Shafa Ortho J. 2015 February; 2(1):e445. DOI: http://dx.doi.org/10.17795/soj-445

Published online 2015 February 21. **Review Article**

Optimal Timing and Antibiotic Prophylaxis in Periprosthetic Joint Infection: Literature Review and World Consensus (Part Two)

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Received: December 3, 2014**; Revised:** January 2, 2015**; Accepted:** February 1, 2015

Context: There is a need to find the best choice of preop antibiotic prophylaxis to prevent Periprosthetic Joint Infection (PJI) in the situations where the first generation cephalosporins are not indicated.
Evidence Acquisition: Delegates in Workgroup 3 of the Consensus Meeting on PJI reviewed the English literature for relevant articles. Totally, 51 of 221 articles were relevant to the five following questions regarding perioperative antibiotic prophylaxis to prevent PJI.
Results: The choice of antibiotics for patients with preexisting prostheses, such as heart valves, is similar to that for routine elective arthroplasty. Currently, teicoplanin and vancomycin are reasonable alternatives when routine antibiotic prophylaxis cannot be administered. In a patient with a known anaphylactic reaction to penicillin, vancomycin or clindamycin should be administered as prophylaxis. Teicoplanin is an option only in countries where it is available. In a patient with a reported non-anaphylactic reaction to penicillin, a second generation cephalosporin can be used safely, as there is limited cross-reactivity. Penicillin skin testing may be helpful in certain situations to clarify whether the patient has a true penicillin allergy.
Conclusions: Recommendations for choice of perioperative antibiotic prophylaxis in hip and knee arthroplasty were provided based on evidences in the literature and consensus of expert delegates from consensus meeting.

Keywords: Infection; Periprosthetic; Joints; Arthroplasty; Penicillin; Vancomycin

1. Context

Decision making in selecting the best choice of antibiotic prophylaxis for periprosthetic joint infection (PJI) is a challenge for all arthroplasty surgeons. There are special situations where routine use of first-generation cephalosporins is not sufficient, appropriate, or it is even contraindicated. In these situations, e.g. patients with prostheses in other parts of their body, such as heart valves or patients who are allergic to penicillin, the best or most effective antibiotic prophylaxis must be chosen. All delegates of the consensus meeting on PJI voted on the following statements regarding the choice of antibiotic prophylaxis in special situations at the time of hip or knee arthroplasties.

2. Evidence Acquisition

From November 2012 until August 2013, 400 delegates from all over the world formed 15 workgroups to review the current literature and find high level evidence for all issues related to PJI. Workgroup No. 3 (authors) was assigned to review the current literature on perioperative antibiotics. The goal was to find answers and recommendations for more than 264 questions, based on the high level evidence, if present, or reach to a consensus, when there is a lack of high level evidence.

After 10 months of hard work by the delegates from 58 countries and 100 societies, relevant publications reviewed and communications exchanged, finally, a draft was prepared to be presented for vote at the final meeting on 1st of August 2013. The draft included recommendations for management on the basis of high level of evidence if present. Otherwise the cumulative wisdom of 400 delegates from 58 countries and over 100 societies used to reach a consensus about practices lacking higher level of evidence.

3. Results

Question 3: What is the choice of antibiotic in patients who have preexisting prostheses, such as heart valves?

Consensus: The choice of antibiotics for patients with

preexisting prostheses, such as heart valves, is the same as that for routine elective arthroplasty.

Delegate Vote: Agree: 94%, Disagree: 3%, Abstain: 3% (Strong Consensus)

Justification: Patients with preexisting prostheses, such as heart valves, are at risk for infective endocarditis due to bacteremia, which although is relatively rare, it can lead to catastrophic complications and death. Guidelines for the prevention of infective endocarditis have been published by the American Heart Association (AHA) for more than 50 years. The first nine guidelines (published between 1955 and 1997) were based on low-level evidence; only more recently have the guidelines been stratified based upon the lifetime risk of infective endocarditis. Similar to the change in recommendations regarding dental prophylaxis for patients undergoing total join arthroplasty (TJA), the 2007 antibiotic prophylaxis guidelines for infective endocarditis from the AHA and the Infectious Disease Society of America (IDSA) recommend antibiotic prophylaxis only for patients at the highest risk of infective endocarditis and only for selected dental procedures (e.g. those that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa) (1).

