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Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection

Chairmen:
Javad Parvizi MD, FRCS; Thorsten Gehrke, MD

قسمت ششم

(Sixth Section)

Question 13: Until culture results are finalized, what antibiotic should be administered to a patient with a presumed infection?

Consensus: In a patient with a presumed infection when culture results are pending, empiric antibiotic coverage should depend on the local microbiological epidemiology. Culture data should assist in the tailoring of antibiotic regimens.

Delegate Vote: Agree: 96%, Disagree: 1%, Abstain: 3% (Strong Consensus)

Justification: Guidelines based on individual institutional microbiological epidemiology should be developed.[124] In the US, vancomycin is recommended for gram-positive coverage due to a high rate of resistance to methicillin in many cases and gentamicin or a third or fourth generation cephalosporin is recommended for gram-negative coverage. However, in areas with low MRSA prevalence, vancomycin should not be recommended as the first choice of drug until culture results are obtained and other antibiotics should be chosen instead.

Sharma et al. classified the spectrum and antibiotic susceptibility of bacteria isolated from revision hip and knee arthroplasty specimens in order to recommend appropriate empiric perioperative antibiotics before definitive cultures are obtained. They identified 147 patients with positive specimens, yielding 248 microorganisms from 195 tissue specimens, 43 fluid specimens, and 10 swabs. Of the 248 isolated microorganisms, *staphylococcus* species was the most common genus encountered (53%), followed by gram-negative isolates (24%). Eighty-eight percent of gram-negative organisms were detected within 48 hours of inoculation and 94% of gram-positive organisms within 96 hours. Overall, 46% of isolates were susceptible to cephalothin, while only 35% of CNS were sensitive to cephalothin. No gram-positive vancomycin resistance was encountered. Therefore the authors concluded that empiric prophylactic antibiotics for revision hip and knee arthroplasty should include vancomycin for gram-positive organisms and gentamicin for gram-negative bacteria; and if infection is suspected, vancomycin and gentamicin should be continued postoperatively for 96 and 48 hours respectively, unless culture or histology results suggest otherwise.[122]

Knee: In a retrospective review of 121 patients who underwent revision TKA for infection between 1994 and 2008 in the United Kingdom, the most common organism was CNS (49%) and *S. aureus* (13%). The prevalence of CNS appears to be increasing, while that of *S. aureus* and other organisms is decreasing. Vancomycin and teicoplanin were the most effective antibiotics, with overall sensitivity rates of 100% and 96% respectively. Also, the authors reported that based on their theoretical model of comparing microorganism sensitivities against specific antibiotics, gentamicin combined with vancomycin or teicoplanin is the most effective empirical regimen. While the authors recognized the potential serious nephrotoxic side effects, these antibiotics may be added to bone cement relatively safely. The authors also suggested that this empirical regimen can potentially allow for a one-stage revision procedure to be conducted when deep infection arises.[123]

In early, delayed, and late infections observed from data from the SKAR from 1986-2000 in 426 surgically revised cases, CNS was most prevalent (105/299, 35.1%) and twice as common as *S. aureus* (55/299, 18.4%). In hematogenous infections, *S. aureus* was the dominating pathogen (67/99, 67.7%), followed by streptococci and gram-negative bacteria. Methicillin resistance was found in 1/84 tested isolates of *S. aureus* and 62/100 tested isolates of CNS. During the study period of 1986-2000, methicillin resistance among CNS increased (p=0.002). Gentamicin resistance was found in 1/28 tested isolates of *S. aureus* and 19/29 tested CNS isolates. Therefore, the authors conclude that empiric antibiotics should cover CNS, as most early infections were caused by this organism. They also raised the concern that due to high rate of gentamicin resistance among CNS in infected

TKA, other antibiotics should be used in bone cement at revision.[23]

Data from the SKAR have previously been used to report on the microbiology of 357 TKA infections in patients operated on before 1986. *S. aureus* was the most common pathogen (45.4%) followed by CNS (18%).[124] In later studies, staphylococci continued to be the most common pathogens, with *S. aureus* reported to account for 13%-51% of the infections and CNS accounting for 15%-49%.[123,125,126]

Hip: Rafiq et al. retrospectively reviewed the microbiology of 337 one-stage revision hip replacements for deep infection and found that CNS was the predo-minant organism (67%) and that *Staphylococcus* (13%) is becoming more prevalent. The authors also noted an increase in antimicrobial resistance (24% resistance to gentamicin), which lead the authors to suggest that other antibiotics such as erythromycin or fusidic acid be added to bone cement during these procedures.[127]

In a study examining the microbiology of contaminating bacteria during primary THA, Al-maiyah et al. cultured the gloved hands (n=627 impressions) of the surgical team in 50 THA cases after draping, at 20 minute intervals, and then before cementation. They found contamination present in 57 (9%) of impressions and a total of 106 bacterial isolates, with CNS being the most frequent (68.9%), micrococcus (12.3%) and diptheroids (9.4%) following, and *S. aureus* only representing 6.6% of cases. Interestingly, only half (52%) of the CNS isolates were sensitive to cefuroxime, the institutional prophylactic agent of choice, suggesting alternate agents may be indicated.[128]

