1.7. PREVENTION: ANTIMICROBIALS (SYSTEMIC)

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QUESTION 1: Should patients with penicillin or cephalosporin allergies routinely undergo allergy testing, desensitization or a test dose before administering alternative antibiotic prophylaxis?

RECOMMENDATION: A majority of patients with a penicillin allergy can tolerate cephalosporins and do not need routine skin testing. Patients with a non-anaphylactic reaction to penicillins or cephalosporins can be given a test dose of a cephalosporin in the operating room.

STRENGTH OF RECOMMENDATION: Moderate

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

A comprehensive systematic review of the literature was performed to search for all studies dealing with penicillin allergy and antibiotic prophylaxis in patients with a penicillin allergy. The search terms “penicillin allergy,” “cephalosporin allergy,” “antibiotic prophylaxis” and “orthopaedic” were used through February 2018 in the following search engines: Medline, Embase and Cochrane. The search terms were combined with different Boolean operators. Inclusion criteria for our systematic review were all English studies (level I to IV evidence). Exclusion criteria were non-English studies, papers more than ten years old, case reports, non-human studies, papers with less than a ten-patient sample size and papers without follow-up. The original search resulted in more than 5,000 titles. After evaluation, 27 full-text reports were read and 16 were included in this review.

According to the recommendation by the World Allergy Organization, drug hypersensitivity reactions are categorized by the timing of the onset of symptoms as immediate (i.e., develops within one hour of drug exposure) or delayed-type (i.e., onset after one hour of drug exposure) reactions. An immediate-type reaction is a true immunoglobulin E (IgE) mediated hypersensitivity, with the most common symptoms being urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm or anaphylaxis and anaphylactic shock [1]. Most of the delayed-type reactions present as maculopapular exanthemas or delayed urticaria. However, severe and life-threatening reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis can also occur [2]. A penicillin allergy remains one of the most common patient-reported drug allergies, with an approximate prevalence of 8 to 12% in the general population [3–6] and is the most common patient-reported antibiotic allergy [7]. However, many studies conducted across a variety of patient populations suggest that penicillin allergy is markedly over-diagnosed [3,5,8,9]. Multiple studies estimate that up to 90% of patients reporting an allergy are actually able to tolerate penicillin and its derivatives [3,10–15]. Reported allergies are rarely validated with proper testing, and the lack of symptom classification prevents the distinction of non-IgE-mediated reactions and true, life-threatening type I hypersensitivity reactions [8,16,17]. Furthermore, large discrepancies exist between reactions reported in patient interviews and those recorded on patient medical records [18]. Unfortunately, unconfirmed penicillin allergies remain on patients’ medical records indefinitely, potentially leading to the underutilization of the entire classes of antibiotics [9,17,19]. This occurs despite recent literature showing that cross-reactivity between penicillin and cephalosporins is much lower than the alleged 10%, as administration of cephalosporin in penicillin allergic patients often only result in a reaction rate of 0.1% [20,21]. Interestingly, the IgE-mediated hypersensitivity to penicillin also decreases with time, with over half of skin test-positive patients losing sensitivity by five years and 80% by ten years [22,23]. To better establish an antibiotic regimen for patients who report an allergy to penicillin, a clear characterization of the penicillin allergy is essential. Of paramount importance is taking an appropriate clinical history for diagnosis and characterization of the patient’s prior allergic reaction to penicillin [24,25].

Since history of delayed-type hypersensitivity reaction to penicillin is a contraindication to skin testing, graded dose challenge and desensitization, patients with a self-reported penicillin allergy should be questioned thoroughly about previous and current reactions to penicillin, including the route of administration, concomitant medications, the time between the dose of penicillin and the appearance of symptoms and how the reaction was managed [26].

Immediate-type hypersensitivity can only be correctly diagnosed by a skin test. It consists of a skin-prick and intradermal testing with the major determinant (penicilloyl-polylysine), the minor determinant (penicillin G), a negative control (normal saline) and a positive control (histamine). The test has a negative predictive value of 97 to 99%. Tests should be performed by a board-certified allergist [27–30]. When the skin test is negative, a confirmatory oral challenge, usually with amoxicillin, should be performed [27]. Studies by Macy et al. and Solensky et al. have shown that patients with a negative penicillin skin test are able to tolerate repeat oral doses of penicillin with low rates of resensitization [31,32]. Furthermore, the literature demonstrates that most patients (99%) with a positive penicillin skin test will still be able to tolerate a cephalosporin [33,34] Prior literature has even shown that in penicillin skin test-positive individuals who were accidently given therapeutic penicillin, only one-third to one-half have any clinically relevant reaction, meaning there are most likely high false-positive rates in skin-testing [14,35].

Since the cross-reactivity of penicillins and cephalosporins have been demonstrated to be much lower in recent literature than the purported 10%, these patients might best be tested for allergy to cephalosporin and if negative may be given a cephalosporin as prophylaxis. The optimal environment to receive an antibiotic may be the operating room under the watchful eye of an anesthesiologist, where reversal agents can be quickly administered.

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QUESTION 2: What is the alternative choice of prophylactic antibiotic when the patient has an anaphylactic allergy to penicillin/cephalosporins?

RECOMMENDATION: The choice of prophylactic antibiotic for patients with a known anaphylactic penicillin or cephalosporin allergy includes vancomycin, teicoplanin or clindamycin. Cephalosporins for patients with anaphylactic penicillin allergies may be given following skin testing.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 5%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Because gram-positive bacteria are the most common infective organisms after total joint arthroplasty, first- or second-generation cephalosporins are recommended for antibiotic prophylaxis [1]. The use of cephalosporins is usually avoided in patients with penicillin allergies because of the fear of cross-reaction between penicillin and cephalosporins, which is strongly related to the structural similarities found in their R side chains. In earlier years, the risk of cross-reaction was reported to reach 10%, but in those studies only first generation cephalosporins that may have been contaminated with penicillin were observed [2,3]. Later studies have shown that cephalosporin allergy alone is less frequent with an overall reaction rate of 2% [4]. Moreover, the cross-reaction with third- or fourth-generation cephalosporins is negligible [5]. Therefore, patients with a reported penicillin allergy should undergo skin testing, and, if the test is positive, oral challenge is recommended [6].

