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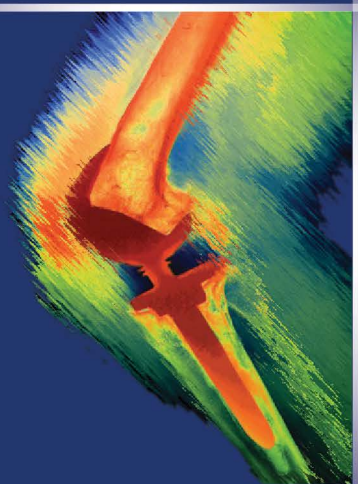
PERIPROSTHETIC JOINT INFECTION

Updated Practical Management Guide



Editor
Javad Parvizi

Section Editors
Jonathan R Danoff
James F Fraser
R Andrew Henderson
Christopher P Bechtel
Asim M Makhdom

2nd Edition

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Contents

Section 1: Basics of Infection

Jonathan R Danoff

1. **Definition of Periprosthetic Joint Infections** 3
   Jonathan R Danoff

2. **Incidence and Burden of Periprosthetic Joint Infection** 9
   Jonathan R Danoff

3. **Economic Burden of Periprosthetic Joint Infection** 17
   Jonathan R Danoff

4. **Common Antibiotics and Mechanism of Action** 25
   Nana O Sarpong

5. **Biofilm** 37
   Alexander L Neuwirth

6. **Multidisciplinary Approach to Management of Periprosthetic Joint Infections** 45
   Matthew J Grosso

7. **Future Trends and Challenges** 52
   Joseph A Karam, Peter F Sharkey

Section 2: Preoperative Medical Optimization

Jonathan R Danoff, Christopher P Bechtel

8. **Predisposing Factors for Periprosthetic Joint Infection** 61
   Jonathan R Danoff

9. **Perioperative Management of Diabetes Mellitus and Hyperglycemia** 69
   Jonathan R Danoff

10. **Malnutrition and Obesity** 75
Matthew J Grosso

11. **Cigarette and Tobacco Risks** 80
Rahul Goel

12. **Prior Intra-articular Joint Injection and Risk of Infection** 85
Nana O Sarpong

13. **Perioperative Management of Home Medications and Supplements** 90
Nana O Sarpong

14. **Inflammatory Arthropathy** 96
Matthew J Grosso

15. **Total Joint Arthroplasty in Patients with Prior Septic Arthritis** 102
Joseph A Karam

16. **Perioperative Management of Concomitant Infections** 110
Alexander L Neuwirth

17. **Conversion Arthroplasty with Hardware in Situ** 115
William V Arnold

18. **Liver and Kidney Disease** 123
Christopher P Bechtel, Antonia F Chen

19. **Anemia** 131
Christopher P Bechtel, Javad Parvizi

20. **Peripheral Vascular Disease** 136
John Kozy, Christopher P Bechtel

21. **Alcohol and Drug Use** 140
Christopher P Bechtel

22. **Depression and Other Psychiatric Illnesses** 144
Christopher P Bechtel

23. **Anticoagulation and Prosthetic Joint Infection** 147
Blake A Eyberg

24. **Infection Prevention Guidelines** 156
Noam Shohat, Christopher P Bechtel

Section 3: Intraoperative and Postoperative Optimization

Asim M Makhdom

25. **Preoperative Skin Preparation: Decolonization and Antisepsis** 165
Vinay Aggarwal, Anthony Tokarski

26. **Operating Room Environment** 177
Matthew Silijander

27. **Incise Drapes** 194
Alvin Ong, Asim M Makhdom

28. **Antibiotic Prophylaxis** 199
Nora Almadani, Asim M Makhdom

29. **Workup of Patients with Suspected Urinary Tract Infection** 205
Nora Almadani, Asim M Makhdom

30. **Irrigation Solutions in Total Joint Arthroplasty** 211
Matthew Silijander

31. **Cement and Antibiotics** 218
Claudio Diaz-Ledezma

32. **Blood Conservation** 230
Christopher P Bechtel, Daniel Baquet

33. **Wound Closure and Drain Use** 240
Asim M Makhdom

34. **Postarthroplasty Antibiotic Prophylaxis** 249
Fabio Orozco, Asim M Makhdom

Section 4: Diagnosis of Infection

Christopher P Bechtel

35. **Available Diagnostic Laboratory Tests and Molecular Biomarkers** 257
Majd Tarabichi

