention needs to be individualized for each patient, it is unlikely that multiple I&D procedures can serve a patient well in the long run. If several attempts at I&D fail to control infection in a patient, consideration should be given to implant removal.[13,45] Mont et al. found it reasonable to perform multiple debridements in their series of 24 acute TKA infections.[46] On the other hand, failure of a single I&D procedure is recommended to be a consideration for implant removal.[47] Another study found that a need for a second debridement is an independent risk factor for failure of treatment.[19] In the absence of conclusive evidence, we recommend that no multiple I&D procedures should be performed in patients with acute PJI. However there is evidence to perform multiple I&Ds within a specific protocol.

Question 10: Should culture samples be taken during I&D? If so how many and from

where?

Consensus: Representative tissue and fluid samples, between 3 and 6, from the periprosthetic region should be taken during I&D.

Delegate Vote: Agree: 98%, Disagree: 2%, Abstain: 0% (Strong Consensus)

Justification: Despite attempts, distinction between benign hematoma and acute infection may not always be possible. Thus, during I&D of a joint, tissue or fluid samples should be sent for microbiological examination. The information obtained from culture can then be used to determine the course of treatment for the patient. Five to 6 samples should be taken from areas that macroscopically appear most clinically infected to the surgeon. These should include the superficial, deep, and periprosthetic layers and the interfaces between modular components. If definitive components are removed, the bone/prosthetic interface should also be sampled. The samples should be submitted for aerobic and anaerobic culture.[48] Some authors have shown that antibiotic prophylaxis at the time of induction does not alter the results of the microbiological cultures obtained during the surgery and should not be withheld.[49]

Question 11: Should extended antibiotic treatment be given to patients following I&D? If so, what are the indications, type of antibiotic, dose, and duration of treatment?

Consensus: No. Extended antibiotic should only be administered to patients that meet the criteria for PJI (see workgroup 7). The type, dose and duration of antibiotic treatment for infected cases should be determined in consultation with an ID specialist.

Delegate Vote: Agree: 75%, Disagree: 20%, Abstain: 5% (Strong Consensus)

Justification: Patients subjected to I&D should be worked up appropriately for infection, including ordering erythrocyte sedimentation rate, C-reactive protein, aspiration of the joint (either prior to or during surgery), and culture. These investigations allow the treating medical team to determine if there is high likelihood of PJI. For patients in whom there is a high suspicion for PJI, extended antibiotic treatment should be administered. For others with normal

serological and synovial parameters and no evidence of active infection during surgery, antibiotic therapy may not be indicated.

Question 12: Is there a role for intra-articular local antibiotic treatment after I&D? If so, define indications.

Consensus: No. There is inadequate evidence to support administration of continuous intra-articular antibiotics for the treatment of PJI.

Delegate Vote: Agree: 89%, Disagree: 7%, Abstain: 4% (Strong Consensus)

Justification: Although the concept of administering continuous intra-articular antibiotic appears logical in that it allows higher local concentrations of antibiotics, this procedure requires further evaluation. The practice of continuous intra-articular antibiotic administration was introduced by Whiteside et al. and has been shown to be successful in a case series.[50] No multivariate analyses have been performed to demonstrate that the practice of intraarticular administration of antibiotics is an independent factor enhancing success. It is likely that a combination of factors such as meticulous surgical debridement may explain the high success rate that was observed in that case series.[4,51] There are some potential risks associated with this practice, including drug reactions, added expense, need for an additional surgery (to remove the Hickman catheter), and possibly development of antibiotic resistance. The use of continuous intra-articular antibiotics for the treatment of chronic infection, with a reported success rate of 94%, also deserves further evaluation.[50] Those and other case series need to be further evaluated.[52,53]

Question 13: Is there a role for the use of resorbable antibiotic-impregnated pellets (calcium sulfate, etc)? If so, define indications for use.

Consensus: No. Currently there is no conclusive evidence that the use of antibiotic-impregnated resorbable material improves the outcome of surgical intervention for I&D.

Delegate Vote: Agree: 88%, Disagree: 6%, Abstain: 6% (Strong Consensus)

Justification: A number of case series have evaluated the role of antibiotic-impregnated resorbable material for treatment of PJI. Although initial reports of these series have been encouraging, there are no randomized, controlled studies to demonstrate that the use of these materials enhances the outcome of surgical intervention.[53] In one study evaluating the outcome of I&D in 34 patients in whom resorbable gentamicin was utilized, a success rate of 73% was described which appears to not be much higher than what one would expect with conventional I&D.[54]

The use of resorbable material is not without problems. Besides the cost, which depending on the material can be substantial, local reaction to the resorbable material has been described.

Calcium sulphate pellets have been shown to increase wound exudates.[55,56] A possible cytotoxic effect of these material has also been described. Newer materials such as nanoparticle hydroxyapatite have been described.[57] Future studies are desperately needed to evaluate the role of resorbable antibiotic-impregnated material, as currently no concrete evidence exists that could support their use.

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Workgroup 11: Antibiotic Treatment and Timing of Reimplantation

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Question 1: Can oral antibiotic therapy be used instead of intravenous for the initial treatment of periprosthetic joint infection (PJI) following resection?

Consensus: There is evidence to support pathogen-specific, highly bioavailable oral antibiotic therapy as a choice for the treatment of PJI.

Delegate Vote: Agree: 79%, Disagree: 11%, Abstain: 1% (Strong Consensus)

Justification: PJI is traditionally treated with intravenous (IV) antibiotics in order to obtain the minimum inhibitory concentration in the shortest time possible. Once this goal is met and there is clinical evidence of improvement, some IV antibiotic regimens can be switched to oral regimens. There is scarce literature reporting on the use of oral (combined or single) antibiotic therapy for the treatment of PJIs without an initial IV regimen.[1-5] Most of these studies were conducted in cases where the prosthesis was retained. There is one study in which no oral or prolonged IV regimen was used after debridement and the use of antibiotic-impregnated cement spacers led to a 87% eradication rate.[6] No literature conclusively supports the use of only oral (combined or single) antibiotic therapy prior to reimplantation. The recently-published guidelines of the Infectious Diseases Society of America (IDSA)[7] suggest that pathogen-specific, highly bioavailable oral therapy (eg linezolid or fluoroquinolones) may be an alternative as initial therapy for some cases of PJI. Concerns against the routine use of appropriate oral agents in the treatment of PJI largely comprise questions of patient medication compliance and the long-term use of medication therapy with less intensive efficacy and toxicity monitoring.

Question 2: Is oral antibiotic therapy appropriate after an initial IV antibiotic course?

Consensus: There is evidence that pathogen-specific, highly bioavailable oral antibiotic therapy is an appropriate choice for the treatment of PJI after an initial IV antibiotic regimen.

Delegate Vote: Agree: 98%, Disagree: 1%, Abstain: 1% (Strong Consensus)

Justification: An IV antibiotic regimen is preferred in order to obtain the ideal plasma concentration in the shortest time possible. Switching to oral regimens, if possible, lowers the financial burden on patients and payers, reduces the risks of vascular access, and increases the possibility of home-based therapy. Most studies use a protocol of 4 to 6 weeks of IV antibiotics

followed by 2 to 4 weeks of an oral regimen,[8-10] although some studies use the IV regimen alone. A recent study with only 14 days of an IV regimen followed by 6 to 8 weeks of oral therapy showed no relapse.[11] We support the use of oral antibiotic therapy after an initial course of IV antibiotics for sensitive pathogens.

Question 3: What is the ideal length of antibiotic treatment following removal of the infected implant?

Consensus: There is no conclusive evidence regarding the ideal duration of antibiotic therapy. However, we recommend a period of antibiotic therapy between 2 to 6 weeks.

Delegate Vote: Agree: 93%, Disagree: 5%, Abstain: 2% (Strong Consensus)

Justification: The ideal duration of antibiotic therapy (IV alone or combined IV and oral) is not known. Decreasing the time of antibiotic regimens reduces cost and development of resistance and complications inherent to a single or combined therapy.[8-16] Most of the literature recommends antibiotic therapy with duration between 6 and 12 weeks. A prospective non-randomized study by Bernard et al.[17] concludes that 6 weeks of antibiotic treatment (with one week of an IV antibiotic regimen) was sufficient to control infection, but this study includes groups of patients treated with irrigation and debridement (I&D), single-stage exchange arthroplasty, and two-stage exchange arthroplasty. Other investigators have suggested a shorter parenteral course; Stockley et al.[6] used a non-oral and non-prolonged regimen (2 weeks of IV) after debridement and placement of an antibiotic-impregnated cement spacer, with an 87% eradication rate.

Question 4: How should the length of antibiotic treatment be determined? (Inflammatory markers, clinical signs, etc).

Consensus: There is no conclusive evidence on how to determine the length of antibiotic therapy. A combination of clinical signs and symptoms and biochemical markers may be employed. There is the need for a marker that can determine the optimal timing for reimplantation.

Delegate Vote: Agree: 96%, Disagree: 3%, Abstain: 1% (Strong Consensus)

Justification: Improvement of clinical signs has been used as a proxy for control of infection while antibiotics are administered. Unfortunately, improved clinical signs during antibiotic therapy alone do not reliably predict eradication of infection or determine the length of antibiotic therapy. For this reason, progressive sequential decreases in the values of inflammatory markers, namely erythrocyte sedimentation rate and C-reactive protein, have been used as an adjunct along with improvement in clinical signs to determine the ideal time for termination of antibiotic therapy and for reimplantation.[18-23] In addition, no ideal cut-off value has been determined for these inflammatory markers to predict the ideal time for discontinuation of antibiotic treatment or for reimplantation.[19,24] Further large-scale studies are needed to validate and determine the parameters of use of new inflammatory markers such as pro-calcitonin,[25] leukocyte esterase,[26-28] IL-6, and others.[29]

Question 5: Should there be an antibiotic holiday period prior to reimplantation?

Consensus: There is no conclusive evidence supporting a holiday period following discontinuation of antibiotic treatment and prior to reimplantation surgery as a means of ensuring eradication of infection.

Delegate Vote: Agree: 74%, Disagree: 22%, Abstain: 4% (Strong Consensus)

Justification: Although Bejon et al.[30] did not find evidence to support the clinical utility of an antibiotic-free period, this was a retrospective analysis published before the new definition of PJI from the Musculoskeletal Infection Society workgroup[31-33] was available. In practice, improvement of clinical signs is frequently used as a proxy for infection control and effective antibiotic therapy. However, these improved clinical signs may persist only while such antibiotic therapy is in place and it is desirable to identify persistence of infection before reimplantation. For these reasons, some practitioners feel that a holiday period of antibiotics prior to reimplantation opens the opportunity for ongoing observation, where stability or clinical improvement could indicate eradication of the infection while deterioration might indicate recurrence. No evidence conclusively supports the need for an ideal length of such a holiday period.

Question 6: Does the use of rifampin in conjunction with IV antibiotic therapy following removal of the infected implant lead to a more rapid and definitive eradication of staphylococcal infection (particularly methicillin-resistant *Staphylococcus aureus* [MRSA])?

Consensus: There is no evidence to support the use of rifampin in conjunction with IV antibiotic therapy as a more adequate treatment option than either agent used alone following implant removal.

Delegate Vote: Agree: 77%, Disagree: 18%, Abstain: 5% (Strong Consensus)

Justification: There is adequate evidence to support the use of rifampin in combination with other antibiotics for the treatment of staphylococcal PJI, especially in the setting of retained hardware.[1,34,35] Evidence supporting its use when infected hardware has been removed is less convincing. Rifampin is not to be used as monotherapy due to its low barrier for development of resistance.[36] The limitations to mandatory use of rifampin include significant drug interactions and adverse effects. Rifampin stains most bodily secretions orange and causes gastrointestinal intolerance, hepatotoxicity, and other less common adverse effects.[37] It is a significant hepatic enzyme inducer, and as such, increases the metabolism of many important and common drug classes, such as other antibiotics and antifungals, anticoagulants (including warfarin and the oral direct thrombin inhibitors), and immunosuppressants.[38]

Question 7: What is the optimal time to start rifampin treatment?

Consensus: There is no conclusive evidence regarding the best time to start rifampin treatment. Good oral intake and adequate administration of a primary antimicrobial agent should be well-established before starting rifampin. Potential side effects and drug interactions should be addressed prior to the start and at the conclusion of therapy.

