Review Article

Antibiotic Stewardship for Total Joint Arthroplasty in 2020

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Abstract

Projections indicate an increase in primary and revision total joint arthroplasties (TJAs). Periprosthetic joint infections (PJIs) are one of the most common and devastating causes of failure after TJA. Perioperative administration of systemic and/or local antibiotics is used for both prophylaxis and treatment of PJI. Antibiotic stewardship is a term that has been met with clinical acceptance and success in other specialties of medicine. Identifying antibiotic best practice use in the fight against PJI is limited by studies that are extremely heterogeneous in their design. Variations in studies include antibiotic selection and duration, surgical débridement steps, type of antibiotic delivery (intra-articular, local, intravenous, and prolonged oral), mix of primary and revision surgery cohorts, both hip and knee cohorts, infecting organisms, and definitions of treatment success/failure. This review highlights the current challenges of antibiotic stewardship in TJA.

Periprosthetic joint infections (PJIs) are one of the most common causes for failure after primary and revision total joint arthroplasties (TJAs).[1,2] Studies have demonstrated that 5-year mortality rates after PJI are worse than two of the top five most common cancers and have a threefold increased mortality when compared with aseptic revision.[3,4] The reported successful eradication rates of PJI in the past decade range from 66% to 95% after two-stage exchange arthroplasty, depending on how success is defined.[5]

Antibiotic administration is a standard practice for both prophylaxis against and treatment of PJI after TJA. However, the Centers for Disease Control (CDC) reports that a large percentage of all antibiotics prescribed in acute care hospitals is estimated to be unnecessary or inappropriate.[6] This can lead to an increase in antibiotic resistant organisms and expose patients to side effects without providing clinical benefit. Antibiotic stewardship programs were designed to improve the appropriate use of antibiotics by optimizing antibiotic selection, dose, and duration while minimizing potential adverse events and antibiotic resistance.[7] Despite improvements in the standardization of infection treatment and prophylaxis at the hospital level, some measures implemented through antibiotic stewardship programs may conflict with more recent evidence focused on TJA. A proper perspective of antibiotic stewardship in TJA requires an understanding of the unique issues surrounding PJI.[8] Thus, the purpose of this review is to review the most up-to-date literature regarding perioperative antibiotic prophylaxis, local antibiotic delivery, two-stage exchange arthroplasty, and antibiotic use associated with débridement, irrigation, and implant retention (DAIR).

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Preoperative Prophylactic Antibiotics

In 2017, the CDC recommended against postoperative antibiotics for clean-contaminated surgery, including TJA, proposing a significant practice shift.[9] However, these recommendations were formulated mostly on general surgical procedures, and the few orthopaedic studies included in the review were outdated. However, a recent retrospective study reviewing the postoperative antibiotic usage after TJA has provided some evidence to support the CDC's decision.[10] Considering that any true same day TJA procedure will only receive one dose of perioperative intravenous antibiotic, this issue should be investigated further.

