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General

How are Oral Antibiotics Being Used in Total Joint Arthroplasty? A Review of the Literature

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While the role and benefit of perioperative intravenous (IV) antibiotics in patients undergoing total joint arthroplasty (TJA) is well-established, oral antibiotic use in TJA remains a controversial topic with wide variations in practice patterns. With this review, we aimed to better educate the orthopedic surgeon on when and how oral antibiotics may be used most effectively in TJA patients, and to identify gaps in the literature that could be clarified with targeted research.

Extended oral antibiotic prophylaxis (EOAP) use in high-risk primary, aseptic revision, and exchange TJA for infection may be useful in decreasing periprosthetic joint infection (PJI) rates. When prescribing oral antibiotics either as EOAP or for draining wounds, patient factors, type of surgery, and type of infectious organisms should be considered in order to optimally prevent and treat PJI. It is important to maintain antibiotic stewardship by administering the proper duration, dose, and type of antibiotics and by consulting infectious disease when necessary.

INTRODUCTION

The role and benefit of perioperative intravenous (IV) antibiotics in patients undergoing total joint arthroplasty (TJA) is well-established and largely uncontroversial.[1] While the details of which antibiotics are used may be debatable, 100% compliance with perioperative IV antibiotic administration for patients undergoing TJA is a goal of every hospital and orthopedic surgeon. Additionally, prolonged IV antibiotics are widely considered an important part of treatment for patients with periprosthetic joint infection (PJI),[2,3] with a duration of 2-6 weeks in most reports.[4] These parenteral antibiotics require durable IV access and are therefore typically administered in an acute care setting, infusion center, or in conjunction with a home infusion agency. Logistics of coordinating these infusions and monitoring patients for tolerance of antibiotics are best managed by a multidisciplinary care team, and orthopedic surgeons do not commonly prescribe IV antibiotics outside of these limited contexts.

On the other hand, oral antibiotics are easily accessible as they are widely available at outpatient pharmacies and typically do not require close monitoring for short courses. The simpler logistics of using oral antibiotics mean they are significantly easier for patients to take and are much less expensive.[5] Orthopedic surgeons often prescribe oral antibiotics to TJA patients for a variety of reasons, albeit with wide variations in practice patterns and little guidance on when or what may be most appropriate.

The aims of this article are (1) to review the use of oral antibiotics in TJA, with the goal of better educating the orthopedic surgeon on current evidence available on when and how they may be used most effectively in TJA patients, and (2) to identify gaps in our understanding that could be clarified with targeted research.

METHODS

A comprehensive literature review was performed using PubMed, Google Scholar, and bibliography review. Articles were searched for using keywords such as “extended oral antibiotic prophylaxis”, “antibiotics”, and “total joint arthroplasty”. There were no restrictions for review based on publication dates, but many articles reviewed and included describe the most updated and recent research on the topic.

ROUTINE PERIOPERATIVE ANTIBIOTIC PROPHYLAXIS

While prophylactic perioperative antibiotics are universally recommended, there is not a universal consensus on the optimal duration of use after TJA. The Centers for Disease Control (CDC) and the World Health Organization (WHO) do not recommend the use of prophylactic antibiotics after surgical closure; however, this is a blanket recommendation for all surgical procedures and does not sub-stratify among higher risk orthopedic procedures that involve implantable devices.[6] In contrast, the American Association of Hip and Knee Surgeons (AAHKS) recommends prophylactic antibi-

otic use for 24 hours post-arthroplasty,[7] a strategy that has been shown to be effective.[8]

With many TJA patients now leaving the hospital as a same day discharge, it becomes prohibitive to administer 24 hours of IV antibiotics postoperatively. The role of oral antibiotics to meet AAHKS recommendations is unclear and inconsistently practiced. Some outpatient TJA protocols prescribe oral antibiotics after discharge, while others use a single preoperative IV dose.[9-11] Compared to the well-studied use and protocols regarding postoperative IV antibiotics, there are no current guidelines in place for the use of oral antibiotics following outpatient arthroplasty, warranting more research on the topic. However, the infection rates reported in studies using a single preoperative IV dose, which meets CDC and WHO guidelines, suggests this approach is likely sufficient.[12,13]