Infections that complicate heart valve replacement and prosthetic joint replacement have several features in common. *Staphylococcus aureus (S. aureus)* and *Staphylococcus epidermidis (S. epidermidis)* are common pathogens and infection rates are similar (2, 3). It is generally accepted that antimicrobial prophylaxis reduces the frequency of early postoperative infections; however, when such infections do occur, they are difficult to control without removing the prosthesis. The antibiotics that are recommended for endocarditis prophylaxis are similar to those of prophylaxis against PJI. Also, when an infection is known or suspected to be caused by *S. aureus*, the antibiotic regimen should contain an antistaphylococcal penicillin or a cephalosporin; whereas vancomycin should be used in those in whom an infection is known or suspected to be caused by methicillin resistant *S. aureus* (MRSA) (4).

While there is literature to support the use of prophylactic antibiotics for up to 48 hours postoperatively in cardiac surgery, to prevent deep and superficial sternal wound infection, this is not relevant to our discussion of TJA surgery in a patient with a preexisting heart valve (4, 5). Interestingly, there have been several studies showing an increase in the routine use of vancomycin for routine valve surgery prophylaxis over the past years. Haydon et al. reviewed the national practice patterns for antibiotic prophylaxis in cardiac surgery in Australia and found that between 2004 and 2008, there was a doubling in the proportion of cardiac units using vancomycin for routine prophylaxis from 31% to 62% ($P < 0.001$) (6).

Question 4: What alternatives are available for routine prophylaxis when cephalosporins are not an option?

Consensus: Currently teicoplanin and vancomycin are reasonable alternatives when routine antibiotic prophylaxis cannot be administered.

Delegate Vote: Agree: 73%, Disagree: 22%, Abstain: 5% (Strong Consensus)

Justification: Teicoplanin has proven to be an effective and safe prophylactic agent in prosthetic implant surgery in Europe, but is not yet available in the US, Canada, or China (7-10). Due to the increased frequency of MRSA and MRSE infections in recent years, the prophylactic use of alternative antibiotics such as glycopeptides (vancomycin and teicoplanin) in hospitals where MRSA/MRSE are prevalent may be justified (11). As vancomycin is more difficult to administer and has a shorter half-life and poorer tolerability profile than teicoplanin, the latter may be a better choice in these settings. Teicoplanin is notable for having a long half-life (70-100 hours), low toxicity, and good tissue penetration, which allows it to achieve therapeutic concentrations in bone and surrounding soft tissues (11-13).

Ceftaroline (fifth generation cephalosporin) has the same spectrum of activity as ceftriaxone with additional MRSA activity. The US Food and Drug Administration and the European Medicines Agency have provided indications for the use of ceftaroline for treatment of complicated skin and soft tissue infections only, and not for prophylaxis.

In one multicenter Randomized Controlled Trial (RCT), Periti et al. compared the administration of a single dose of teicoplanin (400 mg intravenous (IV) bolus at time of anesthesia) versus that of five doses of cefazolin over a 24 hours period (2 g at induction and 1 g every 6 hours postoperatively) as prophylaxis in patients undergoing TJA. They randomized 846 patients and noted that six patients (1.5%) in the teicoplanin group and seven patients (1.7%) in the cefazolin group developed a surgical wound infection during their hospital stay, which was a non-significant difference. Additionally, an insignificant difference in adverse events was recorded in the two groups, with three (0.7%) of the teicoplanin patients and nine (2.1%) of the cefazolin patients (10).

Question 5A: What antibiotic should be administered in a patient with a known anaphylactic penicillin allergy?

Consensus: In a patient with a known anaphylactic reaction to penicillin, vancomycin or clindamycin should be administered as prophylaxis. Teicoplanin is an option in countries where it is available.