A recent meta-analysis was done to determine the efficacy and duration of surgical antibiotic prophylaxis in TJA on surgical site infections (SSIs) and subsequent rate of PJI comparing single preoperative dose with continued postoperative prophylactic antibiotic dosing. The pooled effect for this comparison was 0.96 (95% confidence interval [CI] 0.73-1.26), suggesting no difference in effect. Similarly, no difference was observed in pooled effect in patients who received prophylactic antibiotics for <24 hours or >24 hours. However, the authors note that the studies included in this meta-analysis were underpowered, highly heterogeneous regarding duration and antibiotic choice, and biased.[11] A recent retrospective review of the Veteran's Administration Surgical Quality Improvement Project (VASQIP) database was performed to identify the relationship between duration of surgical antimicrobial prophylaxis and postoperative SSIs after major cardiac, colorectal, vascular, and TJA procedures.[12] Seventy nine thousand fifty-eight patients were eligible for inclusion in the study, with 96.3% men, 27.3% diabetic patients, and 29.1% smokers.[12] The authors found that antimicrobial prophylaxis administered for >24 hours postoperatively did not lead to SSI reduction and that courses >24 hours were independently associated with an increased risk of postoperative acute kidney injury and *Clostridium difficile* (*C. diff*) infection, which increased with each additional day of antibiotics.[12] Given the retrospective nature of this study, however, it is unclear why antibiotic doses were extended in these particular patients, and the study cohort were predominantly male veterans making it difficult to draw definitive conclusions. Furthermore, the orthopaedic data did not detail the exclusion of PJI, which would necessitate extended IV antibiotic use and would confound the authors' findings. The results of this retrospective database review may not be reflective of common elective TJA patients, and the results should be interpreted with caution.[12] A prospective, multicenter, randomized controlled trial at Duke University is currently underway to better understand the risks and benefits of single preoperative versus multiple-dose perioperative antibiotic prophylaxis in TJA (Table 1).

The current TJA antibiotic prophylaxis guidelines recommend weight-based antibiotics consisting of the following: cefazolin 2 g (60 to 120 kg) or 3 g (>120 kg), cefuroxime 1500 mg, vancomycin 15 mg/kg (up to 2 g) for patients with beta-lactam allergy or current methicillin-resistant *Staphylococcus aureus* (MRSA) carriers, or clindamycin 900 mg for patients with beta-lactam allergy.[8] Some authors have reported that both vancomycin and clindamycin used in isolation for TJA prophylaxis may lead to increased rates of PJI, but this may be due to subtherapeutic dosing at least regarding vancomycin.[13,14] Kheir et al evaluated 1,828 patients who underwent primary TJA and found that 2% (32/1828) of patients who received vancomycin as preoperative prophylaxis subsequently developed PJI, compared with 1% (62/2,810) who received cefazolin (odds ratio [OR], 1.587 [1.004-2.508]; P = 0.048).[15] In procedures where vancomycin was used as monotherapy, only 28% were adequately dosed. A concerning 94% had received a fixed dose of 1 g vancomycin, resulting in 64% of these patients being underdosed.[15] Similar adherence issues were reported in Australia by Chandrananth et al[16] with a preoperative dose of any indicated antibiotic. These studies highlight the importance of guideline adherence and illustrate the need to appropriately dose antibiotics in the perioperative period. Subtherapeutic dosing may lead to an increased risk of infection and possible contribution to bacterial resistance.

Antibiotic stewardship controversy exists regarding primary TJA patients who are at high risk of PJI, including smokers, diabetic patients and obese patients.[17,18] Research efforts have investigated administering extended oral antibiotics for high-risk patients undergoing primary TJA. Inabathula et al[19] found a fourfold increase in 90-day postoperative PJI in patients at high risk without prolonged antibiotic therapy versus those who received extended oral antibiotics for at least 7 days postoperatively. One patient in the extended antibiotic group reported an adverse effect of candidiasis. Risks associated with prolonged antibiotic therapy, including negative systemic effects and contribution to antimicrobial resistance, remain to be defined in this cohort. Although this study provides evidence for extended prophylactic antibiotics for high-risk patients, it remains controversial, and more research is needed to validate this treatment.

Another area where TJA antibiotic stewardship programs require better evidence includes prophylactic dual