EXTENDED ORAL ANTIBIOTIC PROPHYLAXIS IN HIGH RISK PRIMARY TJA PATIENTS

With the burden of PJI increasing,[14,15] there is a growing need for research regarding new strategies to reduce the risk of PJI after TJA. There has been significant research aimed at identifying risk factors that may increase risk of PJI, such as obesity, diabetes, smoking, autoimmune disease, chronic kidney disease (CKD), or nasal colonization with *Staphylococcus aureus*.[16-21] Preoperatively targeting these modifiable risk factors may help to reduce surgical risk of PJI,[16-18] and further studies to mitigate the elevated risk associated with these comorbid conditions with additional perioperative interventions have been performed.[19, 22-25]

Use of extended oral antibiotic prophylaxis (EOAP) beyond 24 hours in high-risk patients has recently become an area of interest (Table 1), as well as an area of controversy, among arthroplasty surgeons. In 2018, a study by Inabathula et al. retrospectively studied 2181 primary TJAs in "high risk" patients (defined as patients with BMI ⩾ 35 kg/m^2, diabetes, active smokers, CKD, autoimmune disease, and/or nasal colonization with MRSA/MSSA). The authors compared rates of 90-day postoperative PJI between those receiving EOAP for a week or more and those who received standard perioperative infection control practices. Patients that did not receive EOAP had a significantly higher risk for developing PJI for both total knee arthroplasty (TKA) (2.1% vs. 0.4%; p = 0.01) and total hip arthroplasty (THA) (4.3% vs. 1.1%; p = 0.02), and for the patients not receiving EOAP, their risk for developing PJI were 4.9 (p=0.01) and 4.0 (p=0.04) times higher than those who did receive EOAP for TKA and TKA, respectively.[19] A subsequent study by Kheir et al. from the same institution comparing one-year PJI rates found "high-risk" patients (same definition as above) receiving EOAP had a significantly lower PJI rates for TJA than those who did not receive EOAP (0.9% vs 2.6%; p< 0.01).[23] A follow-up economic analysis study by Lipson et al., using break-even modeling, also found that EOAP in high-risk patients was a cost-effective strategy to significantly reduce the rate of PJI after TJA.[24]

While encouraging, the larger data do not universally support a benefit to EOAP. A study of 650 cases by Carender et al. found no significant difference in PJI rates at 90 days between patients with a BMI 40 kg/m^2 who received EOAP when compared with those who did not receive EOAP (p=0.35). Notably, they also found no association between any patient risk factor (including diabetes, CKD, and *S. aureus* nasal colonization) and risk of PJI.[25] Another concern about the use of EOAP is the possible antimicrobial resistance that may develop.[36,37] In an analysis of Inabathula et al.'s 2018 study, DeFrancesco et al. estimate that this extended antibiotic use would create a projected 50,000 patient years of antibiotic use annually in the USA, which could create a more favorable environment for antimicrobial resistance to develop. The authors also argue that the possibility of increased adverse drug events should be considered, even though the study shows no increased rates in those who used EOAP.[38]

The evidence on the use of EOAP after TJA in high-risk patients is mixed, with some studies showing a benefit and others showing no benefit. Each of these studies acknowledges their own limitations, including their retrospective nature and the lack of analysis of other risk factors known to predispose to PJI, such as anemia and alcohol use.[20] However, it appears there is some agreement that EOAP reduces PJI rates in high-risk patients, but additional studies with higher levels of evidence are needed to validate this.[39]

EXTENDED ORAL ANTIBIOTIC PROPHYLAXIS IN ASEPTIC REVISION TJA PATIENTS

Aseptic revision surgery has also been shown to be an independent risk factor for PJI, possibly due to re-exposure of deep structures and longer operative times.[26,40,41] Rates of PJI after aseptic revision are higher than those after primary TJA, ranging from 2% to 7%.[42-45] Due to these higher rates, extended intravenous antibiotic prophylaxis has been studied in this population as well, albeit with mixed results. Some have shown a lower PJI rate in patients receiving EOAP,[46,47] while this practice has not been shown to affect PJI rates in others[48] (Table 1).

