



## Optimal timing and antibiotic prophylaxis in periprosthetic joint infection (PJI): literature review and world consensus (Part one)

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### Abstract

The questions of type of antibiotics and optimal timing of administration for prophylaxis of PJI are of the most important ones for all arthroplasty surgeons. All delegates of consensus meeting on periprosthetic joint infection voted on the following statements regarding optimal timing and antibiotic prophylaxis for prevention of infection in hip and knee arthroplasties.

**Consensus:** The preoperative dose of antibiotics should be administered within one hour of surgical incision; this can be extended to two hours for vancomycin and fluoroquinolones. Furthermore, surveillance measures are critical in ensuring clinician compliance with this objective. **Delegate Vote:** Agree: 97%, Disagree: 2%, Abstain: 1% (Strong Consensus)

**Consensus:** A first or second-generation cephalosporin (cefazolin or cefuroxime) should be administered for routine perioperative surgical prophylaxis. Isoxazolyl penicillin is used as an appropriate alternative. **Delegate Vote:** Agree: 89%, Disagree: 8%, Abstain: 3% (Strong Consensus)

**Foreword:** Despite all extraordinary discoveries in the fields of microbiology, antibiotics and surgical techniques, the battle against surgical site infection (SSI) is still running. Periprosthetic joint infection is the

fear of every orthopedic surgeon who is involved in orthopedic arthroplasty practice. PJI is a devastating complication that has a huge burden on patients' functionality, time and energy of the health care providers and resources.

This year the orthopedic community of the world experienced one of the unique events in the field of PJI named "World Consensus Meeting on PJI". After 10 months of work and reviewing 3500 publications a draft was prepared for vote at the world consensus meeting on 1<sup>st</sup> of August 2013. The whole process initiated and directed by Dr. Javad Parvizi from Rothman Institute, Thomas Jefferson University in Philadelphia.

This more than 360 pages of document includes recommendations and answers for 207 questions in the field of PJI. There is no doubt that the consensus document is a pillar for "best practice guidelines" that will serve

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\*The review provided here is a report of "international consensus meeting on peri-prosthetic joint infection (PJI)" held in Philadelphia, August 2013. The world consensus approved significantly by various scientists across the world including William Arnold, Katherine Belden, Mohammad Ghazavi, Goran Bicanic, Stefano Bini, Fabio Catani, Jiying Chen, Karine M, Godefroy, Erik Hansen, Paul Holham, Hamid Hosseinzadeh, Kang II Kim, Klaus Kirketerp-Moller, Lars Lidgren, Jian Hao Lin, Jess H Lonner, Christopher Moore, Panayiotis Papagelopoulos, Lazaros Poultsides, Khalid Saleh, Julia V Salmon, Edward Schwarz, Randi Silibovsky, Jose Stuyck, Markus Vogt, Annette W Dahl, Koji Yamada.

many of our patients for many years to come.

I was proud to serve as a member of the workgroup on perioperative antibiotic and the following is a selection of only 2 questions which is part of more than 50 pages of document answering 22 questions in the field of perioperative antibiotic prophylaxis.

**Question 1: What is the optimal timing of the preoperative dose of antibiotics?**

**Consensus:** The preoperative dose of antibiotics should be administered within one hour of surgical incision; this can be extended to two hours for vancomycin and fluoroquinolones. Furthermore, surveillance measures are critical in ensuring clinician compliance with this objective.

**Delegate Vote:** Agree: 97%, Disagree: 2%, Abstain: 1% (Strong Consensus)

**Justification:** The scientific rationale for antibiotic prophylaxis is to inhibit or eliminate contaminating microorganisms that gain access to the surgical site during the procedure, which reduces the probability of an established infection. Thus, the goal of administering preoperative antibiotics is to allow for adequate tissue (blood, soft tissue, and bone) concentrations by the time of incision. These antibiotics should exceed the minimum inhibitory concentration (MIC) for the organisms likely to be encountered for the duration of the operation. This depends on the antibiotic used. There are a number of studies which validate the importance of the preoperative dose of antibiotics in decreasing periprosthetic joint infection (PJI) and surgical site infection (SSI) in total joint arthroplasty (TJA). However, there are conflicting opinions as to the optimal timing of this dose. Some studies suggest that within 2 hours of incision is best, while others recommend scheduling the dose as close to surgical incision as possible. There are several institutional guidelines which support a one hour preoperative dose of antibiotics as a Surgical Care Improvement Project (SCIP) measure. In addition to these guidelines, it is critically important to

have surveillance measures in place to document compliance with these protocols.