36. **Joint Aspiration** 269
Jonathan R Danoff

37. **Imaging for Diagnosis of Periprosthetic Joint Infection** 275
Nachum B Stollman, Ronald A Pitt

38. **Culture Principles** 284
Christopher P Bechtel, Gregory K Deirmengian

39. **Culture-negative Periprosthetic Joint Infections** 293
Christopher P Bechtel, Carlos A Higuera

40. **Diagnosis of Periprosthetic Joint Infection in Inflammatory Conditions** 300
James F Fraser

41. **Diagnosis of Periprosthetic Joint Infection in Adverse Metal Reaction** 305
James F Fraser

42. **Diagnosing Periprosthetic Joint Infection: The Rothman Institute Algorithm** 309
James F Fraser

Section 5: Treatment of Periprosthetic Joint Infection

James F Fraser, R Andrew Henderson

43. **Management of Wound Drainage** 319
James J Purtill

44. **Management of Fungal Periprosthetic Joint Infections** 325
Khalid Azzam

45. **Management of Mycobacterial Infection** 334
Hooman Bakhshi

46. **Management of Periprosthetic Joint Infection Caused by *Enterococcus*** *343*
Michael M Kheir

47. **Periprosthetic Joint Infection Caused by Rare Organisms** 354
Pierce Johnson

48. **Irrigation and Debridement for Periprosthetic Joint Infection** 363
James F Fraser

49. **One-stage Exchange Arthroplasty for Periprosthetic Joint Infection** 370
R Andrew Henderson, Erik N Hansen

50. **Resection Arthroplasty** 383
Daniel S Mangiapani, Pouya Alijanipour

51. **Removal of Well-fixed Hip and Knee Arthroplasty Components in the Setting of Periprosthetic Joint Infection** 398
R Andrew Henderson, Gregory K Deirmengian

52. **Two-stage Exchange Arthroplasty: Antibiotic Spacers** 416
Vinay Aggarwal, Gregory K Deirmengian

53. **Reimplantation Following Two-stage Exchange Arthroplasty for Prosthetic Joint Infection** 438
R Andrew Henderson, Camilo Restrepo

54. **Suppressive Antimicrobial Therapy and Prosthetic Joint Infection** 446
Mitchell R Klement, Meaghan Cotter, Jai Hyung Park

55. **Prognostic Classification for Periprosthetic Joint Infection** 454
Ronald Huang

56. Periprosthetic Joint Infection and Mortality **462**
R Andrew Henderson

57. Current Limitations, Evolving Technologies and Future Directions in the Management of Periprosthetic Joint Infection **467**
Asim M Makhdom

Index *477*

Chapter 4

Common Antibiotics and Mechanism of Action

Nana O Sarpong

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CURRENT EVIDENCE

Antibiotics play a critical role in combating periprosthetic joint infections (PJI). Identifying a microbial pathogen or pathogens is essential both for diagnosis and treatment. Once a pathogen has been identified, in vitro antimicrobial susceptibility testing can be performed to guide antibiotic therapy. Treatment outcomes of PJI rely on the characteristics of the causative organism, including virulence and antibiotic resistance. In up to 40% of PJI, multiple organisms (i.e. polymicrobial) may be isolated from synovial fluid or tissue cultures.[1] Thus, an understanding of the most utilized classes of antibiotics and their mechanism of action is fundamental to select the appropriate antibiotic coverage for each isolated organism.

The microbial coverage, mechanism of action and side effects of the major classes of antibiotics used in the treatment of PJI are highlighted in Table 4.1.[2,3] The various types of antibiotics differ based on their target against different aspects of bacterial cells. For example, penicillins, cephalosporins, monobactams, glycopeptides and carbapenem antibiotics all inhibit bacterial cell wall synthesis. Others act at the level of the

Table 4.1: Microbial coverage, mechanism of action and side effects of the major antibiotics used in the treatment of PJI