Patient-reported allergies have important consequences for antibiotic selection, as cephalosporin agents normally utilized for perioperative prophylaxis are avoided due to the potential for cross-reactivity, even though the associated risks are unclear [5,7,8]. Of consequence, administering suboptimal antibiotics can increase the risk for infection in these patients. Recent studies have suggested that vancomycin monotherapy is correlated with higher rates of periprosthetic joint infection (PJI) when compared to penicillin and cephalosporin regimens, presumably due to its reduced gram-negative coverage [1,9,10]. The current guidelines established by the prior International Consensus Meeting on PJI recommends that vancomycin substitution only be in cases of severe anaphylactic penicillin allergy [11,12]. However, compliance is limited by the lack of proper allergy classification [13,14].

Frequent prophylactic use of vancomycin and alternative antibiotics for penicillin-allergic patients is also associated with increased rates of infection with vancomycin-resistant *Enterococcus* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* with reduced susceptibility to vancomycin [15-18]. In a single-institution study, Lee et al. showed that patients who reported a penicillin allergy were often treated with more than one alternative broad-spectrum antimicrobial agent, including cephalosporins, fluoroquinolones, clindamycin and vancomycin [19]. Evidence suggests that over-use of broad-spectrum antibiotics leads to increased antibiotic resistance, increased clinical complications, as well as markedly longer hospital stays and costs [17,19]. In terms of public health, the presence of resistant organisms in the community further amplifies the burden of infection. Thus, it is important that vancomycin only be used for patients with true type I IgE-mediated reactions to penicillin.

If a patient presents with a true penicillin allergy, alternative antibiotics should be given (vancomycin or clindamycin are recommended in these cases) [10]. Clindamycin has an excellent oral bioavailability of 90%, though its bone penetration is not ideal, reaching 45% [20]. Moreover, clindamycin is a bacteriostatic antimicrobial agent. These characteristics make clindamycin less effective as a prophylactic antibiotic in total joint arthroplasty compared to cefazolin. Further studies are needed to gain more data. Vancomycin is a bactericidal antibiotic that penetrates well into bone, synovium, muscles and hematoma [21]. There are concerns about its use as a prophylactic antibiotic because it has a narrower spectrum of antimicrobial coverage, than that of cefazolin, and because of the potential and unnecessary risk of emerging vancomycin-resistant organisms, such as VRE or vancomycin-resistant *S. aureus*.

The data available for vancomycin used as a single prophylactic antibiotic is somewhat controversial. Tan et al. retrospectively reviewed the charts of 10,391 patients after total joint arthroplasty and found that, compared to cefazolin, vancomycin prophylaxis was associated with a decreased risk of infection with gram-positive bacteria (adjusted odds ratio (OR): 0.25, confidence interval (CI) 0.10 to 0.62, $p = 0.003$) and antibiotic-resistant organisms (adjusted OR: 0.10, CI 0.01 to 0.88). However, vancomycin was also associated with an increased risk of gram-negative infections (OR: 2.42, CI 1.01 to 5.82, $p = 0.049$) [22].

In another retrospective study, Smith et al. analyzed PJIs after switching from cefazolin to vancomycin as antibiotic prophylaxis in total knee and total hip arthroplasty. Reviewing the data of 5,036 patients, they found that PJI decreased significantly from 1% to 0.5% with vancomycin prophylaxis, and there was also a trend in the reduction of MRSA infections, but the latter change was not significant [23].

Ponce et al. reviewed the data of 18,830 elective primary arthroplasties (12,823 knee and 6,007 hip) in a retrospective study. They found, that the overall surgical site infection (SSI) rate was 2.3% with single vancomycin prophylaxis, 1.5% with the use of vancomycin and cefazolin in combination, and 1.3% with cefazolin alone. In penicillin-allergic patients, the SSI rate was 2.0% with vancomycin compared to 1% with clindamycin ($p = 0.18$). Non-penicillin-allergic patients had an SSI rate of 2.6% with single vancomycin prophylaxis compared to 1.6% with vancomycin plus cefazolin prophylaxis ($p = 0.17$), and compared to 1.3% with single cefazolin use ($p < 0.01$) [10].

In a prospective study, Tyllianakis et al. compared the effectiveness of vancomycin, cefuroxime and fusidic acid in total joint arthroplasty prophylaxis and found no difference in the rate of SSIs or PJIs [24].

Sewick et al. performed a retrospective study evaluating the use of a vancomycin-cefazolin combination compared to single cefazolin prophylaxis and could not demonstrate any difference in the rate of SSIs [25].

The inconsistent and controversial data about the effectiveness of vancomycin as a prophylactic agent in total joint arthroplasty may be due to its incorrect dosage. Kheir et al. demonstrated in a retrospective analysis of 1,828 patients that vancomycin was dosed correctly in only 28% of patients

according to weight-based dosage recommendations [26]. Catanzano et al. showed almost the same data: evaluating 216 total joint arthroplasties 69% of the patients were underdosed, and 10% were overdosed [27].

Further studies analyzing the use of vancomycin in combination with other antibiotics and analyzing its proper dosage would be beneficial.

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QUESTION 3: What is the optimal antibiotic for perioperative prophylaxis in methicillin-resistant *Staphylococcus aureus* (MRSA) carriers who are undergoing orthopaedic procedures?

RECOMMENDATION: Vancomycin or teicoplanin is recommended as a perioperative prophylactic antibiotic agent for the current MRSA colonizer undergoing total joint arthroplasty (TJA).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

MRSA surgical site infections (SSIs) are an increasing concern after orthopaedic surgical procedures [1]. It is well-known that MRSA colonization is an independent major risk factor of MRSA SSIs [2–4]. Efforts have been made to screen for MRSA carriers and decolonize preoperatively using nasal mupirocin ointment or povidone iodine [5–7]. However, after the decolonization protocol [8,9], questions still exist as to which glycopeptide (such as vancomycin or teicoplanin) is recommended as the preferred prophylactic preoperative antibiotic for MRSA carriers [10].