Zingg et al. studied 180 consecutive aseptic revision TKAs receiving EOAP and reported PJI rates as 0% at 90d follow-up, 1.8% at 1 year, and 2.2% at 3 years. When compared to published literature, these rates were similar to published rates of PJI for primary TKA and 2-4x lower than published rates of PJI for aseptic revision TKA.[26] Villa et al. analyzed 178 revision TJAs split into two groups, an EOAP (>24 hours) and a standard antibiotic prophylaxis group (<24 hours), which showed no significant difference in PJI rates (2.2% vs. 3.5%; p=0.67),[27] although this study was underpowered with inconsistent dosing regimens. Bukowski et al. analyzed 1107 aseptic revision THAs and found no statistically significant difference in risk of PJI at 90 days between EOAP (mean duration of therapy of 10d) and standard antibiotic prophylaxis groups (p =0.25), 1 year (p =0.28), or at final follow-up (1.4% vs 3.1%; p = 0.09).[28] However, Bukowski et al. did report a trend toward a decreased risk of any infection (p = 0.06), PJI (p = 0.09), re-revision

Table 1. Design and results of Studies on Extended Oral Antibiotic Prophylaxis in TJA

	Study	Patient Demograpic, Surgery type	Follow-up	PJI Rate for Control- No EOAP Group	PJI Rate for EOAP Group	p-value
EOAP following primary or aseptic revision TJA						
	Inabathula et al.[19]	"High-risk" patients, primary TKA/ THA	90 days	2.1%/4.3%	0.4%/1.1%	0.009/ 0.020
	Kheir et al.[23]	"High-risk" patients, primary TJA	1 year	2.64%	0.89%	<0.001
	Carender et al.[25]	Patients BMI 40 kg/m^2, primary TJA	90 days	0.6%	1.7%	0.35
	Zingg et al.[26]	Aseptic Revision TKA	90 days/ 1year/ 3 years	N/A	0%/ 1.8%/ 2.2%	N/A
	Villa et al.[27]	Aseptic Revision TJA	Mean 2.3 years	3.5%	2.2%	0.671
	Bukowski et al.[28]	Aseptic Revision THA	Mean 4 years	3.1%	1.4%	0.085
EOAP following successful exchange for PJI						
	Johnson et al.[29]	Two-Stage Revision THA	Minimum 2 years	13.6%	0.0%	0.087
	Zywiel et al.[30]	Two-Stage Revision TKA	Minimum 1 year	15.8%	3.8%	N/A
	Cordero-Ampuero et al.[31]	Two-Stage Revision TJA	Mean 4 years	N/A	5%	N/A
	Siquera et al.[32]	Two-Stage Revision TJA	5 years	58.9%	31.5%	0.008
	Frank et al.[33]	Two-Stage Revision TJA	Mean 14 months	18.8%	5.1%	0.016
	Yang et al.[34]	Two-Stage Revision TJA	Mean 3.3 years	28.6%	12.5%	0.012
	Kelly et al.[35]	Two-Stage Revision TJA	Mean 2.2 years	21%	15%	0.35

NOTE. – TJA = Total Joint Arthroplasty; PJI = Periprosthetic Joint Infection; EOAP = Extended Oral Antibiotic Prophylaxis; TKA = Total Knee Arthroplasty; THA = Total Hip Arthroplasty; BMI = Body Mass Index.

(p =0.08) and reoperation (p = 0.10) for infection in patients who had EOAP at the final clinical follow-up (mean 4 years).[28] Overall, EOAP after aseptic revision TJA may be beneficial in reducing risk of PJI, but requires further study.