Delegate Vote: Agree: 83%, Disagree: 11%, Abstain: 6% (Strong Consensus)

Justification: There are no studies that address the ideal time to start rifampin therapy. Rapid emergence of rifampin resistance has occurred in the rare case where bacteremia is present.[39] Given the potential for development of resistance, it appears prudent to withhold rifampin until

bacteremia has cleared and/or primary antibiotic therapy has reached adequate tissue concentrations. One study suggests, in a univariate analysis, that the presence of a sinus tract or prolonged wound drainage may increase the risk of rifampin resistance.[40] This association was not confirmed on multivariate analysis. As a significant hepatic enzyme inducer, it is important to account for drug interactions both at the initiation and the conclusion of rifampin therapy. Rifampin activity against any isolated pathogen should also be verified around the time of therapy initiation.

Question 8: How long should antibiotic treatment be given following a single-stage exchange arthroplasty performed for PJI?

Consensus: There is no conclusive evidence regarding the ideal duration of antibiotic therapy for a single-stage exchange arthroplasty. We recommend that parenteral antibiotic be given for 2 to 6 weeks following single-stage exchange arthroplasty, with consideration for longer-term oral antibiotic therapy.

Delegate Vote: Agree: 87%, Disagree: 10%, Abstain: 3% (Strong Consensus)

Justification: Single-stage exchange arthroplasty for PJI has the advantage of being only one major procedure, thus decreasing cost and the risk of complications that could arise from multiple surgeries.[1,34,35] No evidence is available regarding the ideal length of antibiotic therapy.[12,41-43] Bernard et al.[17] concluded that 6 weeks of antibiotic treatment (with one week of an IV antibiotic regimen) was sufficient to control infection; however, this study included I&D and two-stage exchange arthroplasty as well. The recently published guidelines of the IDSA[7] recommend 2 to 6 weeks of pathogen-specific IV antimicrobial therapy in combination with oral rifampin, followed by 3 months of oral rifampin and ciprofloxacin or levofloxacin for staphylococcal PJI treated with single-stage arthroplasty. For organisms other than staphylococci, the IDSA guidelines recommend an initial course of IV therapy for 4 to 6 weeks. Though many practitioners employ it, there is no unanimous recommendation regarding chronic suppressive oral antibiotic therapy in this setting.

Question 9: Is there a role for intra-articular local antibiotic treatment after reimplantation? If so, what are the indications?

Consensus: There is no conclusive evidence to support the use of intra-articular local antibiotic therapy. Further evidence is needed to support the use of intra-articular local antibiotic therapy.

Delegate Vote: Agree: 95%, Disagree: 4%, Abstain: 1% (Strong Consensus)

Justification: Studies by Whiteside et al.[44,45] suggested good results when using intra-articular antibiotic therapy. However, these series were small in size, retrospective, and described the same cohorts. In addition, the studies did not utilize multivariate analyses to isolate intra-articular antibiotic therapy as an independent factor that improves the outcome of surgical intervention.

Question 10: What is the optimal antibiotic treatment for culture-negative PJI?

Consensus: There is no conclusive evidence on the optimal antibiotic treatment for patients with culture-negative PJI. We recommend a broad spectrum antibiotic regimen covering gram-negative and gram-positive organisms (including MRSA) as well as anaerobic organisms. In patients with suspected fungal infection, coverage against common fungi should be considered.

Delegate Vote: Agree: 91%, Disagree: 8%, Abstain: 1% (Strong Consensus)

Justification: The incidence of culture-negative PJI ranges from 3% to 35%. Prior publications have demonstrated great success with control of infection in patients with culture-negative PJI, suggesting that culture negativity may not be a negative predictor of failure.[46] In terms of antibiotic selection, a study evaluating control of infection in PJI treated surgically with two-stage exchange arthroplasty demonstrated no difference between culture-negative patients treated with vancomycin postoperatively and culture-positive patients.[47] A survey of infectious disease physician preference for antibiotic choices for PJI lists combinations of vancomycin and either ceftriaxone or a fluoroquinolone as the preferred antibiotic regimen for treatment of culture-negative PJI of the lower extremity.[48]

Question 11: Is joint aspiration necessary prior to reimplantation?

Consensus: There is no conclusive evidence to support mandatory joint aspiration prior to reimplantation. It may be useful in selected cases. We recommend against infiltration of any liquids into the affected joint and reaspiration in patients with an initial dry aspirate.

Delegate Vote: Agree: 89%, Disagree: 8%, Abstain: 3% (Strong Consensus)

Justification: Currently there is no metric by which one can determine the optimal timing of reimplantation or in fact determine if PJI has been eradicated or controlled. Joint aspiration prior to reimplantation may provide useful information regarding the infection status of the joint. If synovial fluid parameters are abnormal (threshold to be determined) then the treating surgeon may decide to delay the reimplantation or subject the patient to further treatment after reimplantation.[19,49-51] This suggestion is limited by the fact that there may be minimal fluid present in patients with a cement spacer in place, with a dry aspiration frequent. There is also the potential of obtaining peri-articular fluid instead of true articular fluid. There is no evidence that infiltration of saline or sterile fluid into the joint and reaspiration increases the yield of pathogens in culture and no evidence that lavage of the joint has any role in isolation of the infecting organism. Other parameters of synovial fluid analysis, such as white cell count and neutrophil differential, cannot be relied on when lavage fluid is being analyzed.

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Workgroup 12: One-stage vs Two-stage Exchange

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Exchange arthroplasty for infection, be it a one-stage or two-stage surgery, is not for the occasional operator. The morbidity and mortality associated with such a surgery is not to be ignored. Team work is paramount to the success of the surgery. A multidisciplinary approach with microbiologists, infectious disease physicians, critical care anaesthetists, plastic surgeons, and orthopaedic surgeons with a particular interest in infection are essential.

Question 1: What are the indications and contraindications for one-stage exchange arthroplasty?

Consensus: One stage-exchange arthroplasty is a reasonable option for the treatment of periprosthetic joint infection (PJI) in circumstances where effective antibiotics are available but not in patients with systemic manifestations of infection (sepsis) in whom resection arthroplasty and reduction of bioburden may be necessary. Relative contraindications to performing a one-stage exchange may include lack of identification of an organism preoperatively, the presence of a sinus tract, or severe soft tissue involvement that may lead to the need for flap coverage.

Delegate Vote: Agree: 78%, Disagree: 17%, Abstain: 5% (Strong Consensus)

Justification: Currently, there are no randomized clinical trials (RCTs) that provide concrete indications or contraindications for one-stage exchange arthroplasty over two-stage exchange arthroplasty. There are little data supporting the use of one-stage exchange outside of total hip arthroplasty (THA) or without antibiotic-impregnated cement or bone graft.[1-10]

Systemic infection with sepsis is a definitive contraindication. In clinical scenarios involving an acutely decompensated patient with PJI as the probable source of sepsis, timely administration of appropriate wide spectrum antibiotics and prompt removal of all implants with thorough debridement is essential. Reimplantation of a prosthesis should be delayed until adequate resuscitation and eradication of the offending organism has been completed.[4,7,10-18]

Although there are reports of effectively treating PJI involving resistant organisms and/or a sinus tract with a one-stage exchange procedure, such cases are generally managed with two-stage procedures, as the presence of a sinus tract may contaminate pre-operative cultures and inhibit

the prerequisite identification of the offending organism. In the case of culture-negative PJI, one-stage exchange arthroplasty may also be contraindicated.[4,7,10,11,14,16-33]

Viable soft tissues affording adequate coverage for the new prosthesis are essential when undertaking one-stage revision arthroplasty and surgeons able to perform flaps and proper soft tissue coverage need to be available at the time of one-stage arthroplasty. If soft tissue coverage cannot be performed at the time of one-stage exchange arthroplasty, two-stage surgery should be considered.[7,17,18]

Question 2: What are the indications for two-stage exchange arthroplasty?

Consensus: Two stage-exchange arthroplasty is a reasonable option for the treatment of PJI. Specific conditions where two-stage exchange may be indicated over one-stage exchange include: 1) patients with systemic manifestations of infection (sepsis); 2) a scenario where infection appears ovious but no organism has been identified; 3) preoperative cultures identifying difficult to treat and antibiotic-resistant organisms; 4) presence of a sinus tract, 5) inadequate and non-viable soft tissue coverage.

Delegate Vote: Agree: 93%, Disagree: 7%, Abstain: 0% (Strong Consensus)

Justification: Currently, two-stage exchange arthroplasty surgery is the most popular surgical regimen for the surgical management of PJI in North America and elsewhere. However, to date there are no RCTs that provide absolute indications or contraindications for two-stage exchange arthroplasty.[4,7,17,18]

Although there is variability in the reported rates of success in eradicating infection, a possible increased morbidity and mortality, and variable time periods prior to reimplantation, direct comparisons with one-stage exchange arthroplasty are difficult due to a patient selection bias in the current literature.[7,9,17,34] However, in a recent systematic review, Romano et al. demonstrated that a two-stage exchange provides, on average, a better outcome with respect to the control of infection in the knee.[35] The same group recently presented similar findings for the hip, although the difference in infection control was less.[36]

Systemic infection and/or sepsis are indications for two-stage exchange where timely administration of appropriate antibiotics and prompt removal of implants with thorough debridement of the soft tissues are needed to address the life-threatening sequelae of PJI.

The immunocompromised patient or the presence of medical comorbidities, including metastatic disease, advanced cardiac disease, and renal and/or liver dysfunction, have been shown to impact the infection eradication success rates and certainly influence morbidity and mortality. It is unknown if the presence of these comorbidities constitute a contraindication for one-stage exchange arthroplasty surgery.[7,14,17,18,32,34]

The presence of compromised soft tissues that may limit adequate implant coverage is an indication for two-stage exchange arthroplasty. The use of tissue expanders, development of musculocutaneous flaps, and possible need for repeat debridement may all be indicated and require further time between initial resection and reimplantation.[7,17,18,32]

Question 3: What is the optimal interval between two stages?

Consensus: There is no definitive evidence in the literature as to the optimal time interval between the two stages. Reports vary from 2 weeks to several months.

Delegate Vote: Agree: 87%, Disagree: 9%, Abstain: 4% (Strong Consensus)

Justification: There should be ample time to complete antibiotic administration, eradicate infection, repeat the debridement if necessary, and allow for adequate soft tissue preparation in the event of compromised soft tissue coverage.

Positive results have been experienced in situations where implantation is conducted within 2 to 6 weeks of resection, the infecting pathogen is not resistant, and systemic antibiotic administration is ongoing.[7,18]

Intravenous (IV) antibiotic therapy lasting 4 to 6 weeks with subsequent cessation of antibiotics for 2 to 8 weeks prior to reimplantation is most commonly employed in the United States and has yielded positive results.[7,37-40]

Evidence suggests time intervals greater than 6 months result in suboptimal results in restoring patient function and eradicating infection. Patients who underwent two-stage exchange with greater than 6 months between resection and reimplantation experienced no improvement in function when compared to those who were reimplanted within 6 months of resection.[41]

The need for serologic evaluation, synovial fluid analysis, and culture of joint fluid aspirate prior to reimplantation is unclear. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are poorly predictive of persistent PJI and studies were unable to define optimal cutoff values for these values. However, a change in value from those conducted at the time of resection was a helpful indicator.[17,42-45]

Question 4: Is there a difference in cost between one-stage and two-stage exchange arthroplasty?

Consensus: Due to the lack of knowledge about the real costs and the absence of comparative studies, we are not able to give a clear statement. If, however, infection is effectively treated without the need for reoperation, one-stage exchange arthroplasty is less expensive than two-stage exchange. Further studies are required.