Table 1

Currently Active Clinical Trials

Title, Study Design, Targeted Completion Date	Site & Clinical Trials ID
Antibiotic prophylaxis in patients undergoing elective TKA-multicenter trial; prospective, randomized, open-label, controlled multicenter trial; October 2022	USA—Duke University; NCT03283878
Vancomycin powder and dilute povidone-iodine lavage for infection prophylaxis in high-risk total joint arthroplasty; prospective, randomized, controlled, open-label, parallel four-arm design, multicenter study; January 2025	USA—NYU Langone Health; NCT04075526
Quality of life assessment in patients undergoing prolonged suppressive antibiotherapy for prosthetic joint infection; prospective case series; September 2022	France—Groupe Hospitalier Diaconesses Croix Saint-Simon; NCT02805803
Short or Long Antibiotic Regimes in Orthopaedics (SOLARIO); noninferiority randomized controlled trial, multicenter; March 2022	UK—Oxford University Hospitals NHS Trust; NCT03806166
Oral antibiotics reduce reinfection after two-stage exchange; prospective randomized controlled trial, multicenter; Study completed according to contact with senior author, results to be published	USA—Rush University Medical Center; ID n/a, Midterm results published in Frank JM, et al; Clin Orthop Relat Res 2017; 475:56-61
Single vs. two-stage irrigation and debridement with prosthetic retention for PJI through the use of intraosseous antibiotics; Prospective randomized controlled trial, multicenter; June 2022	USA—OrthoCarolina; NCT03713528
Intraosseous vancomycin in primary total hip arthroplasty; prospective randomized controlled trial; December 2020	USA—The Methodist Hospital System; NCT04042233
Safety and efficacy in patients treated for hip or knee PJI with vancomycin and tobramycin joint irrigation; prospective, single-arm, open-label, multicenter, interventional trial; November 2020	USA—OrthoCarolina; NCT03721328
One stage versus two stage for periprosthetic hip and knee infection; prospective, randomized, controlled, parallel two-arm design, multicenter study; December 2021	USA—OrthoCarolina; NCT02734134

antibiotic therapy. Dual antibiotic therapy (ie, vancomycin and cefazolin) before surgery may have protective benefits against PJI in patients who are at high risk. High-risk populations may include patients with a known history of a positive MRSA screen, known MRSA infection, healthcare workers, immunosuppressed patients, or institutions with high gram-negative PJIs.[20] There was a "strong consensus" (80%) panel agreement at the 2018 International Consensus Meeting (ICM) on Prosthetic Joint Infection for dual antibiotic therapy.[8] No randomized controlled trials existed on the topic, and current evidence is limited to 13 retrospective studies meeting the ICM's inclusion and exclusion criteria. A recent retrospective study evaluated 1,997 primary TJA patients who underwent surgical prophylaxis with either cefazolin alone or cefazolin with vancomycin (infusion begun within 45 minutes before incision or greater than 45 minutes before incision). They found that the rate of PJI was statistically ($P < 0.01$) lower for patients who underwent dual therapy with vancomycin infusion at least 45 minutes before making incision (0.2%) compared with cefazolin alone (2.1%), and cefazolin and vancomycin infused less than 45 minutes before incision (2.9%). They did not find a significant difference in renal toxicity between the two groups.[21] However, this study was limited by its retrospective design, lack of protocols and standardization, and the fact that vancomycin dosing was fixed at 1 g and not weight based.

Local Antibiotic Delivery

The local administration of antibiotics is an attractive adjunct to PJI prevention and treatment. Local antibiotic delivery potentially allows for much higher local antibiotic concentrations. These concentrations are many times higher than the minimal inhibitory concentration, while potentially avoiding systemic adverse effects and toxicity associated with systemic intravenous (IV) administration. The delivery of antibiotics through cement will be detailed in a separate review article and was purposefully omitted from this review.

Please refer to Table 2 for a summary of local antibiotic delivery studies.

Local Antibiotic Delivery with Powder

The use of powdered intrawound vancomycin has become routine practice for some spine and TJA surgeons. There is a paucity of high-quality TJA literature, with most retrospective studies favoring the use of intrawound vancomycin powder. A recent systematic review and meta-analysis of intrawound vancomycin use in TJA demonstrated a statistically significant decrease in PJI in both primary (OR = 0.44, P = 0.0046) and revision TJA (OR = 0.28, P = 0.0013).[22] The authors concluded that intrawound vancomycin may decrease the rate of PJI but prospective randomized controlled trials are needed.[22] Therefore, the American Association of Hip and Knee Surgeons (AAHKS) recently awarded a grant for a randomized prospective trial of vancomycin intrawound powder and dilute povidone-iodine lavage (VIP) (Table 1).