The American Academy of Orthopedic Surgeons (AAOS), the Centers for Disease Control (CDC), and SCIP guidelines recommend that prophylactic antibiotics be completely infused within one hour before the surgical incision(1). The AAOS recommendation for the use of intravenous antibiotic prophylaxis in primary TJA, recommendation 2, states that “timing and dosage of antibiotic administration should optimize the efficacy of the therapy. Prophylactic antibiotics should be administered within one hour before skin incision.” Due to extended infusion time, vancomycin and fluoroquinolones should be started within 2 hours before incision. When a proximal tourniquet is used, the antibiotic must be completely infused before inflation of the tourniquet(2). The US advisory statement recommends that antimicrobial prophylaxis be administered within one hour before incision and discontinued within 24 hours after the end of the operation (3), while European guidelines recommend a single dose within 30 minutes before incision (4).

Timing < 2hrs: The seminal article on this subject studied the timing of administration of prophylactic antibiotics and the risk of surgical wound infections in clean and clean-contaminated cases at a large community hospital (5). In a study of 2,847 patients (5), 313 (11%) received TJA. The authors found that the rate of infection was lowest for patients who received an antibiotic from 0 to 2 hours before the incision (5). Specifically, of 1,708 patients who received prophylactic antibiotics during this time frame, only 10 (0.6%) subsequently developed SSI compared to 14 (3.8%) of 369 patients who received antibiotics 2-24 hours preoperatively, 4 (1.4%) of 282 patients who received antibiotics within 3 hours after incision, and 16 (3.3%) of 488 patients who received antibiotics 3-24 hours following incision. However, this study was conducted in 1985-1986, when there was considerable variation in timing of administration of the prophylactic antibiotic, and only 35% of pa-

tients received their dose within the contemporary standard of one hour prior to incision. Furthermore, the study found no significant difference in SSI rates when antibiotics were administered within 1 to 2 hours prior to incision compared with antibiotics administered 0 to 3 hours postoperatively.

**Timing <1 hr:** The leadership of the Medicare National Surgical Infection Prevention Project hosted the Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW) meeting and utilized the available literature to draft a consensus paper. The position of the SIPGWW is that the infusion of the first antimicrobial dose should begin within 60 minutes before incision (3,6).

Galandiuk et al. (7) combined the results of two prospective randomized controlled trials (RCTs) that compared antibiotic prophylaxis (either single-dose piperacillin with multi-dose cefoxitin) in elective surgical procedures of the gastrointestinal tract. The authors found that among other negative predictors, administration of an antibiotic for longer than 60 minutes preoperatively was associated with a higher rate of infectious complications.

In a large, retrospective cohort study using National Veterans Affairs data on prophylactic antibiotics of 32,459 surgical procedures from 2005-2009, Hawn et al. (8) found that higher SSI rates were observed for antibiotic administration more than 60 minutes prior to incision (unadjusted odds ratio (OR) 1.34, 95% confidence interval (CI) 1.08-1.66) compared with procedures in which antibiotics were administered within one hour of incision. However, in generalized additive models adjusted for patient, procedure, and antibiotic variables, no significant association was observed between prophylactic antibiotic timing and SSI (8).

**Timing 30-60 minutes:** In a prospective cohort study at a single academic hospital analyzing the incidence of SSI by the timing of antimicrobial prophylaxis in a consecutive series of 3,836 surgical procedures, Weber et al. (9) determined that administration of single-shot prophylactic cefuroxime is more effective in 30-59 minutes before

incision than during the last 30 minutes. The overall SSI rate for this mixed cohort of general, vascular, and orthopedic surgeries was 4.7% (180), and antimicrobial prophylaxis was administered within the final 30 minutes in 59% of all procedures. Multivariable logistic regression analysis showed a significant increase in the odds of SSI when antimicrobial prophylaxis was administered fewer than 30 minutes (crude OR 2.01; adjusted OR 1.95, 95% CI, 1.4-2.8;  $p < 0.001$ ) and 60 to 120 minutes (crude OR 1.75; adjusted OR 1.74; 95% CI 1.0-2.9,  $p = 0.035$ ) when compared with the reference interval of 30 to 59 minutes before incision (9).