Despite the vast body of literature investigating the effect of different antibiotic treatments in various kinds of surgical procedures, to the best of our knowledge, only a few studies have compared SSI rates after orthopaedic surgery among different antibiotic prophylactic regimens in MRSA carriers [11,12]. Iqbal et al. reported in a retrospective study of orthopaedic trauma patients that, among 27 MRSA carriers, none of the 5 patients who received

teicoplanin developed SSIs, whereas 5 out of 22 patients who received cefuroxime developed MRSA SSI [11]. However, Gupta et al. demonstrated different results in their retrospective cohort study of veterans undergoing surgical procedures including orthopaedic surgery. They showed that vancomycin prophylaxis was not associated with a significant risk reduction of SSIs compared to other antibiotics in MRSA carriers with a relative risk (RR) of 0.61 (95% confidence interval (CI) 0.06 to 5.75) [12]. Nevertheless, both studies were retrospective observational studies with flaws that could be classify them as very low-quality.

Although little has been studied in MRSA carriers undergoing orthopaedic surgery, there are several studies that compared MRSA SSI rate between different prophylactic antibiotics in patients undergoing orthopaedic surgery regardless of preoperative MRSA colonization [13–22]. Two moderate-quality randomized controlled trials [16,17] and six low to very low-quality observational studies [14,15,18–21] compared MRSA SSI rate between glycopeptides and first or second-generation cephalosporins. Although two randomized controlled trials (RCTs) [16,17] have shown no significant difference in MRSA SSI development between glycopeptides and cephalosporins, a random effects model meta-analysis of a total of eight studies [14–21] has shown a significantly lower risk in the glycopeptide group (pooled RR: 0.29, 95% CI 0.14 to 0.62, p = 0.001, I^2 = 10%). Subgroup analysis has also revealed that, compared to cephalosporins, both vancomycin and teicoplanin demonstrate lower risks of MRSA SSI after orthopaedic surgery (RR: 0.36, 95% CI 0.15 to 0.90; RR: 0.16, 95% CI 0.04 to 0.65, respectively). Among the eight studies, three [15,18,20] compared dual prophylactic antibiotics (glycopeptide + cephalosporin) with cephalosporin alone. When a selective analysis was performed excluding these three studies, pooled RR was 0.47 with 95% CI of 0.21 to 1.05 I2 = 0%.

As a result, we recommend vancomycin or teicoplanin as a preoperative antibiotic prophylaxis for MRSA carriers, however, with a moderate level of strength due to the lack of high-quality studies performed on MRSA carriers.

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QUESTION 4: What patient factors (allergy status, weight, etc.) should be utilized to alter the choice of perioperative antibiotic prophylaxis?

RECOMMENDATION: A weight-adjusted dose of antibiotics should be administered to patients. A minimum of 2 gm cefazolin is recommended for patients with weight > 70 kg to achieve effective minimum inhibitory concentration (MIC). Vancomycin or teicoplanin should be administered in resistant-strain carriers and those with cephalosporin allergies. Patients with a penicillin allergy, irrespective of immunoglobulin E (IgE) involvement, should be given second or third-generation cephalosporins to minimize cross-reactivity.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 3%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Perioperative antibiotic prophylaxis is one of the most effective strategies to prevent prosthetic joint infections (PJIs) following total joint arthroplasties (TJAs) [1]. Based on the profile of organisms causing early PJI, most current guidelines for perioperative antibiotic prophylaxis recommend intravenous (IV) first or second-generation cephalosporins within an hour of surgical incision, regardless of the surgery being a primary or revision TJA [2]. The recommended dose of cefazolin is 15 mg/kg which equates to 1 gm for patients who weigh less than 80 kg, whereas the standard dose for cefuroxime is 1.5 gm regardless of weight. A cefazolin dose of 2 gm and 3 gm is advised for patients over 80 kg and 120 kg, respectively [2]. However, these guidelines only provide a generalized approach to antibiotic prophylaxis [2]. In the presence of patient factors that cannot be altered, a personalized perioperative antibiotic prophylaxis with an alternative should be considered. Multiple studies provide evidence for alternative antibiotic regimens to be tailored according to carrier status, weight and allergy status.

Resistant Strain Carriers

The most common pathogens cultured in the events of surgical site infections (SSIs) and PJIs in orthopaedic surgery are gram-positive organisms, especially *Staphylococcus aureus* [1], followed by coagulase-negative *Staphylococcus epidermis* [1]. Due to the growing incidence of antibiotic resistant strains, vancomycin or teicoplanin are recommended for nasal carriers of resistant strains [2]. Although clindamycin is also an effective antibiotic against some methicillin-resistant *S. aureus* (MRSA) strains, vancomycin is a more preferred option due to its bactericidal property [1]. However, there is conflicting evidence regarding the effectiveness of vancomycin in preventing SSIs/PJIs in MRSA carriers [3–9].

No significant reduction in SSI/PJI rate was reported when cefazolin was substituted with vancomycin for MRSA carriers in two studies [3,4]. A randomized trial screened 1,028 patients undergoing TJA and identified 228 *S. aureus* carriers. There were 89 were treated with vancomycin perioperatively, whereas 139 were treated in the standard protocol group. Eight patients were MRSA carriers, but the number of MRSA carriers allocated to each group is unknown [3]. The overall PJI rate in carriers between the intervention group and non-intervention group was small (3.4 vs. 4.3%, Table 1) [3].

Five studies screened orthopaedic patients for carrier status and administered either vancomycin or teicoplanin to MRSA carriers [5–9]. The infection rate in this group of patients was compared to patients who were not screened and, therefore, did not receive vancomycin or teicoplanin. Of the five studies, four studies used vancomycin as an alternative to cefazolin [5–7,9], whereas De Lucas-Villarrubia et al. administered teicoplanin instead [8]. In contrast to the previous studies mentioned, all five studies reported a significant reduction in infection rates in patients who were given alternative antibiotics after screening compared to those who received standard protocols (Table 1) [5–9].

Weight/BMI

Patients' weight or body mass index (BMI) also dictated changes in the dosing regimen of antibiotics prophylaxis, as achieving the therapeutic dose is more difficult in obese individuals. Sharareh et al. administered 1 gm and 2 gm of cefazolin to patients weighing under and over 70 kg, respectively [10]. One-dose of preoperative vancomycin was part of the standard protocol, in which every patient was administered 15 mg/kg of vancomycin. No significant differences were observed in the number of patients achieving above cefazolin minimum inhibitory concentration (MIC) between different BMI groups. Furthermore, there was no difference in average concentration of vancomycin in bone per kilogram between the different dosage groups (Table 2) [10].