Local Antibiotic Delivery with Intraosseous

Intraosseous regional administration (IORA) of antibiotics is a relatively new concept in TJA that is used to increase the local tissue concentration of prophylactic antibiotics. Young et al[27] performed a randomized trial to assess whether low-dose IORA vancomycin could achieve tissue concentrations equal or superior to systemic administration at the time of TKA. Thirty patients undergoing primary TKA were randomized to receive either 1 g IV vancomycin or 250 or 500 mg of IORA vancomycin, performed via bolus injection into a tibial intraosseous cannula below an inflated thigh tourniquet before incision. The mean subcutaneous fat vancomycin concentration was 3.2 μg/g in the IV group, 14 μg/g in the 250 mg IORA group, and 44 μg/g in the 500 mg IORA group ($P < 0.01$). For bone, the mean concentrations were 4.0 μg/g,16 μg/g, and 38 μg/g, in the IV, 250 mg IORA, and 500 mg IORA administration groups, respectively ($P < 0.01$). In a separate study, Chin et al[28] found 5 to 9 times higher vancomycin concentrations with IORA compared with systemic administration, and there were no adverse events or infections seen in the IORA group. However, the study design was not powered to show a difference in infection rates between IORA and systemic vancomycin.

Local Antibiotic Delivery with Calcium Sulfate Beads

Antibiotic impregnated calcium sulfate (AICS) beads may be a useful adjunctive antibiotic carrier in the treatment of PJI. Recent studies have demonstrated wound complication rates of 1.7% to 3.2% which are lower than historically seen with other antibiotic bead formulations.[29] A study performed by Flierl et al[30] retrospectively examined a cohort of 32 patients with acute hematogenous (18 patients, one bilateral) or acute postoperative (14 patients) PJI treated with DAIR and AICS beads. At a mean of 12.7 months, 47% acute hematogenous and 50% acute postoperative PJIs failed after DAIR and AICS treatment.[30] Although the authors used the ICM definition of acute PJI (<6 weeks of symptoms), different thresholds defining "acute" have been suggested in the literature and have not been well validated which is another area of opportunity for further research.

Gramlich et al[31] evaluated the use of AICS beads in combination with DAIR for elderly, multimorbid patients, unable to undergo exchange arthroplasty for chronic late onset PJI. All 42 patients (45.2% THA, 28.6% TKA, 26.2% knee arthrodesis) had previously undergone revision arthroplasty for infection and were suffering recurrent or sustained PJI. Each patient underwent DAIR with placement of pathogen-specific AICS and 6 weeks of pathogen-specific systemic IV antimicrobial therapy. At the mean follow-up of 23 months, 73.8% of patients had achieved infection control, whereas 26.2% had failed and either underwent another DAIR procedure and chronic antibiotic suppression (11.9%) or amputation (14.2%). However, the authors concluded that when considering the mortality of two-stage revision, arthroplasty has been reported to be as high as 36.7% in patients older than 80 years DAIR with AICS may be a viable adjunct based on this small retrospective review.[31] Long-term suppressive antibiotic use was not detailed in this report.

