[4] Tornero E, Morata L, Martínez-Pastor JC, Angulo S, Combalia A, Bori G, et al. Importance of selection and duration of antibiotic regimen in prosthetic joint infections treated with debridement and implant retention. J Antimicrob Chemother. 2016;71:1395–1401. doi:10.1093/jac/dkv481.
[5] Senneville E, Joulie D, Legout L, Valette M, Dezèque H, Beltrand E, et al. Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to Staphylococcus aureus. Clin Infect Dis. 2011;53:334–340. doi:10.1093/cid/cir402.
[6] Peel TN, Buising KL, Dowsey MM, Aboltins CA, Daffy JR, Stanley PA, et al. Outcome of debridement and retention in prosthetic joint infections by methicillin-resistant staphylococci, with special reference to rifampin and fusidic acid combination therapy. Antimicrob Agents Chemother. 2013;57:350–355. doi:10.1128/AAC.02061-12.
[7] Berdal J-E, Skråmm I, Mowinckel P, Gulbrandsen P, Bjørnholt JV. Use of rifampicin and ciprofloxacin combination therapy after surgical debridement in the treatment of early manifestation prosthetic joint infections. Clin Microbiol Infect. 2005;11:843–845. doi:10.1111/j.1469-0691.2005.01230.x.
[8] Mont MA, Waldman B, Banerjee C, Pacheco IH, Hungerford DS. Multiple irrigation, debridement, and retention of components in infected total knee arthroplasty. J Arthroplasty. 1997;12:426–433.
[9] Westberg M, Grøgaard B, Snorrason F. Early prosthetic joint infections treated with debridement and implant retention: 38 primary hip arthroplasties prospectively recorded and followed for median 4 years. Acta Orthop. 2012;83:227–232. doi:10.3109/17453674.2012.678801.
[10] Kuiper JWP, Vos SJC, Saouti R, Vergroesen DA, Graat HCA, Debets-Ossenkopp YJ, et al. Prosthetic joint-associated infections treated with DAIR (debridement, antibiotics, irrigation, and retention): analysis of risk factors and local antibiotic carriers in 91 patients. Acta Orthop. 2013;84:380–386. doi:10.3109/17453674.2013.823589.
[11] Matsumoto T, Ishida K, Tsumura N, Nagai K, Muratsu H, Hida Y, et al. Treatment of 50 deep infections after total knee arthroplasty. Orthopedics. 2015;38:e529-e535. doi:10.3928/01477447-20150603-63.
[12] Tsukayama DT, Estrada R, Gustilo RB. Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. J Bone Joint Surg Am. 1996;78:512–523.
[13] Giulieri SG, Graber P, Ochsner PE, Zimmerli W. Management of infection associated with total hip arthroplasty according to a treatment algorithm. Infection. 2004;32:222–228. doi:10.1007/s15010-004-4020-1.
[14] Kessler B, Knupp M, Graber P, Zwicky L, Hintermann B, Zimmerli W, et al. The treatment and outcome of peri-prosthetic infection of the ankle: a single cohort-centre experience of 34 cases. Bone Joint J. 2014;96-B:772–777. doi:10.1302/0301-620X.96B6.33298.
[15] Letouvet B, Arvieux C, Leroy H, Polard JL, Chapplain JM, Common H, et al. Predictors of failure for prosthetic joint infections treated with debridement. Med Mal Infect. 2016;46:39–43. doi:10.1016/j.medmal.2015.11.007.
[16] Sendi P, Lötscher PO, Kessler B, Graber P, Zimmerli W, Clauss M. Debridement and implant retention in the management of hip periprosthetic joint infection. Bone Joint J. 2017;99-B:330–336. doi:10.1302/0301-620X.99B3.BJJ-2016-0609.R1.
[17] Spormann C, Achermann Y, Simmen BR, Schwyzer H-K, Vogt M, Goldhahn J, et al. Treatment strategies for periprosthetic infections after primary elbow arthroplasty. J Shoulder Elbow Surg. 2012;21:992–1000. doi:10.1016/j.jse.2011.10.007.
[18] Weenders SGM, Nijhof MW, Schimmel JJP, Goosen JHM. Debridement, antibiotics and implant retention in early periprosthetic joint infection after primary total hip arthroplasty: 88 percent survival after two years follow-up. Acta Orthop Belg. 2016;82:530–538.
[19] Choi H-R, von Knoch F, Kandil AO, Zurakowski D, Moore S, Malchau H. Retention treatment after periprosthetic total hip arthroplasty infection. Int Orthop. 2012;36:723–729. doi:10.1007/s00264-011-1324-5.
[20] Corona Pérez-Cardona PS, Barro Ojeda V, Rodriguez Pardo D, Pigrau Serrallach C, Guerra Farfán E, Amat Mateu C, et al. Clinical experience with daptomycin for the treatment of patients with knee and hip periprosthetic joint infections. J Antimicrob Chemother. 2012;67:1749–1754. doi:10.1093/jac/dks119.