TABLE 1. Infection rates between standard antibiotics and MRSA-targeted perioperative antibiotic regimen in orthopaedic surgery

Study	Study Design	Study Number	Infection Rate	P-value
De Lucas-Villarrubia [8] (2004)	Cohort study	599 screened + teicoplanin (13 MRSA carriers) 1,228 not screened	Screened + teicoplanin = 0.03% Not screened + no teicoplanin = 0.2%	< 0.05*
Rao [7] (2011)	Cohort study	164 screened + vancomycin 345 not screened	Screened + vancomycin = 0% Not screened + no vancomycin = 3.5%	0.016*
Hadley [4] (2010)	Cohort study	1,644 screened + vancomycin (58 MRSA carriers)	Screened + vancomycin = 1.28% Not screened + no vancomycin = 1.45%	0.809

		414 not screened		
Kim [9] (2010)	Prospective clinical study	7,019 screened + vancomycin (309 MRSA carriers) 5293 not screened	Screened + vancomycin = 0.19% Not screened + no vancomycin = 0.45%	0.0093*
Schweizer [6] (2015)	Pragmatic study	1,122 MRSA carriers	Vancomycin intervention = 15/10000 Pre-vancomycin intervention = 32/10000	0.005*
Malcolm [5] (2016)	Cohort study	2,291 (177 MRSA carriers) screened + vancomycin 1,751 not screened	Screened + vancomycin = 0.4% Not screened + no vancomycin = 0.9%	0.04*
Sousa [3] (2016)	RCT	228 *S. aureus* carriers	Vancomycin = 3.4% Standard protocol = 4.3%	0.219

RCT, randomized control trials; methicillin-resistant *S. aureus* (MRSA)
* Denotes statistical significance at the level of $p < 0.05$.

TABLE 2. Efficacy of weight-adjusted dosing regimen in obese patients undergoing orthopaedic surgery

Study	Study Design	Study Number	First-generation Cephalosporin Concentration Administered	Outcome	P-value
Cies [11] (2012)	Retrospective case-control study	200 pediatric patients	< 70 kg = weight-based dose of cefazolin (maximum 1 gm) > 70 kg = 1 gm dose	*Rate of MSSA SSI* > 70 kg = 35.9% < 70 kg = 20.5%	0.045*
Lübbeke [12] (2016)	Prospective cohort study	9,061 patients	Cefuroxime 1.5 gm for all patients	*Rate of PJI* BMI 35–39.9 = HR = 2.1, 95% CI: 1.1–4.3 Weight ≥ 100 kg = HR = 2.1, 95% CI: 1.3–3.6	 0.001* 0.003*
Sharareh [10] (2016)	Cohort study	34 patients	< 70 kg = 1 gm > 70 kg = 2 gm	*Patients above cefazolin MIC for MSSA* BMI < 24.9 = 100% BMI > 30–34.9 = 86.7% *Patients above vancomycin MIC for MRSA* < 1 gm = 86% 1.5 gm = 100%	0.19 0.80

BMI, body mass idex; CI, confidence interval; HR, hazard ratio; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; PJI, periprosthetic joint infection; SSI, surgical site infection
* Denotes statistical significance at the level of $p < 0.05$.

TABLE 3. Cross-reactivity between self-reported penicillin allergy and cefazolin in orthopaedic surgery

Study	Study Design	Study Number	Reported Allergy Rate	Number of Patients Administered Cefazolin	Adverse Reaction When Given Cefazolin
Haslam [24] (2012)	Cohort study	1,962 patients	196 patients (9.9%) IgE-mediated = 49 (25%) Non-IgE mediated = 147 (75%)	 0 54	0% in both groups
IgE, immunoglobulin E					

This was further supported by two observational studies that investigated the direct relationship between weight-adjusted cefazolin dose and the risk of SSIs/PJIs [11,12]. Cies et al. administered a standard dose of 1 gm cefazolin, irrespective of patient weight, to pediatric orthopaedic patients weighing more than 70 kg. Patients weighing less than 70 kg received weight-adjusted doses. The rate of SSI was significantly higher in the standard group (35.9 vs. 20.5%, p = 0.045, Table 2) showing efficacy of a weight-adjusted dose [11]. Lübbeke et al. reported a significant increase in the rate of PJIs in patients with BMIs greater than 35 when every patient was given 1.5 gm of cefuroxime. More specifically, there was an approximately two-fold and four-fold increase in PJI rate in patients with BMI of 35 to 39.9 and > 40, respectively, when compared to patients of normal BMI. Furthermore, patients weighing ≥ 100 kg exhibited twice the infection rate compared to patients < 100 kg (Table 2) [12]. In patients who are carriers of resistant strains or allergic to penicillin, a 15 mg/kg dose of vancomycin is recommended [13,14]. However, reaching therapeutic concentration is difficult in obese patients. Therefore, Catanzano et al. measured serum trough concentrations as a surrogate outcome of area under the curve (AUC)/MIC and reported that 60% of 216 patients were inadequately dosed [15]. Furthermore, Kheir et al. reported that only 28% of arthroplasty patients were adequately dosed with vancomycin with underdosing being more prevalent in obese patients [16].

Allergy Status

A number of studies recommend the use of second-generation cephalosporin in patients who have a penicillin allergy. This recommendation was based on a high cross-reactivity reported between first-generation cephalosporins and penicillin [2]. Studies report a cross-reactivity between penicillin allergy and cephalosporin ranging from 7.7 to 8.1% [17,18]. Saxon et al. and Kelkar et al. attributed the high rates of cross-reactivity to contamination of the drugs with penicillin during the manufacturing process [19,20]. However, other studies have shown cross-reactivity rates between 0.6 to 1% [21,22]. It is also important to note that many penicillin allergies are self-reported by patients and are often not true allergies. Hence, pre-admission skin testing for penicillin allergy may be of benefit to unmask the patients' true allergy status to administer appropriate antibiotics.

Two non-orthopaedic meta-analyses demonstrated a four-fold increase in incidence of adverse reactions when patients with penicillin allergy were given a first-generation cephalosporin instead of a second-generation cephalosporin [22,23]. Nevertheless, the absolute incidence of adverse reactions associated with first-generation cephalosporins is minimal. This was confirmed in a more recent retrospective cohort study, which found negligible adverse reactions in patients with penicillin allergy who were administered cefazolin [24]. Haslam et al. retrospectively investigated 1,962 patients, of which 196 patients self-reported as having a penicillin allergy (Table 3). There were 54 patients who were administered cefazolin and no patient reported any adverse reaction [24]. In addition, while some studies recommend clindamycin or vancomycin as an alternative to first-generation cephalosporins, superiority of clindamycin in the context of cephalosporin allergy is unclear [21,25].