TREATMENT OF PERIPROSTHETIC JOINT INFECTION

The gold standard for treatment of PJI has long included surgical debridement and prolonged IV antibiotics,[49] however the need for long-term IV administration of those antibiotics has recently been challenged. The oral versus IV antibiotics for bone and joint infection (OVIVA) study was a prospective multicenter RCT which compared 1-year outcomes in patients with bone and joint infections. This compared patients that switched from IV to oral antibiotics within 1 week of antibiotic therapy initiation and patients that only received IV antibiotics for at least 6 weeks IV therapy. The authors found equivalent success rates in treating the infection between the patients that received oral versus IV antibiotic therapy and that treatment costs and vascular device-related complications were significantly lower in the oral antibiotic treated patients.[50] The study implicated prolonged IV antibiotic therapy may be unnecessary for many patients when suitable oral antibiotics are available.[51] While encouraging results were seen in this single well-designed trial, further studies on this topic are necessary.

EXTENDED ORAL ANTIBIOTIC PROPHYLAXIS AFTER SUCCESSFUL TREATMENT OF PJI

Although two-stage exchange[52] has long been considered the gold standard treatment strategy for chronic PJI in the United States, failure rates up to 30% have been reported.[53-57] With the goal of improving these outcomes and minimizing reinfection, some studies have evaluated EOAP after exchange arthroplasty (Table 1).

In 2013, Johnson et al. studied effects of postoperative antibiotic prophylaxis after successful two-stage exchange THA. 44 of the 66 patients who underwent exchange did not receive EOAP, with 6 becoming reinfected. Of the 22 patients who did receive a mean of 36 days of EOAP following second stage, none got reinfected (13.6% vs 0.0%; p=0.09). Although not statistically significant, they report those who received EOAP were not reoperated on for reinfection for a period of 7 years.[29] In an earlier study, Zywiel et al. retrospectively reviewed reinfection rates after two-stage exchange TKA.[30] Only 1 of 28 patients receiving EOAP for a minimum of 28 days developed a reinfection, compared to 6 of 38 patients who did not receive EOAP (3.8% vs. 15.8%). Although this study was underpowered and did not show statistical significance, the authors believed there was sufficient evidence to suggest EOAP following two-stage exchange TKA reduces reinfection rates.[30] Similarly, Cordero-Ampuero et al. prescribed two oral antibiotics for 6 months after two-stage exchange, reported that PJI remained resolved in 38 of 40 patients (95%) at this early time point, and concluded EOAP is effective in augmenting treatment of PJI, shortening hospitalization, and reducing patient discomfort, although this was not compared to a control group.[31]

Other studies examined the effect of even longer EOAP use. Siquera et al. retrospectively studied 379 two-stage revision TJAs and found that patients who received EOAP for a minimum of 6 months post-reimplantation had a higher 5-year infection-free survival rate compared to those who did not receive EOAP (68.5% vs 41.1%; p<0.01).[32]

In a more recent multicenter RCT, Frank et al. randomized patients to 3 months of EOAP versus none following reimplantation. Of the 59 patients receiving EOAP, only 3 developed reinfections at a mean follow-up of 14 months, compared to 9 of 48 patients who didn't receive EOAP (5.1% vs. 18.8%; p=0.01).[33] In another RCT by Yang et al. which had a longer mean follow-up of 3.3 years, similarly randomizing patients to 3 months of EOAP or no further antibiotic treatment, 9 of 72 patients who did receive oral antibiotic prophylaxis developed reinfection, compared to 20 of 70 patients who did not receive EOAP (12.5% vs 28.6%; p=0.01).[34] In the most recent International Consensus Meeting on Orthopedic Infections in 2018, it was generally agreed upon that EOAP after 2nd stage reimplantation for 3 months likely reduces the risk of recurrent PJI.[39,58]

Data are not universally supportive of this protocol, however. Kelly et al. recently showed in a study with mean follow-up of 2.2 years after 2-stage exchange that recurrent PJI rates were similar between patients who received EOAP and patients who did not receive antibiotics (15% vs. 21%; p=0.35), and that use of EOAP following 2-stage exchange increased drug resistance to that antibiotic in subsequent PJI.[35] Specifically, of the patients diagnosed with recurrent PJI, resistant organisms were identified in 16 of 24 patients who received antibiotics compared with 0 of 11 patients who did not receive antibiotics (67% vs. 0%; p=.0001). Given the concern for rising antimicrobial resistance, the desire to optimize the duration of EOAP use becomes much more apparent.