Delegate Vote: Agree: 88%, Disagree: 10%, Abstain: 2% (Strong Consensus)

Question 5B: What antibiotic should be administered in a patient with a known non-anaphylactic penicillin allergy?

Consensus: In a patient with a reported non-anaphylactic reaction to penicillin, a second generation cephalosporin can be used safely, as there is limited cross-reactivity. Penicillin skin testing may be helpful in certain situations to clarify whether the patient has a true penicillin allergy.

Delegate Vote: Agree: 87%, Disagree: 9%, Abstain: 4% (Strong Consensus)

Justification: When patients present with a penicillin allergy, further information should be obtained to determine whether an immunoglobulin E (IgE)-mediated response (anaphylaxis) occurred. In patients with a documented IgE-mediated response to penicillin, third and fourth generation cephalosporins can be used. First and second generation cephalosporins with R1 side chains, similar to that of penicillin (cefaclor, cefadroxil, cefatrizine, cefprozil, cephalexin, or cephradine) should be avoided; first and second generation cephalosporins with different R1 side chains can be prescribed.

Vancomycin and clindamycin are recommended as alternative agents for patients who have a true type I β-lactam allergy, manifested by immediate urticaria, laryngeal edema, or bronchospasm (14). Clindamycin is the preferred alternative for persons with an established β-lactam allergy or with contraindications to its use and at institutions with low rates of MRSA infection. Clindamycin has good bioavailability and at 30 minutes after infusion has been shown to exceed the MICs for *S. aureus* in both animal and human cortical bone samples (15). However, clindamycin is a bacteriostatic agent. In addition, vancomycin alone has a relatively poor activity against *S. aureus* and clinical studies suggest that vancomycin, as prophylaxis alone, increases the risk for surgical site infection (SSI). Therefore, a second agent should be considered (levofloxacin, moxifloxacin) in addition to vancomycin (16).

Cross-reactivity between penicillin and cephalosporin is overestimated and much lower than reported in earlier studies. The 10% risk estimate of for allergic reactions to cephalosporins in penicillin-allergic patients is based on data collected and reviewed in the 1960s and 1970s. It is due, in large part, to the widely referenced reviews of Dash and Petz, which reported allergic reactions in 7.7% and 8.1%, respectively, of penicillin-allergic patients (allergy was based on patient history) and only included first generation cephalosporins and second generation cefamandole (17, 18). The high cross-reactivity found in earlier studies may be due, in part, to the contamination of the study drugs with penicillin during the manufacturing process (19). Moreover, the authors of the early studies had a broader definition of allergy and did not account for the fact that penicillin-allergic patients have an increased risk of adverse reactions to any medication (20, 21). Skin testing in penicillin-allergic patients cannot reliably predict an allergic response to a cephalosporin, particularly to compounds with dissimilar side chains (22). However, skin testing may be useful in determining whether a true allergy to penicillin exists (23).

Twenty-seven articles on the topic of the cross-reactivity of penicillin and cephalosporin were reviewed, of which two were meta-analyses, 12 were prospective cohorts, three were retrospective cohorts, two were surveys, and nine were laboratory studies. The authors demonstrated that penicillin has a cross-allergy with first generation cephalosporins (OR 4.8; 95% CI 3.7-6.2) and a negligible cross-allergy with second generation cephalosporins (OR 1.1; 95% CI 0.6-2.1). Moreover, laboratory and cohort studies indicate that the R1 side chain, not the β-lactam ring, is responsible for this cross-reactivity. The authors conclude that the overall cross-reactivity between penicillin and cephalosporin is lower than previously reported, at 10%, although there is a strong association between amoxicillin and ampicillin with first and second generation cephalosporins that share a similar R1 side chain. The overall cross-reactivity between penicillin and cephalosporin in individuals who report a penicillin allergy is of approximately 1% and in those with a confirmed penicillin allergy, 2.55%, respectively. For penicillin-allergic patients, the use of third or fourth generation cephalosporin (such as cefuroxime and ceftriaxone), with dissimilar side chains than the offending penicillin, carries a negligible risk for cross allergy (24).