Class (typical example)	*Activity against*	*Mechanism of action*	*Potential side effects*
Penicillins (cloxacillin)	Wide range of infections; penicillin used for streptococcal and enterococcal infections; carbenicillin, ticarcillin, mezlocillin, piperacillin are also active against *Pseudomonas*	Disrupt the synthesis of the peptidoglycan layer of bacterial cell walls	Gastrointestinal upset, diarrhea, allergy with serious anaphylactic reactions, brain and kidney damage (rare), Coombs-positive hemolytic anemia, seizures
Aminoglycosides (gentamicin)	Gram-negative bacteria: *Escherichia coli, Klebsiella* and particularly *Pseudomonas aeruginosa*; also aerobic bacteria (not obligate/facultative anaerobes)	Binds to the bacterial ribosomal subunit, inhibiting the translocation of the peptidyl tRNA from the A-site to the P-site and also causing misreading of mRNA	Nephrotoxicity, neuromuscular blockade, vertigo, ototoxicity
Carbapenems (imipenem/cilastatin)	Both gram-positive and gram-negative organisms (bactericidal), useful for empiric broad-spectrum antibacterial coverage (Note: MRSA resistant to this class)	Inhibition of cell wall synthesis	Rash and allergy, gastrointestinal upset and diarrhea, nausea, seizures and headache

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Class (typical example)		Activity against	Mechanism of action	Potential side effects
Cephalosporins	First generation (cefazolin)	Gram-positive infections	Disrupt the synthesis of the peptidoglycan layer of bacterial cell walls	Gastrointestinal upset and diarrhea, nausea (if alcohol taken concurrently), allergic reactions including rash and pruritus
	Second generation (cefuroxime)	Reduced gram-positive coverage, improved gram-negative coverage		
	Third generation (cefixime)	Improved coverage of gram-negative organisms, except *Pseudomonas*; reduced gram-positive coverage		
	Fourth generation (cefepime)	*Pseudomonas*		
	Fifth generation (ceftaroline fosamil)	MRSA		

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Class (typical example)	Activity against	Mechanism of action	Potential side effects
Glycopeptides (vancomycin)	Gram-positive bacteria, including methicillin-resistant organisms (i.e. *Staphylococcus* and *Enterococcus*)	Inhibit later stages of bacterial cell wall peptidoglycan synthesis	Hypersensitivity, phlebitis, fever, chills, ototoxicity, nephrotoxicity and red man syndrome (vancomycin)
Lincosamides (clindamycin)	Gram-positive cocci, anaerobes	Bind to 50S subunit of bacterial ribosomal RNA, thereby inhibiting protein synthesis	Hypersensitivity reactions, pseudomembranous enterocolitis, myopathy
Lipopeptides (daptomycin)	Gram-positive organisms, including MRSA and vancomycin-resistant enterococci[18]	Binds to the plasma membrane and causes rapid depolarization, leading to inhibition of DNA, RNA and protein synthesis	Paresthesias or reversible paralysis (e.g. Bell's palsy)
Macrolides (erythromycin)	Aerobic gram-positive cocci and bacilli	Bind reversibly to 50S ribosomal subunit and inhibit protein synthesis	Hepatotoxicity, gastrointestinal toxicity, cardiac toxicity, auditory impairment, visual disturbance

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Class (typical example)	Activity against	Mechanism of action	Potential side effects
Monobactams (aztreonam)	Gram-negative pathogens, especially *Pseudomonas*	Disrupts cell wall synthesis	Nausea, vomiting, diarrhea
Oxazolidinones (linezolid)	Multidrug-resistant gram-positive cocci such as MRSA	Inhibit bacterial translation at the initiation phase of protein synthesis	Peripheral neuropathy, rash, nausea, vomiting, bone marrow suppression, tongue discoloration
Quinolones (ciprofloxacin)	Gram-negative organisms including activity against Enterobacteriaceae, *Staphylococcus aureus* (variable) and *S. epidermidis*	Inhibit the bacterial DNA gyrase or the topoisomerase IV enzyme, thereby inhibiting DNA replication and transcription	Nausea (rare), anaphylaxis, vasculitis, irreversible damage to central nervous system (uncommon), tendinopathies, hypo or hyperglycemia, photosensitivity, serum sickness-like reactions, increased Q-T intervals
Rifamycin (rifampin)	Bactericidal against many gram-positive and gram-negative bacteria	Inhibit protein synthesis by preventing transcription to RNA	Orange-red discoloration of body fluid, hepatitis, mild immunosuppression