Delegate Vote: Agree: 91%, Disagree: 5%, Abstain: 4% (Strong Consensus)

Justification: The economic impact of PJI is immense; therefore, developing and utilizing cost-effective and efficient surgical treatment strategies that provide satisfactory restoration of function and resolution of pain and guard against recurrence are essential.[46-48]

Differences in cost between one-stage and two-stage exchange arthroplasty are not straightforward to analyze. Costs may vary due to factors associated with hpsital facilities, patients, surgeons, and the infecting organism. There is no definitive evidence that takes into account all factors contributing to overall expenditures.[4,46,47,49-51]

The direct monetary cost of PJI treatment utilizing one-stage versus two-stage arthroplasty varies greatly. However, it may generally be accepted that patient morbidity, operative time, operating room utilization, hospital and surgeon fees, and duration of antibiotic administration are less when undergoing one procedure versus a minimum of two major procedures.[4,7,46,49-51]

A cost analysis by Klouche et al. revealed that two-stage revision of septic THA cost 1.7 times more than a one-stage revision.[52]

However, if the results of one-stage and two-stage exchange arthroplasty are comparable, one-stage may be preferred due to the advantages of decreased patient morbidity, lower cost, improved mechanical stability of the affected limb, and shorter period of disability.[30,53]

Reinfection rates may be higher when employing a one-stage exchange arthroplasty as compared to a two-stage. However, the cost of additional diagnostic tests and clinical evaluation, coupled with possible reoperation and consideration of quality-adjusted life years, highlights the efficacy of a single-stage revision.[54] A Markov expected-utility analysis by Wolf et al. favored a one-stage exchange over two-stage exchange when taking into account the health endpoints of quality-adjusted life years.[54] Methicillin-resistant *Staphylococcus aureus* (MRSA)-associated PJI has emerged as difficult and expensive to effectively eradicate, and is associated with greater expense. Some authorities believe that two-stage exchange may be the preferred treatment for PJI caused by highly virulent organisms and may incur lower total costs.[31,55,56]

Question 5: How many exchange arthroplasty should be attempted in patients with PJI?

Consensus: There is no definitive evidence that supports limiting the number of septic exchanges that should be attempted. Reimplantation is appropriate if the infection is adequately controlled following repeat resection, the patient is able to tolerate additional surgery, and such surgery will allow for a functioning joint with adequate soft tissue coverage.

Delegate Vote: Agree: 98%, Disagree: 2%, Abstain: 0% (Strong Consensus)

Justification: Key factors for the consideration of two-stage exchange are the causative organism, duration and extent of infection, patient willingness and medical fitness to undergo such surgery, and adequate bone stock and viable soft tissues capable of facilitating adequate reconstruction.

Reimplantation is feasible if the infection is adequately controlled following repeat resection.[17,31,55,57,58]

The success rate of subsequent two-stage exchange is often favorable but may be lower than with the first attempt.[3,7,17,57-63]

Patients with resistant organisms including MRSA and Enterococcal PJI experienced higher rates of salvage surgery (definitive resection, fusion, or amputation) and should be counseled regarding possible outcomes.[1,23,25]

Involvement of the tibial tuberosity may be an indicator of possible functional failure of two-stage exchange in the knee. Arthrodesis in the event of severely compromised extensor musculature may be required.[28]

Question 6: What are the indications for knee arthrodesis?

Consensus: The literature is deficient in providing guidance on this issue. Knee arthrodesis may be an appropriate option for patients who have had failed multiple attempts at reconstruction and stand an unacceptably high risk of recurrent infection with repeat arthroplasty procedures and/or have a deficient extensor mechanism. Surgeons making a choice between arthrodesis and amputation need to take into account the clinical situation of the individual and patient preference.

Delegate Vote: Agree: 96%, Disagree: 1%, Abstain: 3% (Strong Consensus)

Justification: Pain and instability in a joint that is not amenable to reconstruction, with or without prior failed exchange arthroplasty and carries an unacceptably high risk of recurrent infection with further arthroplasty surgery, will likely require knee arthrodesis.[7,9,18,25,43,55,56,59,60,64,65]

Polymicrobial infections or those due to highly-resistant organisms for which there is no effective antimicrobial therapy are more prone to repeatedly failed attempts at exchange arthroplasty and may also benefit from knee arthrodesis.[2,7,18,25,56,66]

Severe immunocompromization inhibits both infection eradication and wound healing and may be prohibitive for staged exchange, thus favoring a salvage procedure.[7,17,18]

Active IV drug abuse may be a contraindication to repeat attempts at staged exchange and may also indicate the need for a salvage procedure.[7]

Contraindications might apply to non-ambulatory patients or those with extensive medical comorbidity that precludes multiple surgeries.[2,7,17,18]

Question 7: If knee arthrodesis is planned for a chronically infected joint, should this be performed in a single stage or two stages?

Consensus: Knee arthrodesis may be performed as one-stage or two-stage, but the decision depends on the individual circumstances and the host factors.

Delegate Vote: Agree: 94%, Disagree: 3%, Abstain: 3% (Strong Consensus)

Justification: Surgical debridement of the infected tissues is a critical factor for success of any surgical procedures for treatment of PJI, in particular arthrodesis of the knee. Thus, inability to perform adequate debridement in one operation should prompt the surgeon to consider two-stage arthrodesis of the knee.

In considering one-stage versus two-stage arthrodesis of the knee, other factors may also be considered. Extensive bone loss associated with chronic infection has been shown to decrease the rate of successful arthrodesis and a two-stage approach may allow for comprehensive treatment of defects following aggressive debridement.[2,65,67-70] Reinfection is uncommon following arthrodesis of the knee performed for PJI. However, infections due to polymicrobial or resistant organisms have a higher propensity for recurrence of infection and failure when treated with a one-stage exchange arthroplasty protocol.[2,4,7,11-18,40,71-74] Eradication of infection prior to arthrodesis provides higher fusion rates and allows an expanded armamentarium for fixation, such as the use of intramedullary and plating devices.[2,73,75-80]

One-stage arthrodesis, using an external fixation device, is successful when conducted in cases of PJI caused by low-virulence organisms and minimal soft tissue compromise.[2,18,25,65,78,81,82]

Question 8: What are the indications for amputation?

Consensus: Amputation for treatment of PJI affecting the knee or the hip may be appropriate in selected cases involving a non-ambulatory patient, necrotizing fasciitis resistant to aggressive debridement, severe bone loss that precludes arthrodesis (knee), inadequate soft tissue coverage, and multiple failed attempts at staged exchange and resection arthroplasty, or peripheral vascular disease and neurovascular injury.

Delegate Vote: Agree: 98%, Disagree: 1%, Abstain: 1% (Strong Consensus)

Justification: Salvage of a failed total joint arthroplasty in the setting of infection with recalcitrant necrotizing fasciitis, resistant organisms, failed arthrodesis, and bone loss is difficult and may not respond to further attempts at reconstruction.[2,7,17,18,25,56,59,83,84] Amputation above the knee results in suboptimal functional outcomes and should be reserved for non-ambulatory patients unless other indications are present and all attempts at infection eradication have failed.[3,84,85] Except in emergency cases, referral to a center with specialist experience in the management of PJI is advised before amputation is carried out, due to high mortality rates.[45,84,85] Other indications not directly related to PJI include periprosthetic fracture, peripheral vascular disease, pain, or neuropathy.[2,84]

Other salvage operations for management of recalcitrant hip infection include excisional arthroplasty that is performed by some surgeons. Although functional outcome in these patients may not be optimal, excision arthroplasty can be very successful in the control of infection and allow for assisted ambulation.[86]

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Workgroup 13: Management of Fungal or Atypical Periprosthetic Joint Infections

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Question 1: What is the definition of fungal or atypical periprosthetic joint infection (PJI)?

Consensus: A fungal or atypical PJI is an infection of a joint arthroplasty caused by fungi or atypical bacteria.

Delegate Vote: Agree: 89%, Disagree: 7%, Abstain: 4% (Strong Consensus)

Justification: Generally a fungal or atypical PJI is believed to exist when fungal organisms or atypical bacteria are isolated from the joint fluid or intraoperative tissue samples and these organisms are believed to be the dominant infecting agents in the prosthetic joint.
Fungi may be moulds/molds, yeasts, or dimorphic fungi. Moulds are fungi that grow in the form of multicellular filaments called hyphae. The vast majority were *Candida* infections (which represent more than 80% of PJIs). In contrast, fungi that can adopt a single celled growth habit are called yeasts. Dimorphic fungi can exist as mold forms or as yeast. Atypical bacteria are bacteria that have deviations of one or more of the following characteristics of a typical bacterium: cell wall (containing peptidoglycan), cell membrane, no nuclear membrane, reproduction by cell fission, and susceptibility to antibiotics but not to antifungal agents.[1-3]

Question 2: When should fungal organisms be considered as a cause of PJI?

Consensus: A PJI caused by fungi can be considered if fungal pathogens are isolated from periprosthetic tissue cultures or joint aspirations in a patient who has other signs or symptoms of PJI, such as abnormal serology and joint aspiration parameters (neutrophil count and differential). If clinical symptoms raise suspicion for a fungal PJI, repeated joint aspiration may be needed to isolate the infecting organism.

Delegate Vote: Agree: 94%, Disagree: 4%, Abstain: 2% (Strong Consensus)

Justification: As there are no specifically evident clinical symptoms or laboratory signs for a fungal PJI, repeated joint aspiration is mandatory. In one-third of the reported cases of a fungal PJI repeated (2 or 3) joint aspirations had to be performed to confirm the fungal PJI.[4-10]

Question 3: Which host factors (concomitant disease and other factors) predispose to fungal PJI?

Consensus: Predisposing host factors to fungal PJI are: immunosuppression (decreased cellular immunity, neutropenia, corticosteroids or other immunosuppressive drugs, history of organ transplantation, and acquired immunodeficiency syndrome), malignancy and/or the use of antineoplastic agents, drug abuse, prolonged use of antibiotics, presence of indwelling catheters (intravenous, urinary, or parenteral hyperalimentation), diabetes mellitus, malnutrition, rheumatoid arthritis, history of multiple abdominal surgeries, severe burns, tuberculosis, and preceding bacterial infection of the prosthesis

Delegate Vote: Agree: 95%, Disagree: 2%, Abstain: 3% (Strong Consensus)

Justification: Fig. 1–Frequency of concomitant diseases in 46 reported fungal PJIs after total knee arthroplasty (data collected from 36 publications).

Concomitant diseases	Number of cases	Percentage
Diabetes	10	22
Autoimmune diseases	6	13
Prior PJI with prolonged antibiotic therapy	10	22
Immunosuppression caused by medication	7	15
Malignant diseases	4	9
HIV	1	2

Question 4: When fungal organisms are considered, what specimens should be collected, which additional diagnostic tools should be used, and how should they be processed to optimize diagnosis?

Consensus: Fungal selective media must be included and it should be observed that prolonged culture may be required. In specific cases one should expand diagnostic testing to include tissue samples for histological examination, especially in cases where there is a high index of

clinical suspicion. Resistance of *Candida* species to fluconazole has been reported in the literature and susceptibility testing may be requested when resistance to fluconazole is suspected based on isolated species. Antifungal susceptibility testing remains less well developed and utilized than antibacterial testing.

Delegate Vote: Agree: 96%, Disagree: 2%, Abstain: 2% (Strong Consensus)

Justification: In only 9 of the 59 articles published so far on the treatment of fungal PJIs (including 91 cases) the authors reported microbiological details about the number of cultures. In none of the studies was the growth medium or the time of incubation further specified. Although fungi can be non-fastidious and grow on most media, the growth requirements for fungi often differ from those for bacteria, most notably with regard to optimal growth temperature and media. Fungal selective media must be included and should have prolonged incubation according to national laboratory standards.
Most routine manual and automated blood culture systems are able to support the growth of yeasts such as *Candida spp.* However, if suspicion is high for a fungal infection and routine cultures are negative, then it may be reasonable to consider a request for alternative test methods that are optimally designed to support the growth of most yeast. Moulds, especially dimorphic fungi, often grow poorly in typical instrumented blood culture systems. Alternative culture techniques include the lysis centrifugation method, in which the lysed and pelleted blood specimen can be used. Identification of the isolate to species level is mandatory because treatment may differ based on species. Samples from tissues and body fluids can be also investigated using alternative procedures. Among these are standard histology, immunohistochemistry, *in situ* hybridization, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF), mass spectrometry, and analysis of samples by polymerase chain reaction (PCR)-based procedures. These techniques have been positively evaluated in some studies, but they are not generally available, and third-party evaluation of their accuracy has not been carried out so far.[14]

Question 5: What is the best way to surgically manage fungal PJI: irrigation and debridement, one-stage exchange, two-stage exchange, or permanent resection arthroplasty?