With the above data, the optimal protocol duration remains unclear. A recent study by Fang et al. sought to evaluate the effect of different durations of prophylactic antibiotic use in two regional medical centers in China. 62 of 64 patients receiving <1 month of antibiotics post-reimplantation remained infection free at 24 months. This was statistically not significantly different than the 92.7% rate in the group of patients who received antibiotics for >1 month (p=0.68). The authors concluded antibiotics for <1 month achieves a similar infection control rate to more extended use >1 month.[59] Although most these studies have shown that the use of extended prophylaxis significantly reduces reinfection rates after two-stage exchange arthroplasty, the duration of oral antibiotic prophylactic use remains unclear, and more research is needed on this subject.

ORAL ANTIBIOTICS FOR DRAINING WOUNDS

Prolonged wound drainage is a strong predictor of PJI.[60-62] The estimated risk of PJI after TJA in patients with prolonged wound drainage has been reported to range from 1.3% to 50%.[60,63,64] Prolonged wound drainage may also increase length of hospital stay, number of surgical procedures, and healthcare costs.[65] Treatments for a draining wound after TJA include local wound care, serologic testing (ESR, CRP), joint aspiration, oral antibiotics, and reoperation.[66,67] While many risk factors for prolonged wound drainage after TJA have been described,[60] the optimal treatment protocol to minimize the risk of developing a deep infection in TJA patients with draining wounds, including when to aspirate and whether to use oral antibiotics, has not been agreed upon.

The use of oral antibiotics for draining wounds has traditionally been discouraged due to fear they may conceal an underlying infection and increase the risk of false negative cultures.[68,69] However, by aspirating the joint before starting antibiotics, it is believed that the risk of missing a true infection is low, especially if the protocol is only applied to wounds that do not appear clinically infected.[70] Guirro et al. reported benefits of oral antibiotics in postoperative patients with superficial infections, which successfully prevented deep infection in 87% of patients while the remaining patients were successfully treated with oral antibiotics and surgical debridement.[71] Similarly, because it can be difficult to differentiate between cellulitis and benign postsurgical reactive erythema when evaluating a draining wound, oral antibiotics after aspiration are a reasonable treatment option.[70]

Duration of wound drainage is an important factor when considering treatment with oral antibiotics. It has been

shown that patients with 5-7 days of drainage or greater are at an increased risk to develop deep infection,[72,73] with one report stating that patients with >5 days of drainage were 12.7 times more likely to develop a deep infection when compared to patients with less drainage time.[62] Prior studies have also found that each day of prolonged wound drainage increases the risk of deep infection by 42% in THA and 29% in TKA,[60] prompting interest in oral antibiotic prophylaxis during the period of drainage. One recent study found that 72% of primary or revision TJA patients with drainage for more than 48 hours that were treated nonoperatively with local wound care and prophylactic oral antibiotics for 2 to 4 days had uneventful resolution of drainage and required no further treatment.[72] The International Consensus Meeting on PJI recommended surgical irrigation and debridement of wounds still draining for 5-7 days after the initial procedure.[74] Even with this recommendation, 23% of participants did not agree that surgical intervention was required on wounds still draining for 5-7 days after surgery.[68] The role of oral antibiotics in this context was not discussed. This disagreement suggests there is variability in practice patterns, and the appropriate treatment with oral antibiotics for draining wounds remains controversial.