Alternative Forms of Antibiotic Prophylaxis in High-Risk Patients

"Alternative" forms of prophylaxis have been suggested in patients with risk factors for PJI including intraosseous regional antibiotic administration (IORA) [26,27], dual antibiotic prophylaxis with a cephalosporin and vancomycin [28] and extended oral antibiotics [29–31]. Such regimens are postulated to provide more effective prophylaxis against PJI, but with disadvantages including increased cost, risk of side effects, concerns regarding antibiotic stewardship and promoting emergence of resistance. It has been suggested to restrict their use to patients with known risk factors for PJI, such as high BMI [32], male sex [33], diabetes mellitus [34], smoking [35], previous surgery [36] and immunosuppression [37]. Currently, there is insufficient evidence to support the use of dual or extended antibiotics in patients undergoing routine orthopaedic procedures.

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QUESTION 5: What are the indications for dual perioperative antibiotic prophylaxis in patients undergoing orthopaedic procedures? What are the optimal combinations of antibiotics?

RECOMMENDATION: In the absence of high-level data, we recommend that dual antibiotic prophylaxis should be reserved only for patients at high risk of infection, such as those undergoing revision surgery or at high risk for methicillin-resistant *S. aureus* (MRSA) infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 80%, Disagree: 15%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies related to the indications for dual antibiotic prophylaxis in patients undergoing orthopaedic surgery as well as the optimal combination of antibiotics. Searches for the terms "total joint arthroplasty," "orthop(a)edic," "antibiotic prophylaxis," "dual" and "combination" in various combinations and with different Boolean operators were performed through February 2018 using the search engines Medline, Embase and Cochrane. Inclusion criteria for our systematic review were all English studies (level I to IV evidence) that reported on dual perioperative antibiotics for total joint arthroplasty. Exclusion criteria were non-English language articles, studies over ten years old, non-human studies, retracted papers, case reports, review papers, studies with less than ten patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were followed. The initial search resulted in 2,283 papers. After removal of duplicates, 201 titles were evaluated, 35 full-text papers were read and 13 studies met the full inclusion and exclusion criteria to allow for the analysis.

While the use of first or second-generation cephalosporins is recommended as first-line perioperative antibiotics due to their broad range of pathogen coverage [1–3], patients who are proven or potential carriers of MRSA or those with a cephalosporin allergy (not penicillin allergy) may receive alternative antibiotics. For penicillin-allergic patients, the use of a third or fourth-generation cephalosporin (such as cefuroxime and ceftriaxone) with dissimilar side chains than the offending penicillin carries a negligible risk of cross-reaction [4]. The most common alternative used is vancomycin that has poor gram-negative coverage and should not be used as monoprophylaxis; and, hence its use should be combined with another antibiotic such as an aminoglycoside for gram-negative coverage. In addition, vancomycin dosing should be weight-based at 15 mg/kg [5]. Recent studies have demonstrated that vancomycin monotherapy is associated with an increased risk of infection compared with cefazolin [5,6], particularly by gram-negative organisms [7]. Furthermore, despite the reduction in the rate of MRSA infections, vancomycin should be used with caution due to the potential for the emergence of organism resistance, most notably vancomycin-resistant *enterococccus* (VRE) and vancomycin-resistant *Staphylococcus aureus* [8], and its potential for nephrotoxicity [9]. There are no randomized controlled trials, but there are several retrospective studies examining the use of dual perioperative antibiotic prophylaxis (Table 1).

TABLE 1. Summary of studies that evaluated the efficacy of dual antibiotic prophylaxis including a beta-lactam and a glycopeptide

Author/Year	Type of Study (Period)	Type of Surgery	Antibiotic Prophylaxis (n)*	Outcome	Infection Rate (P-value)	MRSA Rate
Capdevila 2016 [22]	Retrospective cohort study (2012-2013)	Femoral neck fracture	Cefuroxime 1.5 gm induction of anaesthesia + 1.5 gm after 2h + teicoplanin 800 mg (657)	SSI according to CDC criteria	2%	0.15%
Sewick 2012 [10]	Retrospective cohort study (2008-2010)	Primary THA and TKA	Cefazolin (500) vs. cefazolin + vancomycin (1328)	SSI according to CDC criteria	1.4% vs. 1.1% (> 0.05)	0.8% vs. 0.07%
Ponce 2014 [6]	Retrospective cohort study (2005-2009)	Primary THA and TKA	Cefazolin (15422) vs. vancomycin (1500) vs. cefazolin + vancomycin (1062) vs. clindamycin (846)	SSI	1.3% vs. 2.3% vs. 1.5% vs. 1.1% (< 0.05 for cefazolin vs. vancomycin)	Information not collected

Tornero 2015 [20]	Retrospective cohort, before and after changing the prophylaxis regime (2010-2013)	Primary THA and TKA	Cefuroxime 1.5 gm induction of anaesthesia + 1.5 gm after 2h (995) vs. cefuroxime + teicoplanin 800 mg (791)	PJI according to MSIS criteria	3.5% vs. 1.3% (< 0.05)	0.5% vs. 0%
Branch-Elliman 2017 [12]	Retrospective cohort study (2008-2013)	Primary THA and TKA	Single (beta-lactam or vancomycin) vs. beta-lactam + vancomycin	SSI within 30 days	1.26% vs. 1.43% (p > 0.05)	Information not collected
Burger 2018 [18]	Retrospective cohort study (2012-2016)	Primary THA and TKA	Cefazolin (1044) vs. cefazolin + vancomycin 1 gm B45 (476) vs. cefazolin + vancomycin W45 1 gm (477)	PJI according to MSIS criteria	2.1% vs. 0.2% vs. 2.9% (p = 0.01)	0.4% vs. 0% vs. 0.3%
Liu 2014 [13]	Retrospective cohort, before and after changing the prophylaxis regime (2009-2012)	Revision TKA	Cefazolin (190) vs. cefazolin + vancomycin 1 gm (1.5 gm > 80 kg) (224)	SSI according to CDC criteria	7.89% vs. 3.13% (< 0.05)	2.63% vs. 0%

CDC, Centers for Disease Control and Prevention; MSIS; Musculoskeletal Infection Society; PJI, prosthetic joint infection; SSI, surgical site infection; THA, total hip arthroplasty; TKA, total knee arthroplasty; B45, vancomycin infusion was initiated 45 minutes before the surgical incision; W45, vancomycin infusion was initiated less than 45 minutes before the surgical incision.