Local Antibiotic Delivery with Intra-articular Catheters

Local intra-articular (IA) antibiotic infusion with a Hickman catheter has been described by Whiteside et al in both TKA and THA PJI.[32-34] In 2011, they described a 100% clearance rate in 18 patients with MRSA TKA PJI treated with a single-stage exchange arthroplasty and IA vancomycin 500 mg once or twice daily for six weeks. Systemic antibiotics were avoided after 24 hours.[33] In 2012, Whiteside et al also reported on 18 patients who had previously failed 2-stage revision TKAs, where the protocol was similar to the 2011 study. At follow-up, 94% of the knees achieved infection control, with a mean follow-up of 6.1 years, with one patient undergoing revision and another course of IA antibiotics, and one patient requiring an above the knee amputation.[32] In addition, Whiteside et al used their unique protocol and observed excellent clinical outcomes in a cohort

Table 2

Local Antibiotic Delivery in PJI

Lead Author, Journal, Year	Antibiotic Delivery Device	Patients (n)	Primary Outcome	Antibiotic-Associated Complications	Author Conclusions
Chung et al[37]	High-dose antibiotic cement beads at first DAIR	83	Clinical infection control without revision surgery	None	Prompt initiation of double DAIR protocol in primary and revision PJI after symptom onset seems to improve outcomes versus traditional DAIR
Chin et al[28]	IORA	22	Subcutaneous fat and bone concentration of antibiotics administered IORA	None	Low-dose IORA provides high local antibiotic concentration in high BMI patients undergoing TKA vs systemic vancomycin
Lum and Pereira[29]	AICS	56	AICS-associated wound complications, revision surgery, reinfection	1 patient with wound drainage	AICS with 100% pure calcium sulfate is a safe adjunct to TJA and revision arthroplasty with minimal wound complications
Riesgo et al[23]	Intrawound vancomycin & iodine	36	Failure of DAIR after Vanc & Iodine protocol	None	Iodine lavage and intrawound vancomycin results in decreased reinfection and failure rate after DAIR
Flierl et al[30]	AICS	33	Failure of DAIR after AICS	None	Adjunct AICS beads do not seem to improve outcomes of DAIR
Whiteside and Roy[34]	Intra-articular antibiotics	30	Failure of treatment with 1-stage THA revision	No long-term sequalae	Single-stage revision for chronically infected THA with adjunct intra-articular antibiotics is useful even with high-virulent organisms
Whiteside et al[33]	Intra-articular antibiotics	18	Reinfection after failed 2-stage TKA revision	No long-term sequalae	Reinfection after failed revision TKA can be managed with aggressive exposure, débridement, soft-tissue coverage, and noncemented fixation with adjunct intra-articular antibiotics
Whiteside et al[32]	Intra-articular antibiotics	18	Outcomes of 1-stage TKA revision	No long-term sequalae	One-stage revision TKA and 6-week intra-articular antibiotics-controlled MRSA infection with no complications

AICS = Antibiotic impregnated calcium sulfate; DAIR = débridement, irrigation, and implant retention; IORA = Intraosseous regional administration; TJA = total joint arthroplasty

of acutely and chronically infected THAs managed with either one-stage exchange arthroplasty (21 patients) or DAIR (9 patients). Ninety-seven percent of patients were able to clear their infection at a mean of 63 months. No patients developed permanent renal damage, a chronic fistula, or had significant drainage from the catheter site.[34] IA infusion of antibiotics may be a good method for treating PJI; however, these results need to be replicated in other centers with large scale prospective trials demonstrating the extent of its efficacy and safety.

Antibiotic Administration after Irrigation and Débridement and Implant Retention

DAIR is considered a treatment for acute infection before the establishment of mature biofilm. Studies have sought to determine factors associated with positive outcomes after DAIR (Table 3). DAIR in TKA has been demonstrated to be most effective when performed within two weeks of index TKA or in patients with <2 days of symptomatology.[35,36] For instance, Narayanan et al[36] showed an 82% success rate versus a 52% success rate when DAIR was performed within 2 weeks of *index* TKA. However, Klare et al[35] found that symptoms less than 2 days were associated with greater success in a cohort of TKAs that were not acute postoperative. The use of long-term oral antibiotic use in both of these studies is not defined.