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Class (typical example)	*Activity against*	*Mechanism of action*	*Potential side effects*
Streptogramins (quinupristin/dalfopristin)	Most gram-positive organisms: vancomycin-resistant *Enterococcus* (VRE) *faecium*, MRSA, MRSE	Bind to 50S subunit of bacterial ribosomal RNA thereby inhibiting protein synthesis[19]	Itching, pain, burning, vomiting and diarrhea, phlebitis, myalgia[20]
"Novel" Lipoglycopeptide (dalbavancin, oritavancin)[13,14]	New in vitro studies in animals demonstrate good activity against staphylococcal biofilms	Inhibits D-alanyl-D-alanine terminus of growing peptidogylcan	Rash, pruritus, ALT elevation, red-man syndrome (with rapid IV use)

Abbreviations: MRSA: methicillin-resistant *Staphylcoccus aureus*; MRSE: methicillin-resistant *Staphylcoccus epidermidis*

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ribosomal subunit to inhibit protein synthesis. These include aminoglycosides, macrolides, lincosamides, oxazolidinones and streptogramins. Quinolones and rifampin, on the other hand, affect bacterial DNA and RNA, respectively, to prevent propagation of the microbe. Lipopeptides inhibit protein, DNA and RNA synthesis by disrupting the plasma membrane.[4]

With the rapid emergence of multidrug-resistant bacteria in hospitals and healthcare facilities, extreme caution should be exercised in selecting the appropriate antibiotic or combination of antibiotics. This is especially true in polymicrobial infections where isolates often contain enterococcal species, gram-negative bacilli, methicillin-resistant *S. aureus* (MRSA) and anaerobic bacteria.[5] Thus, the treating surgeon should ensure the aforementioned microbes are adequately covered when suspecting a polymicrobial infection. Certain antibiotic combinations may offer a synergistic effect and decrease the chance of drug resistance. An example of such synergy is highlighted in polymicrobial infections with the use of a first-generation cephalosporin, like cefazolin, which offers great gram-positive and negative bacilli coverage, can be coupled with an aminoglycoside like gentamicin, which also offers gram-negative coverage as well as a synergistic effect to cover enterococcal species.[6]

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Rothman Institute Current Practices

- Bacterial cultures and specimens are always obtained before antibiotic initiation.
- Institutional antimicrobial sensitivities are utilized prior to initiation of antibiotics.

Antibiotic Use in Cement and Intra-articular Injection

An alternative means of localized antibiotic delivery to an infected joint includes utilizing antibiotic cement as a delivery mechanism. The following antibiotics have been found to be heat-stable and can be utilized in antibiotic cement: penicillin (including cefazolin), erythromycin, cephalosporin (cefotaxime), aminoglycosides (gentamicin, tobramycin), vancomycin, fluoroquinolones (ciprofloxacin), clindamycin, daptomycin, teicoplanin, amphotericin B. Further details on the use of antibiotic spacers and their drug elution properties can be found in Chapter 31. Other surgeons have treated chronically infected TKA and THA cases with intra-articular infusions of vancomycin, utilizing a surgically implanted Hickman catheter with limited success.[7-9] At present, the international consensus is not to utilize this technique given the limited case series documenting its usage and associated potential risks with this practice.[10]

CHALLENGES

A significant challenge often encountered in the treatment of PJI is the presence of biofilms, which protects the bacteria from the host immune system and systemic antibiotics. These infections are difficult to treat and are characterized by chronicity, recurrence, antibiotic resistance, poor prognosis and high economic cost. As a result, antimicrobial therapy is often unsuccessful unless the biofilm is physically disrupted by surgical debridement.[11] The glycocalyx is positively charged (carbohydrate residues on its exterior), deeming it relatively impenetrable to the positively charged hydrophilic antibiotics, such as aminoglycosides and polypeptides.