* Antibiotic dose is given when the information was provided in the report.

Sewick et al. [10] retrospectively reviewed 1,828 primary total joint arthroplasties (TJAs) that received either a dual antibiotic regimen of cefazolin and vancomycin or received cefazolin alone in order to determine the rate of surgical site infections (SSIs) as well as the microbiology of subsequent SSIs. There were a total of 22 SSIs (1.2%) with no significant difference in the infection rate between the dual antibiotic prophylaxis group compared to the single antibiotic regimen (1.1 and 1.4% respectively, p = 0.636). However, while the addition of vancomycin to cefazolin did not decrease the rate of SSIs, it did decrease the incidence of MRSA infections (0.08 vs. 0.8% p = 0.022), but with a high number needed to treat. Ponce et al. [6], in a recent study, reported that there was no difference in SSI rate between patients receiving cefazolin monotherapy or cefazolin plus vancomycin. Elliot et al. [11] developed an economic model to explore the cost-effectiveness of vancomycin and/or cephalosporin as antibiotic prophylaxis in patients undergoing total hip arthroplasty (THA). Combination therapy (such as vancomycin plus a cephalosporin) was recommended when the rate of MRSA SSI was 0.25% or greater, and the rate of non-MRSA SSI was 0.2% or greater. Branch-Elliman et al. [12] demonstrated that dual antibiotics (beta-lactam plus vancomycin) versus single antibiotic (vancomycin or a beta-lactam) had no differences in SSI rates after total joint arthroplasty (1.43 vs. 1.26%, adjusted rate ration (RR): 1.09).

While the literature does not support the use of dual antibiotics for primary TJA, a recent study by Liu et al. [13] has demonstrated that the targeted use of vancomycin and cefazolin among patients undergoing revision total knee arthroplasty (TKA) significantly reduced the rate of overall infections (7.89 to 3.13%, p = 0.046), particularly MRSA (4.21 to 0.89%, p = 0.049). It is important to note that the author's institution had a high baseline rate of PJIs due to MRSA and methicillin-susceptible *S. epidermidis* (MRSE). Thus, there may be a potential indication to use a combination of cefazolin and vancomycin for high-risk surgical patients, including revision cases where infection risk is higher than a primary TJA or in regions or institutions with high MRSA rates.

Ahmed et al. [14] retrospectively reviewed 1,500 patients undergoing hip fracture surgery comparing the use of gentamicin plus flucloxacillin (dual antibiotics) vs. cefuroxime alone in order to evaluate the rate of deep SSIs. Paradoxically, there was an increase in deep SSIs in the dual antibiotic group compared to the cefuroxime group (2.5 vs. 1.1%), reaching statistical significance (p = 0.036).

Another precaution for using dual antibiotics is the propensity for developing acute kidney injury, which is not an infrequent situation with the use of antibiotic combinations, particularly those including gentamicin [15–17] and vancomycin [9]. It should be noted that in the study by Courtney et al. [9], dual antibiotic (vancomycin plus cefazolin) prophylaxis was found to be an independent risk factor for acute kidney injury (AKI) after primary THA/TKA (adjusted odds ratio (OR): 1.82, 95% confidence interval (CI) 1.25 to 2.64, p = 0.002). In contrast, Burger et al. [18] did not find a higher difference in renal toxicity when combination antibiotic prophylaxis was used. A potential explanation is that in the first study is that vancomycin was administered for 24 hours, while in the second study only one intraoperative dose of vancomycin was given. Since teicoplanin is less nephrotoxic than vancomycin and could be infused in < 20 minutes with a very low risk of Redman Syndrome, we consider that teicoplanin should be the glycopeptide of choice in countries that have it available. The recommended dose is 800 mg administered during the induction of anaesthesia. Since teicoplanin is not available in the USA, vancomycin would still be the first-line option. Current guidelines [2] recommend that the administration of 15 mg/kg of vancomycin (according to actual body weight) in order to obtain a serum concentration ≥ 15 mg/L until the completion of surgery. In order to avoid Redman Syndrome, it should be infused at a maximum rate of 1 gm per hour. A recent study showed that only 28% of cases received a correct dose of vancomycin [5]. The authors calculated the expected levels using pharmacokinetic equations and demonstrated that a weight-based protocol would have resulted in fewer patients having unacceptably low vancomycin levels (< 15 mg/L). Indeed, a previous study in cardiac surgery demonstrated that a dose of 20 mg/kg resulted in achieving therapeutic vancomycin levels in all patients [19]. Therefore, it is necessary to adjust the vancomycin dose based on body weight.

As mentioned above, when using dual antibiotics, teicoplanin can be used as an alternative to vancomycin. It can be infused over 20 minutes without the risk of Redman Syndrome and has a better safety profile than vancomycin. Tornero et al. [20] showed a reduction in the rate of PJIs when using teicoplanin and cefuroxime in combination was compared to cefuroxime as monotherapy (1.26 vs. 3.51%, p = 0.002). Soriano et al. [21] demonstrated similar results when evaluating antibiotic prophylaxis for patients with femoral neck fractures undergoing surgery and found that the combination of teicoplanin and cefuroxime reduced infection rates compared to cefuroxime as monotherapy (2.36% vs. 5.07%, p < 0.05). In a follow-up study from the same institution, Capdevila et al. [22] retrospectively reviewed the rate of infection in the same cohort ten years after the implementation of dual antibiotic prophylaxis in patients with femoral neck fractures and found that the rate of infection remained low at 2%.

Bosco et al. [23] demonstrated that the addition of an EGNAP (expanded gram-negative antimicrobial prophylaxis), such as gentamicin or aztreonam, to cefazolin decreased the rate of PJIs in patients undergoing primary THA but not in TKAs. This is partly because at their institution, gram-negative organisms caused 30% of the SSIs following hip procedures and only 10% of SSIs after knee procedures.