Riesgo et al[23] performed a single institution retrospective review examining PJI treated with DAIR and adjunctive povidone-iodine lavage and VIP groups. Compared with a consecutive matched control group, the VIP group had 6/36 (16.7%) patients fail treatment at 1-year follow-up versus 14/38 (37%) in the control group ($P < 0.05$). However, three patients in the VIP group were on chronic antibiotic suppression at follow-up.[23] The findings of Riesgo et al have been confirmed by some authors and rejected by other authors.[24-26]

More recently, Chung et al[37] retrospectively reported on a minimum 1-year follow-up (mean 41.8 months) of 83 patients undergoing a 2-stage DAIR ("double" DAIR) with an 82.9% and 89.6% success rate in THA and TKA, respectively. The first DAIR included placement of high-dose local antibiotic beads which were removed during the second DAIR performed 5 days later. Long-term oral antibiotic use after 6 weeks of IV antibiotics was not considered a failure and was selectively applied in 55% of patients in this study.

Antibiotic choice after DAIR has been associated as a risk factor for failure. Tornero et al[38] retrospectively examined 143 patients who underwent DAIR for acute PJI (defined as symptomatic <21 days) and were followed for at least 2 years to evaluate the failure rate after oral antibiotic cessation. The postoperative antibiotic protocol consisted of 7 to 10 days of IV antibiotics and then transitioned to oral biofilm active antibiotics for at least six weeks (maximum 210 days). For Gram (+) infections, they found that rifampicin administered with linezolid, cotrimoxazole, or clindamycin was associated with a higher failure rate (28%) compared with rifampicin with levofloxacin, ciprofloxacin, amoxicillin (8% failure), or monotherapy with linezolid or cotrimoxazole alone (0%, $P = 0.03$). Furthermore, patients with Gram (−) infections treated with fluoroquinolones also exhibited a significantly lower failure rate (7% vs 38% $P = 0.04$). The authors concluded that because rifampicin is a potent P450 inducer, the serum antibiotic concentrations of cotrimoxazole, clindamycin, and linezolid are reduced when coadministered with rifampin.

Future studies need to determine whether strict adherence to the factors associated with successful DAIR and the potential benefits of local antibiotic administration will lead to improved infection control and improved antibiotic stewardship compared with controls. The success of DAIR with and without the use of chronic suppressive antibiotics is also a variable that requires clarification in the future. A prospective, multicenter, randomized controlled trial is currently underway investigating IORA in DAIR for acute TKA PJI at OrthoCarolina (Table 1).

Antibiotics in Two-stage Exchange Arthroplasty (Not including Bone Cement)

Antibiotic usage in the setting of two-stage revision arthroplasty remains a significant challenge. A recent observational study of 196 patients assessed the utility of continuous antibiotic treatment before revision surgery compared with a 2-week drug holiday before reimplantation.[39] At 96 weeks after reimplantation, 91% of patients in the continuous antibiotic group versus 79% in the drug-holiday group had remained infection free (OR 3.32, 95% CI, 1.3 to 8.44; $P = 0.02$). These findings are interesting because routine methods of PJI workup (inflammatory markers and joint aspiration) in predicting reimplantation success remains limited. Therefore, continuous antibiotic administration up to the point of reimplantation may be appropriate, but more well-constructed studies are necessary.[39]

Other authors have demonstrated the efficacy of extended postoperative antibiotics in the setting of two-stage exchange arthroplasty for PJI (Table 4). Johnson et al[40] reviewed 66 patients with previous THA PJI with a minimum 24-month follow-up. Thirty-three percent of patients were prescribed extended antibiotics for at least 14 days (mean 36 days, range 14 days-lifelong), whereas 44 patients did not take additional antibiotics other than standard prophylaxis. These patients were then compared with 410 hips who underwent revision for aseptic loosening without extended antibiotics. They found no reinfections in the extended antibiotic group versus six reinfections (13.6%) in the standard-of-care group, compared with 0.5% reinfection rate in the aseptic loosening group. They did not observe any adverse reactions because of extended antibiotic administration. This suggests that extended postoperative antibiotics