Consensus: On the basis of the current literature, two-stage exchange arthroplasty is the recommended treatment option to manage fungal PJI. However, the success rate is lower than that of bacterial cases.

Delegate Vote: Agree: 95%, Disagree: 2%, Abstain: 3% (Strong Consensus)

Justification: The reported initial surgical treatment of fungal periprosthetic knee infections is heterogeneous. As in bacterial PJI, treatment modalities for fungal PJI (retention of the implant, removal and reimplantation, or resection arthroplasty) depend to a large extent on the time of diagnosis of the infection after implantation, the results of eventual previous attempts to treat infection, and the presence of comorbidities.

To date 91 cases of fungal PJI have been reported. Resection arthroplasty was the initial intervention for 42 of these patients. Extensive and radical intraoperative debridement of all infected and necrotic tissue as well as removal of all cement was emphasized as highly important regarding the outcome. Permanent resection arthroplasty was the treatment of choice in 5 infected total hip arthroplasties (THAs) and in 2 infected total knee arthroplasties (TKAs). After initial resection arthroplasty 27 hips and 20 knees underwent a delayed reimplantation of the prosthesis (two-stage-procedure). Intraarticular spacers were used in 25 of the reported 91 patients. To prevent bacterial superinfection the spacers were impregnated with combined antimicrobial medication (gentamicin and vancomycin, tobramycin and vancomycin, teicoplanin and amphotericin B, vancomycin and amphotericin B, vancomycin, vancomycin and piperacillin, and cefamandole). The majority of the successful cases were managed with a two-stage exchange procedure.[1,8,10-26]

Question 6: What are the optimal systemic antifungals administered (type and dose) in the treatment of fungal PJI?

Consensus: Well-established agents for a systemic treatment are the azoles and amphotericin products given either orally or intravenously for a minimum of 6 weeks. Resistance of certain *Candida* species to fluconazole has been reported in the literature and susceptibility testing should be performed, in collaboration with the microbiologist.

Delegate Vote: Agree: 93%, Disagree: 5%, Abstain: 2% (Strong Consensus)

Justification: There are few reports on local antifungal agent administration. Local antifungal medication during the primary surgical treatment was either applied by implanting an impregnated cement spacer as mentioned above, by placing intraarticular powder (100mg amphotericin B)[8,13] or by daily intraarticular lavage (fluconazole 200mg/d).[17,27]
A systemic antifungal agent was administered in all but one reported patient and the most frequent agents for a systemic treatment were fluconazole and amphotericin B given either orally or intravenously.

Additionally, in descending order, the following drugs have been administered: 5-flucytosine, itraconazole/ketoconazole/voriconazole, and caspofungin and other echinocandins. A combination of antifungal medication or a sequential antifungal therapy with exchange of medication was present in about 25% of the reported cases.[1,3,8,13,15-17,21,22,27-33]

Question 7: When treating fungal PJIs in a staged manner, which antifungal or antibacterial medications should be used for the cement spacer? What is the recommended dose?

Consensus: Recent literature confirms that antifungal agents are released in high amounts for local delivery, but there are no clinical studies yet to document the clinical effectiveness. The use of liposomal amphotericin B, loaded in bone cement, has more than an order of magnitude greater release than conventional amphotericin B deoxycholate. There is also controlled release data for azole antifungals, with specific data on the elution of voriconazole from bone cement. There should be a consideration for adding an antibacterial to the bone cement for local delivery in addition to the antifungal.

Delegate Vote: Agree: 94%, Disagree: 2%, Abstain: 4% (Strong Consensus)

Justification: Several studies have reported on the successful use of spacers loaded with antifungal drugs in fungal PJI treatment. Although release of these drugs from bone cement has been documented *in vitro*, limited data exist from *in vivo* studies.[3,18,27,29,34] Similar to bacteria in biofilm there is higher resistance of fungi in biofilms, the surgical procedure that decreases the biofilm, and fungal load is probably the most important aspect of the treatment. Good results

have also been obtained by using no local delivery. When the surgeon decides to provide local delivery of antifungals in adjunct to systemic therapy, amphotericin B products or azole antifungals are reasonable selections. When voriconazole is chosen, loss of mechanical strength should be kept in mind when fabricating spacers.[3,18,27,29,34-45]

Question 8: Which investigations are recommended to monitor fungal PJI and determine timing of reimplantation?

Consensus: C-reactive protein and erythrocyte sedimentation rate are recommended to monitor fungal PJI. There is no clear evidence for the timing of reimplantation based on laboratory tests.

Delegate Vote: Agree: 89%, Disagree: 8%, Abstain: 3% (Strong Consensus)

Justification: Review of the current literature did not detect a laboratory test to specifically monitor fungal PJI. Thus the generally accepted laboratory tests that are used to monitor bacterial PJI are suggested.[28] The serum 1,3 β-D-glucan test for *Candida* has been used in non-orthopaedic settings and this may be an area that can be developed in the future for monitoring of effective treatment of candidal PJI.[46] Repeated aspiration prior to reimplantation may help the surgeon determine timing.

Question 9: What is the duration for systemic antimicrobial (antifungal) agent administration in the treatment of fungal PJI?

Consensus: Systemic antimicrobial (antifungal) agent administration in the treatment of fungal PJI should be started at the time of removal of the implants (stage one) and continued for at least 6 weeks. It should then be stopped before reimplantation (stage two), the timing of which is based on clinical judgment and laboratory tests. There are no good data to support antifungal agent administration after reimplantation.

Delegate Vote: Agree: 85%, Disagree: 10%, Abstain: 5% (Strong Consensus)

Justification: Review of the reported cases on fungal PJI shows that there is a broad variation in the duration of perioperative systemic antimicrobial (antifungal) agent administration. For the most frequently administered agents, fluconazole and amphotericin B, the following durations of systemic antifungal agent administration have been described:

Fluconazole: Duration varies from 3 to 6 weeks or longer (up to 26 weeks) before reimplantation and from no treatment (in the majority of cases) after reimplantation up to 2 to 6 weeks or longer after reimplantation.

Amphotericin B: Duration is often 6 weeks, only before reimplantation.[1,3,16,18,21,22,27-29,31-33,47]

It is important to note that the Infectious Diseases Society of America's guidelines on the treatment of invasive Candidiasis recommends treatment duration of 6 to 12 months for osteomyelitis.

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Workgroup 14: Oral Antibiotic Therapy

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Introduction:

This panel has reviewed the indication and duration of oral antibiotics for periprosthetic joint infection (PJI) in the following situations:

1) Acute (early or late) PJI treated with debridement without implant removal and exchange of the modular components, whenever modular components can be safely removed. In general, these infections do not require suppressive antibiotic therapy (SAT).

2) Indications for the use of SAT include:

a) Patients who refuse surgical treatment.

b) Patients who cannot be surgically treated because of a high surgical risk due to comorbidities.

c) Patients treated with inadequate surgery such as: 1) debridement without implant removal in late chronic PJI or 2) debridement without implant removal in acute (early or late) PJI but without exchanging the modular components.

d) Patients who undergo optimal surgical treatment in acute PJI but receive suboptimal antibiotic treatment in the following situations: 1) not receiving rifampin in PJI due to *Staphylococcus spp*, 2) PJI due to methicillin-resistant *S. aureus* (MRSA), 3) not receiving a fluoroquinolone in gram-negative infections, and 4) fungal infections.

e) Patients in whom it is suspected that the infection is not eradicated according to clinical, laboratory, or imaging data.

Question 1: What are the appropriate oral antibiotic or antibiotic combinations following adequate surgical treatment for acute (early or late) PJI in which the implant has been retained?

Consensus: Regimens containing rifampicin, when feasible, should be used in gram-positive PJI and fluoroquinolones in gram-negative PJI. There is no consensus as to when rifampicin should be started.

Delegate Vote: Agree: 87%, Disagree: 7%, Abstain: 6% (Strong Consensus)

Justification: In acute PJI, open debridement and implant retention is associated with a wide variation in success rates. Once the decision to switch to oral therapy is made, a combination of antibiotics should be used. The reasons for this discrepancy include: 1) characteristics of the patients,

2) surgical technique including the exchange of modular polyethylene liner, and 3) the type of antibiotic or combination of antibiotics administered, especially within the first month after debridement.[1,2] There is concern with the use of rifampin during the first days of intravenous (IV) treatment in order to reduce the risk of selecting resistant mutants.[54] *Staphylococcus aureus* and coagulase-negative *staphylococcus* for the most part is best treated with combination therapy.

In terms of antibiotic treatment, it is necessary to analyze the results according to the isolated microorganism. A review of the published literature where staphylococci were the main pathogen included 17 articles and 525 cases of PJI managed with open debridement and retention of the implant. The study showed a range of success from 14% to 83% with a mean rate of success of 48%[3] and only 32% in patients with rheumatoid arthritis.[4] A more recent review of the literature using Debridement, Antibiotics, and Implant Retention (DAIR), described a success rate below 50%.[5] Of note, the majority of the articles included in these reviews did not use rifampin as part of the antibiotic treatment. In contrast, intravenous vancomycin or β-lactams for the first 4 weeks were the most common antibiotic therapies. *In vitro* data and experimental models on foreign-body infections have shown the poor activity of these antibiotics against bacterial biofilms and the importance of combining antibiotics, preferentially with rifampin.[6-11] Zimmerli et al. performed a double-blind study and found that acute staphylococcal orthopaedic implant infections treated with an open debridement without removing the implant, followed by a combination of ciprofloxacin (750 mg/12 h) and rifampin (450 mg/12 h) administered for 3 months (for hip prosthesis and orthopaedic implant infections) or 6 months (for knee prosthesis infections), was more effective than ciprofloxacin alone (cure rates of 100% and of 53% respectively, $p<0.05$ after 35 months of follow-up). From 2005 up to now other case series have been published using antibiotic combinations with rifampin and support the effectiveness of this strategy, especially when PJI is due to methicillin- and fluoroquinolone-susceptible staphylococci (including *Staphylococcus aureus* and coagulase-negative staphylococci) and the oral therapy was made with rifampin combined with fluoroquinolones,[2,12-21] with success rates, in general, over 70%. The dose of rifampin varied from 300 mg/8h, 450 mg/12h, 600 mg/24h, or 10 mg/Kg/12h. Rifampin is a concentration-dependent antibiotic and the best pharmacodynamic parameter related to its activity is C_{max}/minimal inhibitory concentration (MIC). Rifampin administration in a 600mg monodose is easier to administer and well tolerated but also could result in a higher C_{max}/MIC than every 12h dosage. In addition, rifampin is added for killing biofilms and the doubling time of biofilm bacteria is significantly longer than the planktonic counterpart;[22] therefore, the administration of rifampin once daily as for *Mycobacterium tuberculosis* infections appears reasonable. Ciprofloxacin and levofloxacin are the most widely used fluoroquinolones. Experience with ciprofloxacin is larger; however, levofloxacin has a higher oral bioavailability and it is more active against staphylococci. Moxifloxacin is more active than

levofloxacin for staphylococci but rifampin significantly reduces the moxifloxacin serum concentration.[23] Rifampin also reduces the serum concentration of clindamycin,[24] cotrimoxazol,[25] and linezolid;[26] therefore, close monitoring is necessary when these combinations are used.

The clinical experience when PJIs are due to methicillin-resistant strains is scarce but the available information suggests that the outcome of methicillin-resistant coagulase-negative staphylococci is associated with good results when rifampin combinations are used.[27] In contrast, experience with MRSA has shown a higher failure rate;[14,28-30] however, the majority of these patients were treated with intravenous vancomycin. There is some clinical experience using linezolid with or without rifampin in patients with acute PJI due to MRSA treated with debridement and retention of the implant, with a mean success rate around 60%.[31-36] The toxicity associated with linezolid limits its administration for periods longer than 4-6 weeks; otherwise, serum levels are monitored.[37] Rifampin combined with fusidic acid or cotrimoxazol achieved a 67%[38] or 60%[39] success rate, respectively. Indeed, recent *in vitro* data show that combinations of oral antibiotics including linezolid, fusidic acid, rifampin, or minocyclin using concentrations similar to those achieved in serum[40] have a good activity against S. aureus biofilms *in vitro*; however, more clinical experience is needed.