**Timing <30 minutes:** In a large, prospective, multicenter observational study examining the relationship between antibiotic timing and SSI risk, Steinberg et al. (10) determined that SSI risk increased incrementally as the interval of time between antibiotic infusion and creation of the incision increased. The authors analyzed the antimicrobial prophylaxis of 4,472 randomly selected cardiac, hip or knee arthroplasty, and hysterectomy cases from 29 contributing hospitals, and ascertained SSI through the National Nosocomial Infections Surveillance system methodology. When antibiotics requiring long infusion times (e.g. vancomycin) were excluded, the infection risk following administration of antibiotics within 30 minutes was 1.6% compared with 2.4% associated with administration of antibiotic between 31 to 60 minutes prior to surgery (OR 1.74; 95% CI 0.98-3.04) (10).

In another recent multicenter, observational study from the Netherlands assessing risk factors for postoperative infections in 1,922 total hip arthroplasty (THA) cases, the authors found a similar pattern with a decreased rate of infection in those who received prophylaxis within 30 minutes prior to incision, although it reached no statistical significance (4). The authors collected data about SSI and potential risks factors related to prophylaxis, the patient, and procedure from 11 hospitals that participated in the Surgical Prophylaxis and Surveillance Intervention project and used multivariate lo-

gistic regression analysis to identify those variables that were predictive of SSI. Although there was a non-significant trend for the lowest SSI rate in those patients who received prophylaxis 30 minutes before surgery, the highest ORs for SSI were found in patients who received prophylaxis after incision (2.8, 95% CI 0.9-8.6),  $p=0.07$ ) and prolonged duration of surgery was the only statistically significant risk factor for SSI following THA.

**Timing with Tourniquet Use:** In an RCT of 22 patients in which cefuroxime prophylaxis was administered at various intervals (5, 10, 15, or 20 minutes) before inflation of the tourniquet for total knee arthroplasty (TKA), Johnson et al. (11) measured antibiotic levels of bone and subcutaneous fat throughout the operation. They found that an interval of 10 minutes prior to tourniquet inflation was necessary to obtain adequate prophylaxis. While the patients obtained adequate levels in bone at 5 minutes, an interval of 10 minutes or more was required for patients to have therapeutic levels in the subcutaneous fat (11).

In another similar RCT (12), 24 patients undergoing TKA were randomized to receive cefazolin 1, 2, or 5 minutes before tourniquet inflation. Serum, soft tissue, and bone samples were measured for adequate cefazolin concentration (defined as  $4 \times \text{MIC}_{90}$  ( $\text{MIC}_{90}=1$  microgram/ml). The median percentage of cefazolin penetration into soft tissue and bone for the 5, 2, and 1 minute groups was 14.5% and 4.6%, 6.7% and 3.0%, and 5.9% and 4.6% respectively. The authors also noted that the percentage of patients achieving the ratio of  $4 \times \text{MIC}_{90}$  for soft tissue and bone was highest in the 5 minute group compared with either the 2 or 1 minute groups (12).

In another prospective study by Soriano et al. (13), 908 patients undergoing TKA were randomized to receive either 1.5g of cefuroxime 30 minutes before inflation of tourniquet and placebo 10 minutes before release of tourniquet (standard group) or placebo 30 minutes before inflation of tourniquet and 1.5g cefuroxime 10 minutes be-

fore release of tourniquet. There was no difference among the patients with regard to various risk factors for SSI/PJI. The authors found no significant difference in the incidence of infection at 3.6% for the standard group and 2.6% for the control group at 12 months. The authors concluded that administration of antibiotics just prior to release of tourniquet was not inferior to a standard prophylactic regimen (13).

**Surveillance Measures:** In a study evaluating the impact of a new national project meant to reduce infections in arthroplasty surgery in Sweden, Dahl et al. (14) found that only 57% of patients received preoperative antibiotics during the recommended time frame. In 2009, following the introduction of the World Health Organization surgical checklist and a new Swedish Knee Arthroplasty Register (SKAR) reporting form, which included the time for administration of preoperative antibiotics, the number of patients receiving appropriately-timed doses of preoperative antibiotics increased to 69% in 2009 and 79% in 2010 (14).