Table 3

Factors Associated With Success After DAIR

Lead Author, Journal, Year	TJA Design	Factor
Klare et al[35]	TKA only	Symptoms <2 days, ESR <47 mm/hr (not acute postoperative)
Narayanan et al[36]	TKA only	<2 weeks from *index* procedure
Bryan et al[43]	THA only	McPherson host grade A, *strict* "acute" PJI criteria followed: post op <28 days; hematogenous ≤21 days of symptoms
Tornero et al[38]	TKA & THA	Appropriate, weight-based antibiotic regimen with appropriate serum concentrations

DAIR = débridement, irrigation, and implant retention; TJA = total joint arthroplasty

Table 4

Extended Antibiotic Use in PJI

Lead Author, Journal, Year	Study Cohort	Patients (n), Implant Design	Primary Outcome/ Definition of Failure	Mean Follow-up	Author Conclusions
Bryan et al[43]	DAIR (acute infection)—lifetime antibiotic suppression	90, THA	Pain-free function 83% (grade A 92%), 31 (34%) died all infection free, 26 deaths (84%) in pts on chronic spp w/o antibiotics cause (& no c diff)	6 years	Macpherson grade A had best results 8% vs. 44% in grade C—factors accounting for positive results—rifampin (>50% patients can't tolerate), strict definition of acute infection
Frank et al[41]	Second-stage replant —3-month oral antibiotic	59 antibiotics/48 control, THA & TKA	5% vs. 19% failure antibiotics vs. control—reinfection per MSIS	14-month treatment vs. 10-month control	Extended course may help but need 2-year follow-up
Siqueira et al[42]	DAIR—lifetime suppression vs. no suppression	38, THA & TKA	5 years infection free 64.7% vs 30.4% defined by Diaz-Ledezema	Minimum 6 month	Most beneficial for patients with I&D and with staph; good for TKA & THA
Siqueira et al[42]	Second stage—lifetime suppression vs. no suppression	54, THA & TKA	5 years infection free (as above)	Minimum 6 month	As above
Johnson et al[40]	Second-stage replant—22 with min 2 weeks antibiotics; 44 only 1-3 days; vs 410 aseptic revision	67, THA	0% infection in those getting antibiotics vs. 13.6% no antibiotics vs. 0.5% in aseptic revisions	3.75 years (minimum 2 years)	Promising preliminary results, need larger prospective multicenter studies

DAIR = débridement, irrigation, and implant retention; PJI = periprosthetic joint infection

after the second stage reimplantation may decrease the likelihood of reinfection and may be safe; however, this study was small and retrospective. However, extended postoperative antibiotics may also be simply pushing the eventual PJI failure to a later date versus scenarios where extended postoperative antibiotics are not used.

Recently, a prospective multicenter randomized controlled trial was performed to assess the utility of a 3-month postoperative course of antibiotics after reimplantation of the second stage of a two-stage exchange. All 107 patients included (57 knee PJI, 50 hip PJI) had negative cultures at the time of second-stage reimplantation. Patients were randomized to receive a course of extended oral antibiotics (n = 59) or to receive no additional antibiotics (n = 48). Three patients in the

treatment group were diagnosed with reinfection versus nine in the control group (5% vs 19% hazard ratio [HR] 4.37; 95% CI, 1.30 to 19.75; P = 0.02), with 83% of reinfections occurring before 12 months. Three patients in the treatment group discontinued use of their antibiotic because of adverse effects of antibiotic administration. Although this study supports a 3-month postoperative course of antibiotics, this study report is an interim analysis. The study is now complete, and the final results will be published in the near future.[41]