PJI due to penicillin-susceptible streptococci treated with intravenous penicillin or ampicillin has been associated with a high success rate.[41] In this article, only 2 out of 19 patients failed but both had PJI due to group B streptococci (n=7, failure rate of 28.5%). In contrast, a recent study that retrospectively reviewed 31 streptococcal PJI treated with DAIR described a failure rate of 67% that was similar to the rest of the cases of PJI, where the failure rate was 71%;[42] however, details about antibiotic therapy were not provided. Clinical data on PJI due to enterococcus are limited to one article that described an 80% success rate using debridement, retention of the implant, and intravenous ampicillin with or without gentamicin.[43] The success rate was similar in the monotherapy and combination groups, but nephrotoxicity was significantly higher among those receiving aminoglycosides. Experience with oral antibiotics is scarce in streptococcal and enterococcal PJI but it is reasonable to use a β-lactam with a high oral bioavailability (amoxicillin for enterococci); and, since rifampin is active against streptococci, it is reasonable to recommend the addition of rifampin. Indeed, recent *in vitro* data showed that linezolid or ciprofloxacin combined with rifampin had better activity against enterococal biofilms than ampicillin or ampicillin plus rifampin;[44] therefore, these combinations are potential alternatives.

Evidence of PJI due to gram-negative organisms is scarce but the available information suggests that when fluoroquinolones (oral or intravenous) are part of the antibiotic treatment the success rate is higher than 80%.[45,46]

Overall, SAT is not a hugely successful treatment for PJI. As a summary, the selected antibiotic regimen after debridement is associated with the outcome of the infection. Clinical data from

observational studies suggest that regimens containing rifampin in PJI due to gram-positives and fluoroquinolones in PJI due to gram-negatives are associated with acceptable success rates. Clinical data are scarce about other antibiotic regimens for resistant bacteria or when the patient is allergic or develops adverse events. Some clinical data with linezolid,[18,32-35] cotrimoxazole,[39] and moxifloxacin[47] as monotherapies for staphylococcal PJI have shown relatively good results. Sometimes the use of rifampin is not feasible e.g. drug interactions.

Question 2: How long should antibiotic treatment in acute PJI treated with debridement and retention of the implant be?

Consensus: The duration of intravenous and oral treatment is a question that remains unsolved and there is no clinical trial comparing different durations of antibiotic treatment.

Delegate Vote: Agree: 85%, Disagree: 11%, Abstain: 4% (Strong Consensus)

Justification: Clinical experience with osteomyelitis, including orthopaedic implant infections, has demonstrated that oral therapy or an early switch to oral therapy is as effective as IV treatment.[48-50] The majority of authors consider 2 to 6 weeks of specific IV treatment followed by 3 months of specific oral antibiotics in total hip arthroplasty or 6 months in total knee arthroplasty necessary.[26,51,52] Taking into account the high bioavailability (>90%) of oral antibiotics such as rifampin, fluoroquinolones, cotrimoxazole, tetracyclines, fusidic acid, clindamycin, or linezolid, and the poor activity against bacterial biofilms of the most commonly used IV antibiotics such as β-lactams or glycopeptides,[8,53] it is reasonable to recommend an IV period restricted to the first 5 to 10 days in order to reduce the bacterial inoculum in periprosthetic tissue. An early switch to oral therapy using potent antibiofilm agents with a high oral bioavailability is recommended. This regimen allows patient discharge from hospital and avoids problems associated with IV catheters. The 3 or 6 months total duration of antibiotic treatment is based on clinical experience[14,17-19] and another large series used a mean duration of oral therapy of 1.5 years.[14] In both cases the success rate was >70%. Other authors using a markedly shorter duration of antibiotic regimens (in general ≤ 3 months) have also shown success rates >70%.[3,22,54] This data suggest that more than 3 months do not improve the outcome of acute PJI treated with debridement and retention of the implant. A recent clinical trial randomized patients with early acute PJI due to staphylococci to receive 6 weeks (n=22) or 12

weeks (n=17) of levofloxacin plus rifampin (to be presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy, Denver 2013, by Lora-Tamayo) and no differences in failure rate after one year of follow-up were observed. C-reactive protein (CRP) did not accurately predict the outcome of patients after debridement.[55] Therefore, physical examination and clinical symptoms should guide the duration of antibiotic treatment. According to the literature, when an antibiotic regimen within the first month from debridement includes rifampin for a gram-positive infection[1,13-22] or a fluoroquinolone for gram-negative infection,[45,46] 3 months is associated with good results[22,46,54] and some preliminary data suggest that an even shorter duration could be adequate. However, more information is needed to confirm this result.

Question 3: What is the role of antibiotic combinations for treatment of PJI managed without adequate surgical intervention?

Consensus: We do not recommend administration of antibiotics and open debridement alone without removing the implant in chronic PJI.

Delegate Vote: Agree: 84%, Disagree: 14%, Abstain: 2% (Strong Consensus)

Justification: SAT is defined as the use of oral antibiotics for the prevention of relapsing symptoms and functional failure in those patients with hardware retention. Antibiotic treatment alone in documented PJI is associated with a high failure rate.[56] The rate of failure is markedly higher when the PJI fulfill the criteria of chronic infection, even when these patients undergo open debridement without implant removal.[13,57] However, there is no other alternative when:
a) Patients refuse surgical treatment.
b) Patients cannot be surgically treated because of a high surgical risk due to comorbidities.
c) Patients are treated with inadequate surgery, such as: 1) debridement without implant removal in late chronic PJI or 2) debridement without implant removal in acute (early or late) PJI but without exchanging the polyethylene modular components.
d) Patients have an infection that has not been eradicated according to clinical, laboratory, or imaging data.
e) Functioning patient and implant will have an increased disability secondary to removal of the prosthesis.

In these cases, identifying the microorganism before starting any antibiotic regimen is strongly recommended. Taking into account the low probability of infection eradication and limited clinical experience, the authors recommend the following two phases of antibiotic treatment: 1) induction to remission and 2) chronic suppression. The initial recommendation is to start a potent oral or IV combination of antibiotics, examples of which are listed in Table 1, including rifampin in cases of gram-positive infection or fluoroquinolone in cases of gram-negative infection whenever possible. The first phase of antibiotic treatment should be maintained until clinical signs of infection disappear and systemic inflammatory parameters (eg CRP or erythrocyte sedimentation rate) improve for at least 3 months. After this period, chronic oral antibiotic suppression should be initiated using monotherapy of antibiotics with a good safety profile and high oral bioavailability.

Question 4: How long should suppressive therapy be administered?

Consensus: There is no consensus about the length of time that patients should receive suppressive antibiotic therapy; however, there is consensus that treatment should be individualized.

Delegate Vote: Agree: 94%, Disagree: 4%, Abstain: 2% (Strong Consensus)

Justification: Ideally, suppressive therapy should be administered for the rest of the patient's life. There is no clinical experience about the consequences of stopping SAT and the risk of relapse or infection dissemination and secondary sepsis. However, experience from chronic osteomyelitis suggests that these infections are, in general, localized.

The average length of oral antibiotic suppression was approximately 23 months when different studies were compared. There are some published studies that used oral suppression for a range between 4 to 100 months in patients with chronic PJI,[58-61] with success rates >60% after prolonged follow-up periods; however, other authors did not observe similar results and reported a high rate of adverse events associated with chronic antibiotic therapy.

Question 5: What antibiotics could be useful for suppressive treatment based on type of organism?

Consensus: There is no consensus regarding appropriate antibiotics for suppression therapy. The antibiotic should be chosen according to the susceptibility pattern of the isolated microorganism, preferably obtained from deep samples by joint aspiration or surgical debridement. The list of potential antibiotics and their doses is provided.

Delegate Vote: Agree: 97%, Disagree: 3%, Abstain: 0% (Strong Consensus)

Table 1. Main oral antibiotics for treating prosthetic joint infections.

Antibiotic	BA (%)	Oral dose	Adverse effects
Penicillin V Amoxicillin Amoxicillin-clavulanate Cloxacillin Cephalexin Cephadroxil	60 80 75* 50-70 >90 >90	0.5-1 g/6-8h 1 g/8h 875-125 mg/8h 0.5-1 g/4-6h 0.5-1 g/6-8h 0.5-1 g/8-12h	Skin rash. Anaphylactic reactions. *Clostridium difficile*-associated diarrhea.
Ciprofloxacin Levofloxacin	75 >95	500-750 mg/12h 500-750 mg/24h	Liver toxicity. Achilles tendinitis/ruptures Achilles, irreversible neuropathy. *Clostridium difficile*-associated diarrhea
Clindamycin	90	300 mg/8h	Gastrointestinal symptoms. *Clostridium difficile*-associated diarrhea.
Rifampin***	90**	10-20 mg/kg/24-12h	Liver toxicity. Skin rash. Gastrointestinal symptoms.
Doxycycline Minocycline	95 95	100 mg/12h 100 mg/12h	Skin hyperpigmentation. Liver toxicity.
Cotrimoxazole (trimethoprim/sulfametoxazole)	90/90	160/800 mg/8-12h	Hematological (leucopenia, anemia). Skin rash. Avoid with cumarinics.
Linezolid	100	600 mg/12h	Hematological. (thrombocytopenia, anemia). Avoid with tricyclic antidepressants.
Fusidic acid ****	90	0.5-1 g/8-12h	Liver toxicity.
Fluconazole	>90	400 mg/24h	Liver toxicity. Inhibits CYP3A4.

BA=bioavailability. PB=protein binding.

*Referring to clavulanate. **When taken with an empty stomach. ***Always use in combination therapy. ****Not available in the United States.

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Workgroup 15: Prevention of Late PJI

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Note:

This workgroup overlaps with other groups. For more detailed and/or alternative views on specific concepts, please refer to the other workgroups indicated:

Risk factors for infection	Workgroup 1: Mitigation and Education
Diagnostic procedures and thresholds	Workgroup 7: Diagnosis of Periprosthetic Joint Infection

Question 1: What is the definition of a late periprosthetic joint infection (PJI)?

Consensus: Late PJI can be defined as a PJI that develops at a variable length of time after an index arthroplasty procedure. Late PJI occurs after an initially successful index procedure with no clinical or radiographic signs of PJI. Risk factors for late PJI are similar to those described for PJI (Workgroup 1).

Delegate Vote: Agree 56%, Disagree 39%, Abstain 5% (Weak Consensus)

Justification: The definition of late PJI is variable in the literature. The majority of the members of the consensus felt that any infection occurring after one year should be considered as late. Coventry et al. defined stages of PJI, where Stage I is an acute infection that occurred within 3 months of the index procedure, Stage II is a delayed infection that occurred between 3 months to 2 years after the index procedure where there was no pain-free interval, and Stage III is a hematogenous infection where there is a pain-free stage.[1] Garvin and Hanssen defined a late chronic PJI as one that occurred 4 weeks after the index procedure with an insidious clinical onset.[2] McPherson et al. defined a chronic infection as one that had symptoms for 4 weeks or longer.[3] In Sweden, a late PJI is defined as one that occurs 2 years after the index procedure. Due to the huge variation in time frames, we did not find consensus in defining a timeframe for a late PJI. However, we classified late PJI as late hematogenous PJI, where there was an asymptomatic period followed by clinical and/or radiographical signs of infection. The workgroup feels that late PJI arises as a result of bacteremia at a later stage and should be distinguished with infections arising as a result of intraoperative contamination.
Risk factors for late PJI are similar to those described for PJI in Workgroup 1 (Please see Question 1, Workgroup 1).

Question 2: Which diagnostic procedures have to be done to verify late PJI?

Consensus: The workup of patients with painful joint and suspected (late) PJI should follow the algorithm provided in Workgroup 7.