[21] Zhang C, Yan CH, Chan PK, Ng FY, Chiu KY. Polyethylene insert exchange is crucial in debridement for acute periprosthetic infections following total knee arthroplasty. J Knee Surg. 2017;30:36–41.
[22] Dennison T, Alentorn-Geli E, Assenmacher AT, Sperling JW, Sánchez-Sotelo J, Cofield RH. Management of acute or late hematogenous infection after shoulder arthroplasty with irrigation, débridement, and component retention. J Shoulder Elbow Surg. 2017;26:73–78. doi:10.1016/j.jse.2016.05.018.
[23] Hyman JL, Salvati EA, Laurencin CT, Rogers DE, Maynard M, Brause DB. The arthroscopic drainage, irrigation, and débridement of late, acute total hip arthroplasty infections: average 6-year follow-up. J Arthroplasty. 1999;14:903–910.
[24] Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56:e1–e25. doi:10.1093/cid/cis803.
[25] Piso RJ, Elke R. Antibiotic treatment can be safely stopped in asymptomatic patients with prosthetic joint infections despite persistent elevated C-reactive protein values. Infection. 2010;38:293–296. doi:10.1007/s15010-010-0019-y.
[26] Byren I, Bejon P, Atkins BL, Angus B, Masters S, McLardy-Smith P, et al. One hundred and twelve infected arthroplasties treated with "DAIR" (debridement, antibiotics and implant retention): antibiotic duration and outcome. J Antimicrob Chemother. 2009;63:1264–1271. doi:10.1093/jac/dkp107.
[27] Fink B, Schuster P, Schwenninger C, Frommelt L, Oremek D. A A standardized regimen for the treatment of acute postoperative infections and acute hematogenous infections associated with hip and knee arthroplasties. J Arthroplasty. 2017;32:1255–1261.. doi:10.1016/j.arth.2016.10.011.
[28] Triantafyllopoulos GK, Soranoglou V, Memtsoudis SG, Poultsides LA. Implant retention after acute and hematogenous periprosthetic hip and knee infections: whom, when and how? World J Orthop. 2016;7:546–552. doi:10.5312/wjo.v7.i9.546.
[29] Lee HD, Prashant K, Shon WY. Management of periprosthetic hip joint infection. Hip Pelvis. 2015;27:63–71. doi:10.5371/hp.2015.27.2.63.
[30] Van Kleunen JP, Knox D, Garino JP, Lee GC. Irrigation and debridement and prosthesis retention for treating acute periprosthetic infections. Clin Orthop Relat Res. 2010;468:2024–2028. doi:10.1007/s11999-010-1291-y.
[31] Koyonos L, Zmistowski B, Della Valle CJ, Parvizi J. Infection control rate of irrigation and débridement for periprosthetic joint infection. Clin Orthop Relat Res. 2011;469:3043–3048. doi:10.1007/s11999-011-1910-2.
[32] Koh IJ, Han SB, In Y, Oh KJ, Lee DH, Kim TK, et al. Open debridement and prosthesis retention is a viable treatment option for acute periprosthetic joint infection after total knee arthroplasty. Arch Orthop Trauma Surg. 2015;135:847–855. doi:10.1007/s00402-015-2237-3.
[33] Farhad R, Roger P-M, Albert C, Pélligri C, Touati C, Dellamonica P, et al. Six weeks antibiotic therapy for all bone infections: results of a cohort study. Eur J Clin Microbiol Infect. 2010;29:217–222. doi:10.1007/s10096-009-0842-1.
[34] Armstrong MD, Carli AV, Abdelbary H, Poitras S, Lapner P, Beaulé PE. Tertiary care centre adherence to unified guidelines for management of periprosthetic joint infections: a gap analysis. Can J Surg J Can Chir. 2018;61:34–41.
[35] Bernard L, Legout L, Zürcher-Pfund L, Stern R, Rohner P, Peter R, et al. Six weeks of antibiotic treatment is sufficient following surgery for septic arthroplasty. J Infect. 2010;61:125–132. doi:10.1016/j.jinf.2010.05.005.
[36] Puhto A-P, Puhto T, Syrjala H. Short-course antibiotics for prosthetic joint infections treated with prosthesis retention. Clin Microbiol Infect. 2012;18:1143–1148. doi:10.1111/j.1469-0691.2011.03693.x.
[37] Chaussade H, Uçkay I, Vuagnat A, Druon J, Gras G, Rosset P, et al. Antibiotic therapy duration for prosthetic joint infections treated by Debridement and Implant Retention (DAIR): Similar long-term remission for 6 weeks as compared to 12 weeks. Int J Infect Dis. 2017;63:37–42. doi:10.1016/j.ijid.2017.08.002.
[38] Lora-Tamayo J, Euba G, Cobo J, Horcajada JP, Soriano A, Sandoval E, et al. Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomised clinical trial. Int J Antimicrob Agents. 2016;48:310–316. doi:10.1016/j.ijantimicag.2016.05.021.