DENTAL PROPHYLAXIS

Oral antibiotic prophylaxis for dental procedures is controversial, with little consensus in the literature. Traditionally, antibiotics have been prescribed to patients with TJA prior to dental procedures in order to augment the immune system in eliminating bacteria that gets into the bloodstream.[75] However, recent evidence has shown no association between routine dental procedures and PJI rates, and that antibiotic prophylaxis for dental procedures does not reduce the risk of subsequent PJI.[76] The American Academy of Orthopaedic Surgeons (AAOS) has published a limited recommendation that physicians can consider discontinuing the practice of prescribing antibiotics before dental procedures for TJA patients with implants.[77]

The AAOS and the American Dental Association (ADA) have developed an Appropriate Use Criteria which describes factors that increase the indication for oral antibiotic prophylaxis for dental procedures. These include: (1) more invasive dental procedures involving manipulation of gingival tissue, periapical region of teeth, or perforation of the oral mucosa, (2) patients who may be immunocompromised due to conditions such as rheumatoid arthritis or cancer, (3) patients with diabetes/poor glycemic control, (4) patients with prior history of PJI, (5) patients <1 year status-post TJA.[75,78] Using these criteria, prophylactic antibiotics were considered rarely appropriate for 61% of patient and situational factors and were considered appropriate for only 12% of factors.[78] Ultimate decisions regarding oral antibiotic prophylaxis for dental procedures should be made by patients, dentists, and surgeons after open communication.[75]

MULTIDISCIPLINARY CARE WITH INFECTIOUS DISEASE

If acute PJI is suspected, ESR, CRP and a joint aspiration for cell count, differential, and aerobic and anaerobic culture are recommended by both orthopedic and infectious disease (ID) guidelines.[2,79] It is unclear when the best time to consult ID specialists is for suspected acute PJI, but early inclusion of an ID expert can be helpful to both the orthopedic surgeon and the patient diagnosed with PJI. When there is appropriate expertise available, decisions regarding surgical management should be made with appropriate consult from ID who have experience with arthroplasty patients.[80] It is important for all patients diagnosed with a PJI to work closely with an ID specialist to determine the appropriate course of antibiotics after a revision surgery as this may help reduce morbidity, mortality, and the costs associated with PJI.[2]

Guidelines on formal input from ID regarding other indications for oral antibiotics discussed in this article, such as EOAP or treatment of a draining wound, are less clear at the moment and, while likely not necessary in the majority of cases, are best left to surgeon discretion.

WHICH ORAL ANTIBIOTICS SHOULD BE USED?

There have been a range of oral antibiotics used in TJA patients (Table 3). The International Consensus on Orthopedic Infections recommends that duration, dose, route of administration, and the type of antibiotic administered should be determined by the type of infective organism and its antibiotic sensitivity profile.[81] The most common microorganism causing PJI in TJA patients is *Staphylococcus*[82] which includes coagulase-negative *Staphylococcus*, methicillin-susceptible *S. aureus* (MSSA), and methicillin-resistant *S. aureus* (MRSA). MSSA is commonly treated with oral antibiotics such as cefadroxil, cephalexin, and dicloxacillin,[2,83] while MRSA is commonly targeted with oral antibiotics including tetracyclines such as doxycycline or minocycline, cefadroxil, clindamycin (for patients with allergies to beta-lactams), cotrimoxazole (sulfamethoxazole-trimethoprim), linezolid, fluoroquinolones such as ciprofloxacin or levofloxacin, and rifampin (rarely indicated as monotherapy).[2,83-86] *Streptococci* are the second most common microorganism found in 9-16% of PJI cases[87,88] and can typically be treated with penicillin, amoxicillin, amoxicillin-clavulanate, or cephalexin as an alternative.[2,83,84] *Enterococci* are another microorganism found in PJI which can be treated with penicillin, amoxicillin, or amoxicillin-clavulanate.[2,83,84] Gram-negative bacteria are less common but can be treated with ciprofloxacin or levofloxacin.[2,83,84] Input from ID can be helpful in determining the best oral agent for treatment of PJI.

Oral antibiotics, while generally well-tolerated, are associated with side effects in some patients (Table 2). Common side effects of penicillin, amoxicillin, amoxicillin-clavulanate, cefadroxil, and cephalexin include skin rash, less common, but more severe side effects can include anaphylaxis and Clostridium difficile-associated diarrhea.