One should note the importance of timing of administration of vancomycin. Burger et al. included in their analysis the moment of starting vancomycin infusion. In one group, vancomycin administration was initiated 45 minutes before the surgical incision, and, in the other group, the infusion was initiated less than 45 minutes before the surgical incision. The infection rate was significantly lower when the infusion of vancomycin was started earlier than the group who had the infusion closer to the start of the procedure [18].

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QUESTION 6: Should extended (beyond 24 hours) antibiotic prophylaxis be administered to patients with surgical drain(s) in place?

RECOMMENDATION: No. There is no indication for prolonged antibiotic prophylaxis regardless of the presence of surgical drains. Prolonged prophylaxis is potentially dangerous, because it increases the fraction of resistant microorganisms on the skin microbiome.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 91%, Disagree: 8%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

There is one study analyzing this question in a multicenter, double-blind randomized trial comparing a two-day-course of cefamandole-prophylaxis versus a five-day course of cephazolin-prophylaxis in 965 patients with total hip arthroplasty [1]. The rate of periprosthetic joint infections (PJIs) were similar in both groups (0.7 vs. 0.5%, not significant (NS). No significant difference was observed in the fraction of colonized drains (mean duration of drainage 3.2 $\pm$ 0.3 days). However, the number of cefamandole- and cephalozin-resistant strains was significantly higher in the long-prophylaxis group.

In two other randomized controlled trials in patients with hip and knee arthroplasty, short versus long prophylaxis was analyzed. Nelson et al. [2] reported similar infection rates, namely 3/186 (1.6%) with one-day cefazolin and 4/172 (2.3%) with a seven-day-prophylaxis in patients with hip and knee arthroplasty as well as with hip repair. Similarly, Mauerhan et al. [3] reported in a double-blind randomized trial a non-significantly lower rate with a single dose of cefuroxime 1/187 (0.5%) vs. a three-day cefazolin prophylaxis regimen 2/168 (1.2%) in patients with hip arthroplasty. In the same publication, 1/178 (0.6%) of the patients with knee arthroplasty had a surgical site infection with a single dose of cefuroxime versus 3/207 (1.4%) with a three-day course. Thus, prolonged antimicrobial prophylaxis did not prevent exogenous infections via surgical drains.

In addition, as an analogy to another field, in two trials involving patients with cardiac surgery, the effect of a prolonged postoperative antibiotic prophylaxis has been evaluated. Niederhäuser et al. [4] showed that prophylaxis until removal of the intra-aortic balloon pump did not result in a lower infection rate than regular one-day prophylaxis. Similarly, in an observational study, Harbarth et al. [5] demonstrated after adjustment for possible confounding factors, that > 48-hour prophylaxis was not associated with a decreased risk of surgical site infection as compared to $\leq$ 48 hours. In addition, long-term prophylaxis significantly increased the risk of acquired antibiotic resistance.

Similarly, Stefansdottir et al. [6] looked at the effect of a narrow-spectrum antibiotic prophylaxis on the skin microbiome. They showed that with three prophylactic doses of cloxacillin over a period of 12 hours, the resistance pattern of the microbiome in the groin significantly increased. The rate of methicillin-resistant coagulase negative species in the groin increased from 20% preoperatively to 50% postoperatively ($p < 0.001$).

Taken together, in several well-done studies in the field of joint arthroplasty and cardiac surgery, prolonged prophylaxis was obviously not protective and was even potentially harmful by increasing the rate of resistant strains on the skin microbiome.

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QUESTION 7: Does the presence of implants from prior surgery in the affected joint alter the perioperative antibiotic prophylaxis?

RECOMMENDATION: There is currently no evidence to suggest the use of alternate or additional perioperative antibiotics in joint surgery when prior implants exist from previous surgery. There is an increasing body of literature to suggest that conversion hip and knee arthroplasty carries a risk of surgical site infection/periprosthetic joint infection (SSI/PJI) similar to revision surgery rather than primary surgery and altering antibiotics may be one method to mitigate this risk. However, studies will need to be conducted to either confirm or refute this statement given the lack of evidence.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Hip fractures, dysplasia, femoral-acetabular impingement (FAI), slipped capital femoral epiphysis (SCFE) and Legg-Calve-Perthes disease are common reasons to undergo hip surgery with implants that eventually require conversion to total hip arthroplasty (conversion THA) [1–4]. In addition, anterior cruciate ligament reconstruction (ACLR), multi-ligamentous knee injuries, fractures and osteotomies are common reasons for prior knee surgery with implants before conversion to total knee arthroplasty (conversion TKA) [5–8]. Recent studies have demonstrated that conversion THA [3,4] and TKA [5,9] have complication rates closer to revision total joint arthroplasty (TJA) than primary TJA, including increased SSIs and PJIs. As the complications of conversion procedures become more apparent, should we change the perioperative antibiotic prophylaxis to potentially mitigate the increased risk of SSIs/PJIs?

The use of prophylactic antibiotics has been accepted as an enabling factor to successfully perform surgery in the modern era with a lower risk of surgical site infection [10]. Many prior reports, including randomized, controlled trials and a systematic review of RCTs, have reviewed the subject [11,12]. Many factors have been studied including timing, mode of delivery, dose, duration, frequency and single versus combination therapy [13]. Although we are measured as surgeons and medical centers on appropriate use of prophylactic antibiotics during routine primary arthroplasty, there remains no consensus on the presence of other implants in the affected joint and perioperative antibiotic prophylaxis in total joint surgery [11]. The recent work identifying conversion procedures at higher risk of SSIs/PJIs either used a national database [3,4] or retrospective chart review [5,9] without specification of the antibiotic prophylaxis used, assuming prophylaxis was similar to routine primary TJA.

In conclusion, it therefore seems that the standard dose/selection of perioperative antibiotic prophylaxis for primary TJA may not be adequate for conversion TJA surgery. At this time, it is unclear if the presence of prior hardware, host factors or extended operative duration required for conversion are responsible for increased complications rates, and further research will be required. Additional antibiotics [14], prolonged duration [15] or non-antibiotic adjuncts such as dilute betadine rinse [16] may be required in a similar manner to revision procedures to lower the SSI/PJI rate in conversion TJAs. In the absence of any guiding literature, we cannot recommend for or against altering perioperative antibiotics based on prior surgical hardware before joint surgery. Further studies will be required to see what, if any, perioperative measures will help reduce SSIs/PJIs in these patients.