Authors: Camelia Marculescu, Silvano Esposito

QUESTION 13: What is the most effective combination of antibiotics in the treatment of acute periprosthetic joint infections (PJIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) that has undergone surgical management with debridement, antibiotics and implant retention (DAIR)?

RECOMMENDATION: We recommend a combination of a parenteral antibiotic plus oral rifampin for one to six weeks, followed by rifampin and a companion highly bioavailable oral drug for additional three months, depending on the susceptibility profile of MRSA, patient tolerability and side effect profile.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 10%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Treatment of MRSA PJI that has undergone DAIR remains challenging. An ideal combination of antimicrobial therapy has not been established. Treatment should take into account antimicrobial susceptibilities of MRSA and tailored accordingly. Whenever possible, rifampin-based combinations should be used, but rifampin alone should never be used due to the rapid development of resistance. Rifampin-based combination therapy regimens have been shown to be effective in eradication of staphylococcal organisms and cure PJIs. A widely used algorithm by Zimmerli and the Infectious Diseases Society of America (IDSA) guidelines recommend a quinolone–rifampin combination for susceptible *Staphylococcus aureus* strains and cure rates of 70 - 100% have been reported [1–3]. The duration of antimicrobial therapy for PJI managed with DAIR has not been well established. We recommend two to six weeks of parenteral antimicrobial therapy in combination with rifampin 300 to 450 mg orally twice a day, followed by rifampin plus a susceptible companion oral drug (such as trimethoprim-sulfamethoxazole, ciprofloxacin or levofloxacin, a tetracycline, fusidic acid) depending on the individual tolerance, side effect profile and antimicrobial susceptibility testing [1,4,5]. Certain highly bioavailable drugs such as fluoroquinolones, rifampin, linezolid and trimethoprim-sulfamethoxazole, reach levels in bone that exceed the minimal inhibitory concentration (MICs) for most organisms [6].

Zimmerli et al. have suggested a duration of therapy of three months for total hip arthroplasties (THAs) PJIs and six months for total knee arthroplasties (TKAs) PJIs [1,3]. Shorter courses of therapy (6 vs. 12 weeks) were studied in PJIs treated with DAIR. However, in this study by Chaussade et al. the presence of MRSA, which comprised only 13.8% of infections, was associated with a poorer outcome (remission in 41.7 vs. 73.3% for other pathogens [7]. Chronic oral suppression with trimethoprim-sulfamethoxazole, minocycline or doxycycline based on in vitro-susceptibilities and individual side effect profile and tolerance may be considered following the above regimens and should be reserved for patients who are unsuitable or refuse further surgical therapy. The duration of chronic oral suppression remains unknown.