Table 2. Common side effects of antibiotics used in TJA

Oral antibiotics	Common side effects
Penicillin	Skin rash, anaphylaxis, C. difficile-associated diarrhea[83,86,89]
Amoxicillin	Skin rash, anaphylaxis, C. difficile-associated diarrhea[83,86,89]
Amoxicillin-clavulanate	Skin rash, anaphylaxis, C. difficile-associated diarrhea[83,86,89]
Cefadroxil	Skin rash, anaphylaxis, C. difficile-associated diarrhea[83,86,89]
Cephalexin	Skin rash, anaphylaxis, C. difficile-associated diarrhea[83,86,89]
Ciprofloxacin	Hepatotoxicity, Achilles tendinitis/ruptures, neuropathy, C. difficile-associated diarrhea[83,86,89]
Levofloxacin	Hepatotoxicity, Achilles tendinitis/ruptures, neuropathy, C. difficile-associated diarrhea[83,86,89]
Clindamycin	C. difficile-associated diarrhea[83,86,89]
Doxycycline	Skin hyperpigmentation, hepatotoxicity[83,86,89]
Minocycline	Skin hyperpigmentation, hepatotoxicity[83,86,89]
Rifampin	Hepatotoxicity, skin rash, gastrointestinal upset, drug interactions, interstitial nephritis, cytopenia[83,86,89]
Cotrimoxazole	Leucopenia/anemia, skin rash[83,86,89]
Linezolid	Thrombocytopenia/anemia, serotonin syndrome w/TCAs, myelosuppression, optic neuritis, peripheral neuropathy[83,86,89]

NOTE. – TJA = Total Joint Arthroplasty; TCAs = Tricyclic antidepressants.

Ciprofloxacin and levofloxacin may cause hepatotoxicity, Achilles tendinitis/ruptures, neuropathy, and less commonly, C. difficile-associated diarrhea. Clindamycin may also induce C. difficile-associated diarrhea. Doxycycline or minocycline may cause skin hyperpigmentation and hepatotoxicity. Rifampin may cause hepatotoxicity, skin rash, gastrointestinal upset, drug interactions, interstitial nephritis, and cytopenia. Cotrimoxazole may cause leucopenia/anemia and skin rash. Linezolid may cause thrombocytopenia/anemia, serotonin syndrome w/TCAs, myelosuppression, optic neuritis, and peripheral neuropathy.[83,86,89]

When EOAP is used prophylactically without a known organism, cefadroxil and/or cephalexin are the most commonly used antibiotics in prior studies, typically for 7-14 days.[19,23-26,28] Alternatives reported to be used when cephalosporins were contraindicated include clindamycin, cotrimoxazole, ciprofloxacin, doxycycline, and amoxicillin-clavulanate.[19,23,25-27] Cotrimoxazole has also commonly been used in patients who test positive for MRSA through intraoperative cultures at the time of surgery.[19,23,24]

When EOAP is used prophylactically following a successful exchange surgery for PJI, a 3-month course of oral antibiotics following 4-6 weeks of IV antibiotics has been shown to be effective in reducing reinfection rates,[33,34,58] although studies have shown a minimum of 4 weeks to greater than 6 months of oral antibiotics to be effective.[30-34] Most studies and protocols use organism-specific antibiotic regimens after cultures are obtained to most effectively treat and prevent reinfection.[30-34] Commonly prescribed oral antibiotics after successful exchange surgery for PJI include cotrimoxazole, ciprofloxacin, levofloxacin, doxycycline, combination therapy with rifampin, linezolid, cephalexin, and with occasional use of amoxicillin, clindamycin, and other antibiotics used to specifically target certain microorganisms.[30-35,58]

Oral antibiotics used to treat draining wounds or peri-incisional erythema in prior studies include cephalexin, clindamycin, and amoxicillin-clavulanate,[71,72] although antibiotics can be modified according to the infectious organism based on culture results.[71]