Delegate Vote: Agree 89%, Disagree 9%, Abstain 2% (Strong Consensus)

Justification: Late PJI can present as pain and may not be obvious in all circumstances. For the preoperative diagnosis of late PJI, a systematic approach for workup of these patients must be considered. This workgroup proposes the following workup for patients suspected of having late PJI. The diagnostic workup includes ordering laboratory tests followed by aspiration of the joint with the patient not on antibiotics for two weeks if serology is abnormal or for patients at high index of suspicion for PJI. The serological test should include Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). An ESR > 30mm/hour and a CRP >13.5mg/dL is concerning for PJI affecting total hip arthroplasty (THA) and an ESR > 46.5 mm/hour and a CRP > 23.5 mg/DL is concerning for PJI affecting total knee arthroplasty (TKA).[5] A synovial fluid sample should be drawn from the joint prior to the initiation of antibiotics or when the patient is off antibiotics for 2 weeks. A diagnosis of late PJI should be based on synovial fluid leukocyte counts that are greater than 3,000 cells/μl with a neutrophil differential greater than 80%. In the light of systemic manifestation, blood cultures can be considered. Nuclear medicine imaging techniques may be used as an adjunct for diagnosing late PJI.[6-18] Tissue biopsies can be performed preoperatively to obtain a diagnosis.

For intraoperative diagnosis of PJI, microbiology culture is still the gold standard. We recommend that a minimum of 3 tissue samples should be obtained.[19] Histology should be considered as part of the diagnostic criteria.[20] Gram stains should not be used for diagnosing late PJIs.[21] Adjunct diagnostic methods, including sonication of implants, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), mass spectrometry, microarray identification, and fluorescence in situ hybridization, may assist with determining the organism present if available, especially in culture-negative patients. Removed implants should be transported under low-oxygen conditions to the microbiology laboratory where they can be immediately processed. The interpretation of cultures for late PJIs is the same as for early PJI. Multiple studies have determined that elevated inflammatory serum laboratory tests such as ESR and CRP are highly sensitive for detecting PJIs.[22-25] CRP is a more specific laboratory test than ESR, although both can be elevated in light of other infectious/inflammatory processes. There is also some evidence that serum IL-6 can be useful in the diagnosis of PJI.[5,26] Synovial fluid can be tested for multiple factors to determine if there is a late PJI. The most common method is to measure the leukocyte cell count and the neutrophil differential. Besides that, synovial fluid can be tested for culture, CRP, leukocyte esterase, and other molecular markers. The threshold for the leukocyte cell count and neutrophil differential from synovial fluid has varied with time. A study conducted by Kersey et al. determined thresholds to rule out infection

and demonstrated that a leukocyte cell count of less than 2,000 cells/μL and less than 50% polymorphonuclear leukocytes had a 98% negative predictive value.[27] Mason et al. conducted one of the first studies to determine a cut-off value suggestive of PJI in TKA patients. They determined that a leukocyte count greater than 2,500 cells/μL and greater than 60% polymorphonuclear leukocytes was suggestive for infection.[28] A study examining revision TKA determined that leukocyte counts greater than 1,700 cells/μl and neutrophil differentials greater than 65% was highly sensitive and specific for PJI.[29] For revision TKA, a synovial fluid white count greater than 3,000 cells/μL with elevated ESR and CRP had 100% sensitivity, 98% specificity, and 99% accuracy.[30]

In the setting of revision THA for infection, greater than 3,000 white blood cells/ μL provided the greatest combined sensitivity, specificity, and positive and negative predictive value in patients with elevated ESR and CRP.[23,31,32] CRP is a commonly-tested inflammatory marker in serum that can also be found in synovial fluid.

Recent studies have evaluated the role of synovial molecular markers for the diagnosis of PJI.[5,33] The leukocyte esterase test that is used for detecting bacteria in urine was found to be 80.6% sensitive and 100% specific for detecting infection in prosthetic joints.[34] These values also correlate with elevated polymorphonuclear leukocytes, total white blood cell count, ESR, and CRP. Some other markers that have been found to be elevated in patients with PJI includes synovial IL-6, Interleukin-8, α (2)-macroglobulin, CRP, and vascular endothelial growth factor. One study demonstrated that measuring CRP in synovial fluid using a multiple assay was a more sensitive marker than serum CRP (84 vs 76%).[5,33]

The diagnosis of late PJI can be confounded by culture-negative results. Extending the incubation of culture (7 to 14 days) can help minimize this situation. In one study the detection rate of infecting organisms after 7 days of incubation was 73.6% and this increased greatly when cultures were incubated for 13 days.[35] Additionally, if a synovial fluid aspirate yields a culture-negative result, taking synovial tissue for testing instead of an aspirate yields a sensitivity of 82% and a specificity of 98%.[36]

Advanced diagnostic methods can also be employed to identify organisms responsible for infection.[37] The use of sonication to remove bacteria from explanted prostheses has been shown to increase the sensitivity of detecting bacteria (60.8% sensitivity with tissue culture and 78.5% sensitivity with sonicated fluid culture), but both tests have similar specificities.[38] Additionally, there were 14 patients whose bacteria were detected by sonicated fluid culture but not by tissue culture.

Other advanced diagnostic methods can be used to amplify bacteria that are present within the tissue or from sonicated samples. PCR [39-42] amplifies existing bacteria DNA, while RT-PCR[43, 44] amplifies RNA. This increases the sensitivity of detection if there is a small amount of bacteria present.[45]

Question 3: Does the type, dose, and length of anticoagulation for prophylaxis influence the incidence of surgical site infection (SSI) following total joint arthroplasty (TJA)?

Consensus: Yes. The type, dose, and length of administration of anticoagulation drugs for prophylaxis against venous thromboembolism influence the incidence of SSI following TJA.

Delegate Vote: Agree 76%, Disagree 9%, Abstain 15% (Strong Consensus)

Justification: Multiple high-level studies have compared different methods of anticoagulation for prophylaxis after TJA. Most studies concluded that there were no differences between different anticoagulation methods and SSI, or parameters associated with surgical infections (eg wound infection, wound dehiscence, and wound hematoma). However, not many of these studies were powered to detect a difference in SSI and they were conducted mostly for the assessment of the efficacy of anticoagulation. The more effective an anticoagulation agent is the more likely it is for the patient to develop a hematoma or have excess wound drainage, both of which are associated with SSI.

The risk for these adverse events could be based on the type, dose, and length of administration of anticoagulation. An extensive search of the literature was performed to identify studies that evaluated hematoma formation, wound drainage, SSI, and/or PJI formation with administration of anticoagulation. There is a wide variability in the incidence of later adverse events in all of these studies. Some studies show no difference in the incidence of hematoma formation when Dextran-70, warfarin (15mg loading, 5mg subsequent, for 3 weeks), and low-dose heparin (5000IU twice a day (BID) for 3 weeks were utilized.[46] Another study did not find a difference in the incidence of deep wound infections when aspirin, warfarin, or injectable anticoagulation was utilized.[47] The dose of prophylactic injectables and the length of administration were variable in the latter study. Another study comparing enoxaparin versus control/graduated compression stockings/intermittent pneumatic compression did not find a difference in the incidence of superficial infections.[48] In one study earlier administration of low

molecular-weight heparin (LMWH) was found to have no correlation with SSI when compared to a control group of uninfected patients.[49] On the other hand, anticoagulation resulting in an INR greater than 1.5 was found to result in a higher likelihood of wound-related problems that had a greater chance of developing into an infection. All patients received deep vein thrombosis prophylaxis with warfarin for 6 weeks.[50] Another study showed that administration of LMWH resulted in a high incidence of hematoma formation and return to the operating room.[51]

One consideration with regard to the amount of anticoagulation is the ability to reverse these agents. Drugs such as warfarin can be reversed with vitamins and LMWH can be reversed with protamine. Unfortunately, there are no direct agents to reverse fondaparinux, rivaroxaban, or dabigatran. Administration of Factor VII is the only available modality to deal with the excessive bleeding that may occur as a result of using the latter anticoagulation agents.

Question 4: Should a patient with TJA be given routine dental antibiotic prophylaxis?

Consensus: The use of dental antibiotic prophylaxis in patients with TJA should be individualized based on patient risk factors and the complexity of the dental procedure to be performed.

Delegate Vote: Agree 81%, Disagree 16%, Abstain 3% (Strong Consensus)

Justification: Based on the available literature, within which there is no consensus, there is increased bacteremia after dental procedures, and providing antibiotic prophylaxis before dental work can reduce the burden of the bacteria load. Additionally, most PJIs occur within the first 2 years after surgery.[52-54] One study found that the use of antibiotic prophylaxis did not reduce the risk of infection, independent of the dental procedure performed in a 2-year period.[55] Dental procedures may not be associated with the development of PJIs.[56] However, many studies demonstrate that there is increased bacteremia after dental procedures, as the incidence of bacteremia from oral procedures ranged from 5% to 65%.[57-77,78-98] Thus, we conclude that using antibiotic prophylaxis for dental procedures after TJA to decrease the risk of bacteremia following dental procedures is justifiable to decrease the risk of sustaining a PJI within the first 2 years after surgery.

Consensus: We recommend that high-risk patients receive lifetime dental antibiotic prophylaxis after TJA.

Justification: The risk factors for PJI after dental procedures are patient-dependent and the risk for infection is higher in patients who receive dental work.
The orthopaedic and dental literature both detail groups of patients that are at higher risk for developing a PJI after dental procedures and who could benefit from the use of antibiotic prophylaxis. The patients that could receive the greatest benefits include those with:

- Inflammatory arthropathies (eg rheumatoid arthritis).[53,99-101]
- Immunosuppression (drug- or radiation-induced immunosuppression–including oncology or transplant patients and human immunodeficiency virus (HIV) patients).[102,103]
- Insulin-dependent diabetes.[103]
- A major systemic infection.[104]
- Hemophilia.[105]
- The following factors are to be determined by a dental care provider:
    - High gingival score and gingival index.[72,106,107]
    - High plaque score and plaque index.[72,106,108]
    - Gum probing depth.[72,106]
    - Periodonitis.[72]

Consensus: We recommend that an oral antibiotic be given at the following dosages for only one dose prior to dental procedures.

Justification: Using oral antibiotics can reduce the burden of bacteria that is released during dental procedures. The following oral antibiotics are recommended as prophylaxis prior to dental procedures:

- Amoxicillin 2 gm, 1 hour prior to procedure.[81,109-114]
- Azithromycin 500mg, 30 minutes to 1 hour prior to procedure.[115]
- Cefaclor 1 gm 1 hour prior to procedure.[116]
- Cefalexin 2 gm, 30 minutes to 1 hour prior to procedure.[115]
- Clindamycin 600 mg, 1-1.5 hours prior to procedure.[109,115,117,118]
- Erythromycin 1.5 gm, 1-1.5 hours prior to procedure.[119,120]
- Moxifloxicin 400 mg 1-2 hours prior to procedure.[109]

- Penicillin 2 gm, 1 hour prior to procedure.[62,113,121,122]

Consensus: We recommend that one of the following intravenous (IV) or intramuscular antibiotics be given at the following dosages for only one dose prior to dental procedures.

Justification: Using IV antibiotics can reduce the burden of bacteria that is released during dental procedures. The following IV antibiotics are recommended as prophylaxis prior to dental procedures:

- IV Ampicillin 2 gm, 30 minutes to 1 hour prior to procedure.
- IV Cefazolin 1 gm, 30 minutes to 1 hour prior to procedure.[115]
- IV Cefuroxime 1.5 gm, 10 minutes before procedure.[123]
- IV Ceftriaxone 1 gm, 30 minutes to 1 hour prior to procedure.[115]
- IV Teicoplanin 400 mg, immediately before procedure.[111,124]

Question 5: Should patients at high risk of late PJI be given prophylactic antibiotics during viral illnesses?

Consensus: There is no role for the administration of oral antibiotics to patients with TJA who develop viral illnesses.

Delegate Vote: Agree 98%, Disagree 2%, Abstain 0% (Strong Consensus)

Justification: Patients with late risk factors for bacterial infections, such as those undergoing an invasive procedure that produces bacteremia, may benefit from prophylactic antibiotic administration. However, preventative antibiotics for conditions such as viral infections only contribute to emerging antibiotic-resistant organisms and should be avoided in clinical practice. Patients with late risk factors for bacterial infections are those who are susceptible to infection. These risk factors include but are not limited to the following:

- Immunocompromization or immunosuppression (drug-induced, radiation-induced, diabetes, hepatitis, HIV, or malignancy).[125-127]
- Social habits (smoking and drinking alcohol)[126,128] and inflammatory arthritis.[128,129]
- Obesity.[126,129-131]
- Malnourishment.[126]
- Previous joint infection (not currently on suppression antibiotics).