Lifetime Suppressive Antibiotics

The antibiotic stewardship of chronic suppressive antibiotics after revision arthroplasty or DAIR is up for debate. Prolonged suppressive regimens should generally only be considered for patients who have undergone surgical treatment for PJI, have a high risk of relapsing infection, are infected with a virulent organism, or if relapse would be limb- or life-threatening.[42] There are no current guidelines or criteria to direct patients to a suppressive regimen. For patients who are too sick to undergo surgery and those who refuse surgery in the setting of PJI, chronic suppressive oral antibiotics may be indicated.[8]

Bryan et al examined the outcomes after DAIR for acute hip PJI performed 28 days or less from the index procedure or 21 days or less since symptom onset. Seventy-seven percent of patients were treated with lifetime suppressive antibiotics. Treatment failure occurred in 10 of 66 (15%) patients acutely postoperatively and five of 24 (21%) hips after acute hematogenous infection, with 12 patients failing treatment during the initial 6 weeks of IV antibiotics. Overall, 17% of patients failed DAIR treatment, requiring component removal or secondary procedures for failure to eradicate infection with either wound fistula, drainage, intolerable pain, recurrent infection, subsequent removal of component, or PJI-related mortality. Treatment failure was more likely in McPherson host grade C (44%) compared with host grade A (8%) patients (Table 3). For patients who did not sustain treatment failure during the initial 6-week postoperative period, 88% of patients were maintained on suppressive antibiotics at a mean follow-up of 6 years.[43]

Pradier et al examined 39 patients who underwent DAIR, followed by lifetime antibiotic therapy with doxycycline for *S aureus* PJI. Twenty-three PJIs involved the hip and 13 involved the knee, 15 patients were qualified as early (within 3 months of arthroplasty), with MRSA accounting for 22% of the bacteria isolated. Adverse events related to the administered antibiotic (photosensitivity, nausea, and vomiting) occurred in 15% of patients, leading to discontinuation in three patients. The mean duration of treatment was 675 days, with 10 patients undergoing a 2-year course and 29 were undergoing an indefinite course. At a mean follow-up of 994 days, 29/39 (74%) remained event-free, and 10 (26%) failed. In the 10 patients who failed, 8/10 relapsed with the same organism and 2/10 with a subsequent superinfection with *Staphylococcus epidermidis*. Eighty percent of the cases of failure was related to a doxycycline-susceptible organism. The authors concluded that based on these results, oral doxycycline is a viable option for chronic suppressive therapy after DAIR.[44]

Siqueira et al[42] evaluated 655 revision arthroplasties (either undergoing DAIR or 2-stage revision), 92 of which underwent chronic antibiotic suppression for at least six months (mean 63 months). These 92 patients were compared with a matched cohort who did not receive chronic antibiotics. The 5-year infection-free prosthetic survival rate was 69% for the antibiotic suppression group versus 41.1% for the nonsuppression group (HR = 0.63, P = 0.008). After further stratification, patients who benefitted from chronic therapy were those who underwent DAIR and those with *S aureus* PJI. Patients with TKA PJI and those who had multiple previous operations fared poorly.[42] Although chronic suppressive antibiotics are a useful adjunct, patients must be able to contend with possible side effects of medications, and surgeons should be concerned about of their role in facilitating antibiotic resistance. If deemed to be clinically prudent the Infectious Diseases Society of America recommends indefinite chronic antimicrobial therapy after the initial antimicrobial treatment for PJI with either cephalexin, dicloxacillin, cotrimoxazole, or minocycline. The decision should be made based on antibiotic susceptibility, allergies, and tolerance of medication.[45]

Summary

This review presents a broad perspective of the most current literature regarding PJI after TJA within the context of antibiotic stewardship. Compliance with established best practice perioperative antibiotics use should be enforced while allowing the current yet limited research to define future directions for study. Without coming to cross-disciplinary agreement on what constitutes best practice, healthcare providers may continue to use antimicrobials subjectively thereby increasing indiscriminate antibiotic stewardship. Whenever possible, future research should focus on level I- or II-evidence studies to evaluate antibiotic prophylaxis and treatment that will likely require large multicenter randomized trials.

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