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QUESTION 8: Can ceftriaxone be utilized as an alternative to cefazolin in the treatment of orthopaedic infections caused by methicillin-sensitive Staphylococcus aureus (MSSA)? If so, what dosing is recommended?

RECOMMENDATION: There is minimal data in the literature evaluating the use of ceftriaxone and its appropriate dosage to treat orthopaedic infections caused by MSSA. International guidelines state that there is no consensus on the use of ceftriaxone in the treatment of prosthetic joint infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 90%, Disagree: 4%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

MSSA is a potent pathogen and a leading cause of orthopaedic infections including prosthetic joint infections (PJIs) [1]. The antibiotic standard of care therapy (SOCT) for MSSA infections includespenicillinase-resistant penicillins (nafcillin/oxacillin/flucloxacillin) with the first-generation cephalosporin, cefazolin, as an alternative [1–4]. For penicillin-allergic patients, the use of third- or fourth-generation cephalosporin or cephalosporins (such as cefuroxime and ceftriaxone) with dissimilar side chains than the offending penicillin, carries a negligible risk of cross-allergy and may be used in this specific instance for MSSA infections [5–7].

Cephalosporins are broad-spectrum antibiotics with structures based on the beta-lactam ring [8]. They are divided into generations. The first generation, which includes cefazolin (CFZ), are predominantly active against gram-positive bacteria. The third generation of cephalosporins, which includes ceftriaxone, have better activity against gram-negative organisms, but *reduced* activity against gram-positives. Ceftriaxone (CTX) is characterized by a prolonged half-life (eight hours) compared to other cephalosporins and this allows a once-daily dosing regimen [9]. This has proved convenient for certain medical indications including outpatient antibiotic therapy services [10–12]. One potential benefit of cephalosporins over penicillins is lower reported rates of adverse drug reactions for the former group of drugs in clinical studies [13,14] Weiland et al. [15] compared ceftriaxone versus oxacillin for MSSA osteoarticular infections in 124 patients and found no difference in treatment success at three to six months (83 vs. 86%, p = 0.7) and at > six months (77 vs. 81%, p = 0.6) following the completion of intravenous antibiotics. Furthermore, patients receiving oxacillin were more likely to have it discontinued due to toxicity.

The literature regarding the use of CTX as an alternative to CFZ in the treatment of MSSA infections is sparse, with only seven published studies providing direct comparison. These include five retrospective cohort descriptive studies and two prospective, double blinded, randomized controlled trials (RCTs). Of these, three are industry-funded by the manufacturer of CTX (Roche™, Basel, Switzerland) including one of the RCTs (which will be discussed first).

Mandell et al. [16] compared the efficacy of CTX vs. CFZ against various organisms, including gram-negatives, and showed no significant difference in clinical outcomes. Gugliemo et al. [17], in a retrospective cohort study of 31 patients, compared CTX against CFZ in various dosing regimens and found no significant difference in outcomes. Tice et al. [18] reported on the outcome of treating osteomyelitis with various antibiotic regimens in another retrospective cohort study of 454 patients. Despite there being no significant differences found in any of the treatment groups (potentially due to the lack of power in the study), they concluded that the outcome supported the use of CTX.

The independent studies similarly did not show any significant difference in treatment, perhaps due to their design and lack of statistical power. Winans et al. [12], in a well-performed retrospective study comparing the efficacy of CTX against CFZ in MSSA infections, showed no differences between the groups and advised the need for a large RCT. Grayson et al. [19], in an RCT studying the outcome of treating cellulitis with either CFZ combined with probenecid to allow once daily dosing against CTX, showed no significant differences in outcome. However, this study was underpowered. Paul et al. [20] showed a higher 30-day mortality rate in patients with MSSA bacteremia treated with CTX compared to CFZ or oxacillin but again the study lacked power.

In conclusion, there are no robustly-designed or suitably-powered clinical studies to answer the null hypothesis that CTX is as effective as CFZ in treating MSSA infections.

A few experimental and animal studies, however, provide useful additional information. Cephalosporins are known to be protein bound in serum and this is thought to mediate the inoculum effect that increases their minimum inhibitory concentration (MIC). This is described by the developers of CTX based on their in vitro and in vivo data [9] and corroborated by Tawara et al. [21] in their animal study that shows that CTX has higher protein binding than CFZ and this may explain the consistently recorded MICs that CTX has over CFZ against MSSA species.

This leads onto dosing considerations. Due to the protein binding of CTX, numerous authors have suggested that higher dosing regimens are required with experimental data in support [4,21–23]. CTX is licensed at doses of 1 to 2 gm per day, but the studies above suggest that doubling this dose to 2 gm twice a day may be necessary to overcome the protein binding effect [22–24]. Nguyen et al. [25] argues that 2 gm per day is the appropriate dosing, given that the US Food and Drug Administration recommends a ceftriaxone dosage for MSSA of 2 to 4 gm per day based on pharmacodynamic analysis.

In summary, there is no robust data to support the use of ceftriaxone instead of cefazolin in the management of orthopaedic MSSA infections. Infectious diseases leaders also hold this opinion worldwide [1,25,26]. There is a need for multi-center RCTs to answer this question definitively.

Search Methodology: A comprehensive literature review was performed to identify all studies on the use of ceftriaxone in the treatment of orthopaedic infections caused by MSSA. The Medical Subject Headings (MeSH) search strategy included the following terms: ("ceftriaxone*"AND/OR "cefazolin*") AND ("MSSA*" OR "*Staphylococcus aureus**" OR "orthopaedic infections*") in various combinations and with different Boolean operators. The search engines used were: Cochrane, Embase, PubMed, Medline, Google Scholar and Web of Science. The search was conducted for studies through February 2018. Inclusion criteria for our systematic review were all English studies (level I to IV evidence) that reported on ceftriaxone use in treating orthopaedic

infections caused by MSSA. Exclusion criteria were non-English language articles, studies > ten years old, nonhuman studies, retracted papers, case reports, review papers, studies with less than ten patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were followed. The initial search results in excess of 1,000 papers. After removal of duplicates and screening of titles and abstracts, 69 full reports were assessed and reviewed.

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