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Other classes of antibiotics like the β-lactams, quinolones and macrolides, are better suited to penetrate a biofilm.[12]

Novel antimicrobials are being investigated to address the burden of bacterial biofilms and the increasing emergence of multiresistant strains, though the majority of these have been in vitro animal studies.[11,13,14] An example of such novel drug is dalbavancin, an inhibitor of the D-alanyl-D-alanine terminus of the peptidoglycan with bactericidal properties. In an in vitro animal study, dalbavancin exhibited good activity against biofilms of 171 staphylococci associated with PJI.[13] Another agent, BAG-S53P4 (BonAlive® Biomaterials, Turku, Finland) is a bone substitute with osteoconductive and antimicrobial properties, and in in vitro studies, significant biofilm reduction was observed in multiresistant *S. epidermidis*, *A. baumannii* and *K. pneumoniae* on titanium substrates.[11]

In the search for alternative antimicrobials to address the increasing trends in multiresistant organisms, bacteriophage therapy (phage therapy) has recently resurfaced in the literature. Bacteriophages are viruses that act as obligate organisms, occupying bacterial cells, injecting their genomic material, and overtaking the host bacteria's metabolic machinery. Consequently, these phages can replicate and produce specific proteins that result in lysis of the bacterial cell wall and degradation of the polysaccharide matrix of biofilms.[15] Replication of bacteriophages in vivo could make phage therapy valuable, especially if the vasculature around the infection is poor and adjacent to a biofilm layer, as usually seen in infections associated with orthopedic implants.[16] In an in vivo experimental implant-related infection model in rat tibiae, Yilmaz

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et al. reported that when conventional antibiotics and phage therapy were each used individually as monotherapy, both were able to reduce the viable bacterial count. However, the combination of conventional antibiotics and bacteriophages resulted in a more significant reduction in biofilm formation, likely from a synergistic effect.[16] In another in vivo mice model, the use of a local delivery system consisting of *S. aureus* specific bacteriophage along with linezolid (incorporated in a biopolymer) in the intramedullary canal of MRSA-inoculated mice femur bone was explored.[17] The authors reported that mice undergoing "dual therapy" with both phage as well as linezolid showed the maximum reduction in bacterial adherence, associated inflammation of the joint, as well as faster resumption of locomotion and limb motor function. Furthermore, there was no development of resistant strains.[17] Taken together, the results of these studies suggest that the synergistic use of phage therapy and conventional antibiotics may help treat some biofilm-forming prosthetic infections, but further studies regarding the optimum dose and duration of treatment are needed before clinical use can be considered.

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PERIPROSTHETIC JOINT INFECTION

Updated Practical Management Guide

This book represents a concise, yet comprehensive, review of periprosthetic joint infection (PJI). In addition to an up-to-date overview of the clinical and operative aspects of orthopedic management for PJI, the book covers topics ranging from healthcare policy to novel genomic technologies that could impact patients with PJI. While the book could serve the young surgeon or trainee by providing an overview of PJI, it is meant to serve as a quick reference guide for the busy clinician caring for patients with PJI.

Salient Features

- Concise guide to the practical management of infections following orthopedic procedures.
- Designed to help answer clinicians' questions regarding the prevention and treatment of periprosthetic joint infection.
- Organized for rapid review, featuring up-to-date citations and current Rothman Institute Protocols, Practices, and Controversies.



Javad Parvizi MD is James Edward Professor of Orthopedic Surgery at the Rothman Institute and Thomas Jefferson University in Philadelphia. He is the Director and Vice Chairman of research. His clinical practice involves reconstruction of complex pelvis, hip, and knee conditions with special emphasis on joint preservation and periprosthetic joint infection. He has performed over 1000 joint preservation and 5000 joint arthroplasty procedures. He performs around 600 surgical procedures per year. He is a member of numerous National and International Societies and has served in leadership roles in a large number of national committees. He chaired the workgroup of the MSIS workshop that proposed the MSIS definition of PJI in 2010 that has been adapted by the Center for Disease Control as the definition of PJI. He was the president of Musculoskeletal Infection Society in 2013 and as part of his presidential initiative held the International Consensus Group (ICG) on Periprosthetic Joint Infection that brought together over 300 world experts on PJI from 52 countries and 130 different societies. He is a member of various editorial boards for orthopedic journals. He has received wide recognition for his clinical and basic science research including numerous awards from The Hip Society, The Knee Society, The American Association of Hip and Knee Surgeons, The MSIS, and numerous other organizations. He was given the best researcher of the year award in 2011 by the Arthritis Foundation. He has authored over 600 peer-reviewed manuscripts, 120 book chapters, and is the editor of 18 textbooks in orthopedics.

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