While the current IDSA guidelines recommend vancomycin as the primary parenteral agent for treatment of MRSA infections, its utility has been questioned due to increasing reports of heterogeneous resistance, treatment failure, and nephrotoxicity. Vancomycin is not bactericidal against small colony variants (SCV) of MRSA. Moreover, Lenhard et al. showed recently in mixed-population experiments that vancomycin favorably selects for the growth of the SCV subpopulation [6]. Therefore, clinicians should consider glycopeptide combination regimens or alternative antimicrobials in patients with severe persistent MRSA infections in which the SCV phenotype may play a role.

In vitro analyses have identified fluoroquinolones and oritavancin as retaining high levels of vancomycin in vitro against SCVs and β-lactam combinations with daptomycin may offer a new option for combating SCVs [8,9,10]. While optimal treatment for infections caused by staphylococcal SCVs is not known, combination therapy including either rifampin or oritavancin appears to be particularly effective at eradicating intracellular SCVs [11].

REFERENCES

[1] Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al.Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56:e1–e25. doi:10.1093/cid/cis803.

[2] Trampuz A, Zimmerli W. Antimicrobial agents in orthopaedic surgery: Prophylaxis and treatment. Drugs. 2006;66:1089–1105.

[3] Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004;351:1645–1654. doi:10.1056/NEJMra040181.

[4] Leijtens B, Elbers JBW, Sturm PD, Kullberg BJ, Schreurs BW. Clindamycin-rifampin combination therapy for staphylococcal periprosthetic joint infections: a retrospective observational study. BMC Infect Dis. 2017;17:321. doi:10.1186/s12879-017-2429-2.

[5] Peel TN, Buising KL, Dowsey MM, Aboltins CA, Daffy JR, Stanley PA, et al. Outcome of debridement and retention in prosthetic joint infections by methicillin-resistant staphylococci, with special reference to rifampin and fusidic acid combination therapy. Antimicrob Agents Chemother. 2013;57:350–355. doi:10.1128/AAC.02061-12.

[6] Lenhard JR, von Eiff C, Hong IS, Holden PN, Bear MD, Suen A, et al. Evolution of Staphylococcus aureus under vancomycin selective pressure: the role of the small-colony variant phenotype. Antimicrob Agents Chemother. 2015;59:1347–1351. doi:10.1128/AAC.04508-14.

[7] Chaussade H, Uçkay I, Vuagnat A, Druon J, Gras G, Rosset P, et al. Antibiotic therapy duration for prosthetic joint infections treated by Debridement and Implant Retention (DAIR): Similar long-term remission for 6 weeks as compared to 12 weeks. Int J Infect Dis. 2017;63:37–42. doi:10.1016/j.ijid.2017.08.002.

[8] Begic D, von Eiff C, Tsuji BT. Daptomycin pharmacodynamics against Staphylococcus aureus hemB mutants displaying the small colony variant phenotype. J Antimicrob Chemother. 2009;63:977–981. doi:10.1093/jac/dkp069.

[9] Mehta S, Singh C, Plata KB, Chanda PK, Paul A, Riosa S, et al. β-Lactams increase the antibacterial activity of daptomycin against clinical methicillin-resistant Staphylococcus aureus strains and prevent selection of daptomycin-resistant derivatives. Antimicrob Agents Chemother. 2012;56:6192–6200. doi:10.1128/AAC.01525-12.

[10] Ortwine JK, Werth BJ, Sakoulas G, Rybak MJ. Reduced glycopeptide and lipopeptide susceptibility in Staphylococcus aureus and the "seesaw effect": Taking advantage of the back door left open? Drug Resist Updat.2013;16:73–79. doi:10.1016/j.drup.2013.10.002.

[11] Massey RC, Peacock SJ. Antibiotic-resistant sub-populations of the pathogenic bacterium Staphylococcus aureus confer population-wide resistance. Curr Biol. 2002;12:R686-R687.

Authors: Jean Yombi, Marjan Wouthuyzen-Bakker

QUESTION 14: What antibiotic therapy (agent, route, dose and duration) is recommended for gram-negative acute periprosthetic joint infections (PJIs) being treated with debridement, antibiotics and implant retention (DAIR)?

RECOMMENDATION: Following surgical intervention (DAIR), gram-negative acute PJI patients should also receive antibiotic treatment for 6 to 12 weeks based on the type of organism. In fluoroquinolone-susceptible cases, the recommended antibiotic agent is a fluoroquinolone.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 11%, Abstain: 6% (Super Majority, Strong Consensus)