Often, antibiotics are unnecessarily prescribed, especially in conditions such as rhinosinusitis.[132] One study demonstrated that antibiotics were only prescribed in a justified manner in 13.5% of upper respiratory infection cases.[133]
Finally, taking antibiotics for conditions such as viral infections can result in increased antibiotic resistance.[134] This reduces the effectiveness of treatment for potential PJIs.

Question 6: Can transient bactermia be minimized during endoscopic procedures such as colonoscopy to prevent late PJI?

Consensus: The influence of transient bacteremia can be minimized during minor surgical procedures by administering prophylactic antibiotics to individualized patients and especially to high-risk patients.

Delegate Vote: Agree 85%, Disagree 13%, Abstain 2% (Strong Consensus)

Justification: Transient bacteremia can result from gastrointestinal (GI) and genitourinary (GU) procedures, and this bacterial burden can be decreased by administering prophylactic antibiotics. However, GI societies recommend against giving prophylactic antibiotics for minor surgical procedures such as upper endoscopies, sigmoidoscopies, or colonoscopies, while GU societies are mixed on their stance on antibiotic prophylaxis.
GI procedures such as upper endoscopy, sigmoidoscopy, or colonoscopy can produce transient bacteremia. Studies throughout the literature have demonstrated mixed results, but they predominantly support the idea that GI procedures result in increased bacteremia. Prophylactic administration of antibiotics before these procedures can decrease transient bacteremia, especially in high-risk patients. One of the earliest published studies found that there was transient bacteremia when rigid sigmoidoscopies were performed as measured by blood cultures 5 minutes, 10 minutes, 15 minutes, and 30 minutes after the procedure.[135] Three older studies evaluating bacteremia in colonoscopies found the burden of bacteria in the blood to be very low, except in immunocompromised patients, such as those with severe liver disease or carcinomatosis.[136-138] During the same time frame, other studies demonstrated up to 15% bacteremia after colonoscopies.[139,140] Of note, these studies varied in the time points at which they collected the blood samples and not every study collected blood at the peak of bacteremia (5 minutes after the end of the procedure).

A subsequent study by Kumar et al. demonstrated that there was limited bacteremia from colonoscopies in low-risk patients, even when polypectomies or biopsies were performed.[141] This was also found to be true in proctosigmoidoscopies.[142] Based on these studies, GI endoscopic societies such as the American Society for Gastrointestinal Endoscopy and The American Society of Colon and Rectal Surgeons recommend against the use of prophylactic antibiotics prior to colonoscopies and other lower GI endoscopies.[143,144] In a survey of infectious disease program directors, 50% stated that they would not give prophylactic antibiotics before colonoscopies and polypectomies.[145] However, other studies have demonstrated that there is increased bacteremia from colonoscopies (10%) and the highest rate of bacteremia came from endoscopic retrograde cholangiopancreatography (39%).[146] A review paper by Nelson[147] demonstrated that postprocedure bacteremia differed depending on the procedure, including 0.5% for flexible sigmoidoscopies, 2.2% for colonoscopies, 4.2% for esophagogastroduodenoscopies, 8.9% for variceal ligation, 11% for endoscopic retrograde cholangiopancreatography, 15.4% for variceal sclerotherapy, and 22.8% for esophageal dilation.

Bacteremia can also result from exogenous sources such as the equipment being used in the procedure. One systematic review evaluated GI endoscopy and found that salmonella, mycobacterium, and pseudomonas are common organisms that are transmitted by these procedures.[148] Another systematic review demonstrated that esophagogastroduodenoscopy can also be responsible for transmission of serious organisms, such as HIV, salmonella, pseudomonas, *H. pylori*, and hepatitis.[149]

In the orthopaedic literature, there have been some reports of PJI that presented after GI procedures. One case report described a patient who developed a *listeria monocytogenes* PJI after a routine colonoscopy without receiving prophylactic antibiotics.[150] One study reported a 1.9% infection rate in prosthetic joints[151] and another reported that one patient with a prosthetic knee and cirrhosis out of 16 patients developed a serious infection after an endoscopic procedure.[152] Coelho-Prabhu et al. reported that there is an increased risk of PJI associated with esophago-gastro-duodenoscopies performed with biopsies.[153]

Thus antibiotic prophylaxis may be administered to high-risk patients undergoing GI procedures or peritoneal dialysis.[154,155] In addition, high-risk cardiac patients, such as those who have artificial heart valves, acquired valvular dysfunction, vascular grafts, surgical pulmonary shunts, complex congenital cardiac disease, and a history of endocarditis, have a higher likelihood for developing endocarditis and may benefit from antibiotic prophylaxis prior to GI procedures.[156] Immunocompromised patients may also benefit from routine prophylaxis.[157]

GU procedures are similar to GI procedures; prostatic biopsies and cystoscopies can produce bacteremia and/or bacteriuria. Studies have demonstrated that bacteriuria correlates with bacteremia.[158,159] Most of the studies on GU procedures encourage the use of prophylactic antibiotics without exacerbating bacterial resistance.[160] However, in contrast to the GI literature, professional GU societies encourage the use of routine antibiotic prophylaxis.

An early study by Sullivan et al. demonstrated the following rates of bacteremia for certain procedures: 31% for transurethral resection of the prostate, 17% for cystoscopy, 24% for urethral dilation, and 8% for urethral catheterization.[161] *Enterococci* and *Klebsiella pneumonia* were the two most common organisms. These anaerobes were also found to be present after transrectal prostatic biopsies,[162] as well as *Escherichia coli*.[163] *Candida albicans* has also been found in bloodstream infections in patients who have undergone ureteroscopy and ureteral stenting.[164] When evaluating transrectal prostate biopsies, it is recommended that patients receive antibiotic prophylaxis. Ultrasound-guided transrectal biopsies were found to have a rate of 43% *Escherichia coli* bacteremia post-procedure.[165] A study by Thompson et al. demonstrated that when a transrectal prostate biopsy was combined with cystoscopy, the incidence of bacteremia was very high at 73% compared to 13% for cystoscopy alone.[166] The highest rate of bacteremia after transrectal prostate biopsy was reported as 100% by the same group,[167] of which 87% had a postoperative urinary tract infection and 27% were symptomatic. There was a significant reduction in bacteremia when cefamandole, a second generation cephalosporin, was administered as antibiotic prophylaxis. A Cochrane review on the use of antibiotic prophylaxis for transrectal prostate biopsies found that the use of antibiotics for at least 3 days could prevent infectious complications after the procedure.[168] One report described a case of *Klebsiella pneumoniae* periprosthetic knee infection secondary to a prostatectomy for prostatic carcinoma.[169]

Patients who underwent transurethral surgery of the prostate developed subsequent bacteremia that was shown to lead to a 6%-60% incidence of urinary tract infections in patients who did not receive antibiotic prophylaxis.[170,171]

Patients who underwent extracorporeal shock wave lithotripsy had a 5% incidence of bacteremia[172] and a case report described a patient who developed enterococcal endocarditis after this procedure.[173] For women, there is increased bacteremia during labor[174] and with placement of intrauterine devices.[175] Patients who undergo chorionic villus sampling, especially transcervically, have increased rates of bacteremia.[176] Based on these studies, the American Urological Association determined that antibiotic prophylaxis should be administered in specific situations depending on the patient population.[177] For example, patients who undergo

cystography should only receive a fluoroquinolone or trimethoprim-sulfamethoxazole if they are at high risk, but all patients who undergo transrectal prostate biopsy should receive fluoroquinolone antibiotic prophylaxis. Alternatively, the American College of Obstetricians and Gynecologists recommends against antibiotic prophylaxis.[178]

Question 7: What is the role of herbal supplements, probiotics, and alternative medicine in decreasing translocation of bacteria across the intestinal wall?

Consensus: There is insufficient evidence that supports the use of herbal supplements, probiotics, and alternative medicine to decrease translocation of bacteria across the intestinal wall to prevent late PJIs.

Delegate Vote: Agree 95%, Disagree 3%, Abstain 2% (Strong Consensus)

Justification: While certain herbal supplements, probiotics, and alternative medications have demonstrated decreasing translocation of bacteria across the intestinal wall, most of the studies are animal studies and none have level I evidence. Thus, we do not recommend use of alternative medicine products for preventing bacteremia from entering the gut to prevent late PJIs; however,these products may be considered for general health purposes.

Herbal supplements

Vitamin C (ascorbic acid) and vitamin E (alpha-tocopherol) have been shown to reduce bacterial translocation from the intestine and decreases mucosal lipid peroxidation in common bile duct ligation and chronic portal hypertension in rats.[179] Glutamine has been shown to be an effective amino acid for reducing the translocation of bacterial across intestinal walls in animal models.[180,181] The mechanism of action is proposed to be an increase of secretory IgA (sIgA), an increase of villous height, and an increase in mucosal thickness to improve the intestinal barrier and decrease bacterial translocation and adherence. An older study by White et al. demonstrated that the enteral administration of glutamine resulted in decreased bacterial translocation to extra-intestinal sites and that glutamine can reduce intestinal permeability.[182] The protective effects of glutamine also include reduced bacterial translocation in blood. This study was supported a murine acute graft vs host disease model that demonstrated the use of oral glutamine reduced gastrointestinal permeability, reduced TNF-α expression, increased occluding, and resulted in less apoptotic cells in the crypt of the intestine.[183] Arginine is another

amino acid that has also been shown to decrease bacterial translocation, as measured by the decreased level of bacteria in mesenteric lymph nodes in rats.[184] Curcumin is a member of the ginger family that is related to turmeric spice. A study by Karatepe et al. demonstrated that curcumin was able to reduce the amount of intestinal bacterial translocation into blood in a rat model.[185]

Chinese herbal supplements have demonstrated positive effects on gut flora and enhance the immune system. One study by Huang et al. demonstrated that the use of Chinese medicine herbs such as Panax ginseng, Dioscoreaceae opposite, Atractylodes macrocephala, Glycyrrhiza uralensis, Ziziphus jujube, and Platycodon grandiflorum can increase lactobacilli counts in the ileum and decrease coliform counts in the colon. The immune activities of polymorphonuclear leucocytes were also enhanced, including enhancement of the respiratory burst, in weanling pigs.[186] Fermented dietary herbs, such as Rhizoma Atractylodis Macrocephalae, Massa Medicata Fermentata, and Dolichoris Semen, have been shown to protect again lipopolysaccharide, an endotoxin that triggers the systemic inflammatory response.[187] Phosphatidylcholine is a phospholipid that is a component of biological membranes. Studies have shown that the use of phosphatidylcholine supplementation can protect against bacterial translocation in a colitis rat model.[188,189]

Probiotics

Lactobacillus is a naturally-occurring bacterium that resides in human digestive and GU tracts.[184] It is also present in fermented foods such as yogurt and dietary supplements. *Lactobacillus plantarum* has been shown to be effective at adhering to gut mucosa and reducing endotoxin and microbacterial translocation out of the digestive tract.[190] *Lactobacillus plantarum* and *lactobacillus reuteri* reduced bacterial translocation, recreated intestinal microbiology, and decreased enzyme myeloperoxidase in the intestine.[191] *Saccharomyces boulardii*, a beneficial baker's yeast, stimulates host defense mechanisms and increases IgA, which has been shown to decrease the translocation of Candida from the gut to the mesenteric lymph nodes in animal models.[192-194]

Alternative medicine

Growth hormone, when combined with glutamine, improved the intestinal barrier in portal hypertension patients by decreasing intestinal permeability and improving mucosal integrity.[195] Cellulose fiber has been demonstrated to decrease bacterial translocation, but did not prevent bacterial overgrowth.[196-198]

Question 8: Is there a role for post-surgical monitoring of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in the asymptomatic patient?

Consensus: We recommend against post-surgical monitoring of MRSA colonization in the asymptomatic patient.