## **Question 2: Is there an optimal antibiotic that should be administered for routine perioperative surgical prophylaxis?**

**Consensus:** A first or second-generation cephalosporin (cefazolin or cefuroxime) should be administered for routine perioperative surgical prophylaxis. Isoxazolyl penicillin is used as an appropriate alternative.

**Delegate Vote:** Agree: 89%, Disagree: 8%, Abstain: 3% (Strong Consensus)

**Justification:** First or second generation cephalosporin should be administered for routine perioperative surgical prophylaxis because of its broad spectrum of action, cost-effectiveness, and the need to preserve newer and more expensive therapies for drug-resistant micro-organisms and emerging pathogens. These antibiotics cover gram-positive organisms and clinically important aerobic gram-negative bacilli and non-bacteroid anaerobes (6). Additionally, they have excellent distribution profiles in bone, synovium, muscle, and hemato-

mas(15). Many studies have documented that minimum bactericidal concentrations for most non methicillin-resistant staphylococcus aureus (MRSA) organisms are achieved rapidly in these tissues--ie within a few minutes after their administration (16,17). The optimal prophylactic antibiotic should be bactericidal (penicillin, cephalosporin, vancomycin, or aminoglycosides), not simply bacteriostatic (clindamycin, which is a lincosamide). The agent should also have a half-life that covers the decisive interval (the first 2 hours after incision or contamination) with therapeutic concentrations from time of incision to wound closure. Failure to maintain tissue concentrations above the MIC increases the risk of wound infection(18). In Scandinavia and elsewhere, isoxazolyl penicillin is used as an appropriate alternative. Some institutions administer carbapenems (namely imipenem/cilastin and meropenems) to patients with penicillin allergy, as they felt that the potential for cross-reactivity between carbapenems and penicillin is less than traditionally believed (19).

In a multicenter, placebo RCT, Hill et al. (20) convincingly demonstrated the efficacy of cefazolin for antimicrobial prophylaxis in reducing the risk of PJI. In 2,137 THA patients randomized to either 5 days of cefazolin or placebo antibiotic prophylaxis reduced the incidence of deep infection from 3.3% to 0.9% ( $p<0.01$ ).

Tyllianakis et al. (21) performed an RCT comparing cefuroxime to two specific antistaphylococcal agents (fusidic acid and vancomycin) for prophylaxis in THA and TKA in an institution where MRSA and methicillin-resistant *S. epidermidis* (MRSE) prevalence exceeds 25% of orthopedic infections. In 435 patients (260 hips and 175 knees) followed for a minimum of 2 years, the authors found no statistically significant difference between the treatment groups for either THA or TKA, although the authors concede that the power to detect meaningful statistical differences between the groups was low and it was therefore difficult to provide any definitive conclusions (21).

The efficacy of one day of cefuroxime vs. 3 days of cefazolin on postoperative wound infections was studied by Mauerhan et al. in a double-blind, multicenter trial of 1,354 patients undergoing hip and knee arthroplasty. The authors found no significant difference between the two regimens. For the TKA patients, the rate of PJI was 0.6% (1/178) for those receiving cefuroxime vs 1.4% (3/207) for those receiving cefazolin. For the THA patients, the rate of PJI was 0.5% (1/187) for those receiving cefuroxime as compared to 1.2% (2/168) for those receiving cefazolin (22).

In a study investigating the bacterial colonization and resistance patterns of a cohort of patients undergoing primary joint arthroplasty in Sweden, Stefansdottir et al. (23) noted that in Scandinavia, isoxazolyl penicillin derivative cloxacillin is the most commonly used prophylactic antibiotic. Moreover, these  $\beta$ -lactams were effective against 99% of the *S. aureus* strains and 80% of the coagulase-negative staphylococcus (CNS) strains colonizing patients undergoing primary TJA. Furthermore, the gentamicin-laden bone cement used in many of these cases covers against most of the additional CNS strains (23).

### Conclusion

The preoperative dose of antibiotics should be administered within one hour of surgical incision; this can be extended to two hours for vancomycin and fluoroquinolones. Furthermore, surveillance measures are critical in ensuring clinician compliance with this objective. A first or second-generation cephalosporin (cefazolin or cefuroxime) should be administered for routine perioperative surgical prophylaxis. Isoxazolyl penicillin is used as an appropriate alternative.

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