ANTIBIOTIC STEWARDSHIP

It is important to consider antibiotic stewardship when treating patients with antibiotic therapy, particularly when used for prophylaxis as opposed to active treatment. Antibiotic stewardship programs have been designed to improve antibiotic prescribing practices by optimizing clinical outcomes through choice of antibiotic, dosage, and duration while minimizing adverse events, antibiotic resistance, and overall costs.[90,91] Key aspects of antibiotic stewardship include education of involved care teams, set guidelines and clinical pathways, antimicrobial cycling, dose optimization, and inclusion of ID physicians.[90] There is some disagreement between specialties on what constitutes best practice, which leads to some subjectivity when prescribing oral antibiotics.[91] This disagreement negatively affects antibiotic stewardship, leading to less-consistent patient outcomes, which underscores the importance of updated literature on oral antibiotic use in TJA patients. Given that oral antibiotics are more cost-effective than their IV counterparts and usually cause fewer side effects, further prospective research is needed to identify the effectiveness of this approach.

CONCLUSION

The role of oral antibiotics in the setting of TJA, both primary and revision, is fraught with inconsistent and sometimes contradictory literature and much is still left to sur-

Table 3. Oral antibiotics commonly used as reported in various TJA studies

	Oral antibiotics	Oral dose (mg = milligrams, h = hours)	Duration of dose
EOAP following primary or aseptic revision TJA			
	Cephalosporins (cefadroxil and cephalexin)[19,23-26,28]	500 mg/12h, 500 mg/6h[19,23-26,28]	7 days,[19,23,24,26] 7-14 days[25,28]
	Clindamycin[19,23-28]	300 mg/8h[19,23-28]	7 days,[19,23,24,26] 7-14 days[25,27,28]
	Cotrimoxazole[19,23-28]	800/160 mg/12h[19,23-28]	7 days,[19,23,24,26] 7-14 days[25,27,28]
	Ciprofloxacin[25-27]	500 mg/12h[25-27]	7 days,[26] 7-14 days[25,27]
	Doxycycline[25-28]	100 mg/12h[25-28]	7 days,[26] 7-14 days[25,27,28]
	Amoxicillin-claulanate[26,28]	1000 mg/12h[26,28]	7 days[26,28]
EOAP following successful exchange for PJI			
	Cotrimoxazole[30-32]	800/160 mg/12h[30-32]	>4 weeks,[30] 6 months[31,32]
	Fluoroquinolones (ciprofloxacin and levofloxacin)[30-32]	500 mg/12h[30-32]	>4 weeks,[30] 6 months[31,32]
	Doxycycline[30,32,35]	100 mg/12h[30,32,35]	>4 weeks,[30] 3-6 months[32,35]
	Rifampin (combination therapy)[31,32]	300 mg/8h[31,32]	6 months[31,32]
	Linezolid[30,31]	600 mg/12h[30,31]	>4 weeks,[30] 6 months[31]
	Cephalexin[30,32]	500 mg/6h[30,32]	>4 weeks,[30] 6 months[32]
PO prophylaxis used to treat draining wounds or peri-incisional erythema			
	Amoxicillin-claulanate[71]	N/A	Mean of 16.5 days[71]
	Cephalexin[72]	N/A	N/A
	Clindamycin[72]	N/A	N/A

NOTE. – TJA = Total Joint Arthroplasty; PJI = Periprosthetic Joint Infection; EOAP = Extended Oral Antibiotic Prophylaxis; PO = per os (by mouth); mg = milligrams; h = hours.

geon discretion, ideally in consultation with infectious disease and the patient. However, there appears to be some consensus that EOAP reduces PJI rates in high-risk patients, that EOAP after aseptic revision TJA may be beneficial in reducing PJI risk, and that EOAP may reduce re-infection rates after two-stage exchange arthroplasty. Oral antibiotics may also have a role in preventing PJI in patients with superficial infections or draining wounds. Further high-powered, multi-center, prospective studies are needed to determine the effectiveness of these approaches and standardize care.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. TRW and DBN contributed to data curation and writing the first draft of the manuscript. HJC contributed to supervision of the study. All authors reviewed and edited previous versions of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

Each author certifies that he/she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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