A similar review of 44 articles on the evidence of cross-reactivity between cephalosporin and penicillin in human and animal studies supports the finding that cephalosporin can be safely prescribed to a patient with a non-life threatening reaction to penicillin (including type I anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and angioedema) (25). The relative risk of an anaphylactic reaction to cephalosporin ranges from 1:1000 to 1:1000000 and this risk is increased by a factor of 4 in patients with a history of penicillin allergy (26).

Based on an analysis of nine articles that compare allergic reactions to a cephalosporin in penicillin-allergic and non-penicillin-allergic subjects, Pichichero et al. found that first generation cephalosporins have a cross-allergy with penicillin, but cross-allergy is negligible with second and third generation cephalosporins. Specifically, a significant increase in allergic reactions to cephalothin (OR 2.5, 95% CI 1.1-5.5), cephaloridine (OR 8.7, 95% CI 5.9-12.8), and cephalexin (OR 5.8, 95% CI 3.6-9.2) and all first generation cephalosporins plus cefamandole (OR 4.8, 95% CI 3.7-6.2) were observed in penicillin-allergic patients; no increase was observed with second generation cephalosporin (OR 1.1, 95% CI 0.6-2.1) or third generation cephalosporin (OR 0.5, CI 0.2-1.1) (21,22).

In a retrospective cohort of 2933 patients who received a cephalosporin (usually cefazolin) during their procedure, including 413 who were allergic to penicillin, only one of the penicillin-allergic patients may have had an allergic reaction to the cephalosporin; and one of the non-penicillin-allergic patients developed a rash, while the antibiotic was infused, requiring discontinuation of the antibiotic (27).

In a large, retrospective review of 534810 patients who received penicillin, followed by a cephalosporin at least 60 days later, Apter et al. noted that a total of 3877 patients had an allergic-like event (ALE) after penicillin administration, but only 43 (1.1%) experienced a second ALE

after receiving cephalosporin (unadjusted risk ratio (RR) 10.0; 95% CI 7.4–13.6). Interestingly, in a separate analysis reviewing sulfonamide antibiotics, 1.6% of penicillin sensitive patients experienced a second ALE after receiving a sulfonamide (7.2; 95% CI 3.8–12.5), suggesting that patients who are allergic to penicillin are at a higher likelihood of being allergic to other medications in general, not necessarily indicating that cross-reactivity had occurred (28).

Park et al. performed a retrospective cohort study to determine whether patients with a penicillin allergy were at an increased risk of adverse drug reactions when administered cephalosporin. Eighty-five patients with a history of penicillin allergy and positive penicillin skin test and 726 patients with a history of penicillin allergy and a negative penicillin skin test were administered a first generation cephalosporin. Five (6%) of the 85 cases had an adverse drug reaction to cephalosporin, compared to five (0.7%) of 726 of the control population (P = 0.0019). The rate of presumed IgE-mediated adverse drug reactions to the cephalosporin among the cases was 2 (2%) of 85 compared to 1 (0.1%) of 726 among the reference population (P = 0.03) (29).

4. Conclusions

Question 3: What is the choice of antibiotics in patients who have preexisting prostheses, such as heart valves?

Consensus: The choice of antibiotics for patients with preexisting prostheses, such as heart valves, is the same as that for routine elective arthroplasty.

Question 4: What alternatives are available for routine prophylaxis when cephalosporins are not an option?

Consensus: Currently teicoplanin and vancomycin are reasonable alternatives when routine antibiotic prophylaxis cannot be administered.

Question 5A: What antibiotic should be administered in a patient with a known anaphylactic penicillin allergy?

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Question 5B: What antibiotic should be administered in a patient with a known non-anaphylactic penicillin allergy?

Consensus: In a patient with a reported non-anaphylactic reaction to penicillin, a second generation cephalosporin can be used safely as there is limited cross-reactivity. Penicillin skin testing may be helpful in certain situations to clarify whether the patient has a true penicillin allergy.

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