Delegate Vote: Agree 98%, Disagree 2%, Abstain 0% (Strong Consensus)

Justification: Post-surgical monitoring of MRSA colonization has not been shown to lead to reduced SSIs. The rate of *Staphylococcus aureus* colonization has been reported as high as 33% in the 3-30 month postoperative period after TJA[199] and most of the bacteria have unchanged antibiotic sensitivity. Although these organisms may persist, *Staphylococcus aureus* colonization in the postoperative period has not been correlated with increased risk of SSI. Thus, monitoring and decolonizing patients who are *Staphylococcus aureus*-colonized may not prove an efficacious method for infection prevention and should not be encouraged until further studies are performed.

Consensus: We recommend that patients undergo repeat screening for *Staphylococcus aureus* and decolonization prior to additional arthroplasty.

Justification: Because decolonization does not persist in the postoperative phase, we recommend that patients be rescreened and decolonized for subsequent arthroplasty procedures after the index procedure. One study demonstrated that there was 70% persistent decolonization of MRSA and methicillin-sensitive *Staphylococcus aureus* (MSSA) at an average of 156 days after the index procedure.[200] However, at 213 days, 30% of the patients were no longer decolonized. Repeat testing indicated that two new patients developed MRSA and 35 new patients developed MSSA. Thus, rescreening and decolonization of *Staphylococcus aureus*-colonized patients is recommended prior to any repeat arthroplasty procedures.

Question 9: What are the methods to identify extra-articular sources of late PJI?

Consensus: Extra-articular sources that contribute to late PJI should be identified by obtaining history and performing a thorough physical exam, laboratory testing, and imaging of suspected areas of infection.

Delegate Vote: Agree 92%, Disagree 3%, Abstain 5% (Strong Consensus)

Justification: To identify the source of infection, performing a proper history and physical examination can narrow down the region of interest. Once the area of suspected infection is identified, laboratory testing, imaging, and examination by specialists can further refine the source and provide a solution for eradicating the infection. The strongest evidence for an extra-articular source of PJI is cultures of the same pathogen that are found intra-articularly and from the extra-articular source of infection.

The most common method of acquiring a late PJI is by hematogenous spread.[201,202] Thus, most organs that are infected in the body can become an extra-articular source of a late PJI. The main sources of extra-articular PJIs by body systems are as follows: dental, cardiac, lungs, GI, GU, integumentary, and blood stream.

Dental abscesses can also be sources of extra-articular infection. *Actinomyces israelii* is an organism responsible for dental carriers and this organism has been isolated in PJI.[203] *Actinomyces naeslundii* is another organism that has been identified in late PJI secondary to routine dental work on a molar tooth.[204] Patients who have a high suspicion for dental infection should be seen by a dentist and appropriate repairs (eg dental extraction) should be performed.

For cardiac issues such as infective endocarditis,[205,206] an echocardiogram can identify vegetations. Patients who are IV drug users have a higher likelihood of developing infective endocarditis that can produce septic emboli. IV antibiotics are the treatment of choice.

For the lungs, infectious conditions such as pneumonia can be an extra-articular source of infection.[207] Pneumonia can also be superimposed on chronic conditions such as chronic obstructive pulmonary disease and asthma. The use of imaging such as a chest x-ray or computed tomography (CT) scan can identify pneumonia, or pulmonary testing can diagnose chronic obstructive pulmonary disease. Sputum cultures can be used to identify the appropriate organisms to treat with IV antibiotics.

Inflammatory conditions in the GI system[208] such as cholecystitis and cholangitis can seed the prosthesis with bacteria.[209] Other diseases such as diverticulitis can also predispose patients to PJIs, as well as chronic conditions such as liver disease (eg hepatitis).[210] Imaging modalities, such as CT scans with oral contrast, can elucidate GI pathology, in addition to direct visualization using endoscopy. However, endoscopy is not benign, as the performance of health maintenance tests, such as routine colonoscopies, can result in PJIs. One case report described a patient who developed a *Listeria monocytogenes* infection in a TKA.[150]

There are multiple conditions within the GU system that can provide an extra-articular source for a PJI. Systemic bacteremia is increased with routine procedures such as a transrectal prostate biopsy.[167] Performing a prostatectomy for prostatic carcinoma lead to the development of a *Klebsiella pneumoniae* periprosthetic knee infection in one patient.[169] The bacteria from sexually transmitted diseases, such as gonorrhea,[211] can also infect TJA implants. Infections of the urinary tract, including cystitis and pyuria, are extra-articular sources of infection that are associated with increased risk of PJI.[212,213] If a urinary tract infection is suspected, a urine sample should be sent for urinalysis and culture. However, treatment of asymptomatic bacteriuria is controversial.[214] Advance imaging using ultrasound or CT can be preformed to identify the source of infection. Microbiology testing of discharged bodily fluids may also provide cultures by which to guide antibiotic management.

Skin lesions from immunocompromised skin such as with psoriasis[215] or chronic venous ulcers can be a source of extra-articular bacterial leading to PJI; however, some studies have demonstrated that there is no association.[216,217] Thorough checks for breaks in the skin can identify wounds that can be treated by wound care specialists and dermatology consultations. Direct seeding of the bloodstream with bacteria, as in the use of IV drugs, can result in hematogenous spread to the prosthesis.[218] Catheters can become colonized by skin flora and can directly seed the blood stream.[219,220] Removal of catheters can reduce the risk of infection and culturing the catheter tips can provide an organism to treat.

Question 10: When should further workup for postoperative fevers be performed after TJA?

Consensus: We recommend against the routine workup of fevers greater than 38.5ºC in the immediate postoperative period. However, the workup of persistent fevers after postoperative day 3 may be warranted.

Delegate Vote: Agree 81%, Disagree 15%, Abstain 4% (Strong Consensus)

Justification: Fevers in the immediate postoperative period are common after TJA. However, when patients present with temperatures greater than 39.0ºC, especially for multiple days and after postoperative day 3, a workup that includes urinalysis, urine culture, blood culture, and chest x-ray are warranted. Additionally, examination for deep vein thrombosis, infected IV lines,

and drug-related fevers should be included in the workup if there is high clinical suspicion. Treating these infections may reduce the risk of causing a late PJI.

In the immediate postoperative period after TJA, patients commonly sustain elevated body temperatures due to the invasion of surgery.[221-223] This is associated with increased tissue, joint fluid, and serum concentrations of inflammatory molecules, including IL-1β from drain fluid and IL-6, which can be detected in serum and joint fluid.[224] Postoperative fevers may be routine in the postoperative period or can be caused by a multitude of factors, including urinary tract infections, blood borne infections, pneumonia, deep vein thrombosis, pulmonary emboli, SSIs, IV line infections, or drug fevers. These are often evaluated by urinalysis, urine culture, blood cultures, chest x-rays, Doppler ultrasounds, wound or joint cultures, IV line cultures, or ceasing the administration of certain drugs. However, multiple studies within the orthopaedic literature have demonstrated that a postoperative fever, especially within the first 3 days, has a low association with the development of PJI. Kennedy et al. demonstrated that none of the patients that exhibited a temperature greater than 39ºC developed a PJI and that postoperative fevers were correlated with a drop in hematocrit or a subsequent transfusion within 5 days after surgery.[225] Guinn et al. demonstrated that 14/158 (8.9%) TKA patients developed a postoperative fever that could be attributed to laboratory findings. Their study demonstrated that unilateral TKA patients were more likely to sustain a complication and that urinalysis, aggressive pulmonary toilet, and repeat physical exams were helpful with diagnosis.[226] Shaw and Chung demonstrated that out of 100 TKAs and 100 THAs none developed a PJI and that positive urine cultures did not correlate with a febrile response.[227] Postoperative temperatures were greatest on postoperative day 1. When using fever (≤38°C) as a diagnostic test for developing PJI, the sensitivity was 0.286 (95% confidence interval (CI)=0.084-0.581), the specificity was 0.628 (95% CI=0.548-0.704) and the positive predictive value was 0.065 (95% CI=0.018-0.157).[228] Blood cultures have low utility when working up postoperative fevers. In a study by Bindelglass and Pellegrino, blood cultures were drawn on 40/240 TKAs and 31/124 THAs, of which only 2 patients came back with positive results. Both of these results were thought to be contaminants. Performing routine blood cultures to work up postoperative fevers was not found to be cost-effective.[229] A study conducted by Tai et al. demonstrated that patients who were diagnosed with PJIs had peak body temperatures reported on postoperative day 4 and these fevers were often sustained for 3 to 4 days.[230] Thus, postoperative fever workups were recommended in patients who sustained later and prolonged fevers. Additionally, working up all postoperative fevers can be expensive and the cost may not be warranted. A study by Ward et al. demonstrated that the routine evaluation of postoperative fever (>38.5°C) over a 2-year period

was $73,878, which amounted to a charge of $959.45 for a fever evaluation per patient.[231] However, fevers that occurred after postoperative day 3 were sustained for multiple events (<1) and had a temperature > 39.0°C were more likely to be associated with a positive workup. Thus, in this patient population, a febrile workup after TJA may be warranted.

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Future Research

The workgroup has identified the following as potential topics in need of further research.

- Influence of immunosuppression/immunosuppressive state on the incidence of PJI/SSI
- Influence of HIV and/or IV drug abuse on the incidence of SSI/PJI?
- Role of routine urinary tract screening in patients undergoing elective arthroplasty
- Optimal timing for elective arthroplasty for patients with prior septic arthritis
- The threshold for synovial cell count and neutrophil differential indicative of no active infection in patients with prior septic arthritis
- The threshold for synovial cell count and neutrophil differential indicative of active infection in patients with suspected PJI
- The role of preoperative showering or skin wipes for lowering SSI/PJI
- The role of terminal cleansing of hand with alcohol prior to surgery
- Duration of hand wash prior to surgery
- Cross reactivity of cephalosporins in patients with penicillin allergy
- Use of dual antibiotics for prevention of PJI
- The indications for administration of vancomycin for patients undergoing elective joint arthroplasty
- Studies to explore association between patients with preoperative abnormal urine tests and subsequent SSI /PJI
- MRSA screening and decolonization: efficacy of decolonization, incidence of recolonization/persistence of colonization, what element of decolonization (nasal decontamination, skin decontamination or prophylactic antibiotic) are the most effective strategy for prevention of PJI?
- The role of newly introduced agents (such as betadine based products) for decolonization of patients with MRSA prior to elective arthroplasty
- Investigation of newer methods (other than conventional) culture for identification of MRSA colonized patients
- The appropriate prophylactic antibiotic for patients undergoing megaprosthesis/tumor surgery
- Does the use of laminar flow room reduce the incidence of subsequent SSI/PJI following total joint arthroplasty?
- Does the use of body exhaust system reduce the incidence of subsequent SSI/PJI following total joint arthroplasty?
- Should patients wear a face mask during TJA?
- Can an uninfected elective arthroplasty be done after a prior infected case in the operating room?
- The best method of operating room decontamination
- How often should gloves be changed during joint arthroplasty?
- Should incise draping be used during TJA?
- Type/volume/ timing of irrigation solution
- Use of dilute betadine during TJA for prevention of SSI. Determine optimal dose and duration of irrigation
- Does type of draping (disposable vs non-disposable) affect the incidence of SSI/PJI?
- Use of autologous blood derived products for reduction of blood loss and subsequent SSI/PJI
- Best method of skin closure in patients undergoing elective total joint arthroplasty

- Best method of skin closure in patients undergoing surgical treatment for PJI
- Does the use of silver impregnated dressing reduce the incidence of SSI/PJI?
- The best method of hand cleansing prior to surgery
- Use of vancomycin powder in the wound for prevention of PJI in patients undergoing TJA
- Sonication of prosthesis for diagnosis of PJI (reproducing results)
- Study to determine the indications for aspiration of joints prior to revision for assumed aseptic failures
- Risk factors for failure of irrigation and debridement
- Use of resorbable material for delivery of antibiotics for prevention/treatment of PJI
- Randomized study to determine the success of one stage versus two stage
- Study to determine the optimal timing of reimplantation
- Study to identify proper serum or synovial tests to determine timing of reimplantation
- Study to determine the optimal length of antibiotic treatment between two stages
- Indications and length of treatment for suppressive ABx therapy following surgical managements of PJI
- Dental prophylaxis for those with TJA
- The role of maintaining normothermia during orthopaedic procedures
- Study to determine if prophylactic antibiotics are needed for patients undergoing colonoscopy or other minor procedures.