Phillips et al. reviewed the microbiology of deep infection following hip and knee arthroplasty at a specialist orthopaedic hospital in the United Kingdom over a 15 year period. At their institution, CNS was the most common infecting organism (36%), followed by *S. aureus* (25%), *enterococcus* (9%), and MRSA (4%). Of the infecting organisms, 72% were sensitive to routine prophylactic agents. There was no significant change in microbiology over that time period at this institution.[129]

Timing of Infection: A retrospective analysis of 146 patients who had a total of 194 positive cultures obtained at time of revision total hip or knee arthroplasty was performed. Seventy percent of the infections were classified as chronic, 17% as acute postoperative, and 13% as acute hematogenous. Gram-positive organisms caused the majority of the infections (87% or 168/194). The microorganisms were sensitive to cefazolin in 61% of cases, gentamicin in 88% of cases, and vancomycin in 96% of cases. The most antibiotic-resistant bacterial strains were from patients in whom prior antibiotic treatment had failed. Acute postoperative infections had a greater resistance profile than did chronic or hematogenous infections. Bacteria isolated from a hematogenous infection had a high sensitivity to both cefazolin and gentamicin. This led to the following recommendations:

- Until final cultures are available, acute hematogenous infections should be treated with cefazolin and gentamicin.
- All chronic and acute postoperative infections with gram-positive bacteria and all cases in which a gram stain fails to identify bacteria should be managed with vancomycin.
- Infections with gram-negative bacteria should be managed with third or fourth generation cephalosporin.
- Infections with mixed gram-positive and gram-negative bacteria should be managed with a combination of vancomycin and third or fourth generation cephalosporin.
- As 93% (180) of the 194 cultures tested positive by the fourth postoperative day, the authors recommend that if culture results are not positive by the fourth postoperative day, termination of empiric antibiotic therapy should be considered.[59]

In a retrospective review of 97 patients (106 infections in 98 hips), Tsukayama et al. noted that aerobic gram-positive cocci accounted for 109 (74%) of the 147 isolates; gram-negative bacilli, 21 (14%); and anaerobes, 12 (8%). Of the CNS species 27 (48%) were oxacillin-resistant, while all 33 (100%) of the coagulase-positive staph species were sensitive to oxacillin. The authors noted that most of the gram-negative isolates came from the early postoperative and late chronic infections, while isolates from the acute hematogenous infections were exclusively gram-positive cocci.[130]

Irrigation and Debridement (I&D): A retrospective review was conducted to describe the microbiological spectrum of PJI in 112 patients managed with I&D or arthroscopic washout of infected prosthetic joints between 1998 and 2003 in order to guide the choice of empirical antibiotics. Overall, the most frequently isolated organisms were CNS (47%) and methicillin-sensitive *Staphylococcus aureus* (MSSA) (44%), while 8% were MRSA and 7% were anaerobes. In their series, 60% of CNS isolates were resistant to methicillin. Most gram-negative isolates were resistant to cefuroxime and all were sensitive to meropenem. Based on the high rate of early polymicrobial infection, cephalosporin resistance among gram-negative organisms, β-lactamase resistance among gram-negative organisms, and β-lactam resistance among CNS, the authors recommend glycopeptides with a carbapenem in the initial regimen, with modification when culture and sensitivity results are available.[131]

Question 14: What is the appropriate preoperative antibiotic for a second-stage procedure?

Consensus: The appropriate preoperative antibiotic for the second stage should include coverage of the prior organism(s). Cemented arthroplasty components should be inserted with antibiotic-laden bone cement.

Delegate Vote: Agree: 66%, Disagree: 31%, Abstain: 3% (Strong Consensus)

Justification: Patients undergoing reimplantation surgery following a two-stage exchange procedure are at risk of developing recurrent infection.[132,133] The recurrent infection may be either due to incomplete eradication of the prior bacteria during the antibiotic spacer exchange or to a new infection. In order to properly address both potential scenarios, the appropriate preoperative antibiotics should include coverage of the prior organism as well as the most common infecting microorganisms.

Antibiotic-laden bone cement has been shown to decrease septic failure following TJA in high-risk individuals and it is US Food and Drug Administration-approved for use during reimplantation of components in a two-stage exchange. While there is no evidence to support the practice, it makes theoretical sense to add antibiotics that are effective in treating the index infection.

In a systematic review of 31 studies that compared the clinical outcomes achieved with one- and two-stage revision TKA with different types of spacers, the authors noted that after the index revision for infection, deep joint infection was detected in 0%-31% of cases. Of these, the infection was considered recurrent in 0%-18% of cases, while new infection rates varied from 0 to 31%. While the length of follow-up did not appear to influence the rate of recurrent infections, the studies with <4 years of clinical follow-up had fewer new infections.[134]

Azzam et al. retrospectively reviewed 33 patients who had failed an initial two-stage exchange arthroplasty, of whom 18 eventually went on to undergo a second two-stage procedure. Of this cohort, the isolated organism was different from the previous infecting organism in only one of 18 patients.[132]

In a similar study, Kalra et al. retrospectively reviewed 11 patients who developed reinfection after two-stage revision for infected THA and were subsequently treated with a two-stage re-revision. In their series, the infecting microorganisms were polymicrobial in 3 patients and only 2 had reinfection by the initial offending microbe.[133]

In a review of the outcomes of 69 patients with PJI in TKA, Mont et al. determined that in 8 of 9 cases reinfections were from the organism that had caused the initial infection, although in 6 of the 8 patients the sensitivity of the organism to antibiotics had changed.[126]

Kubista et al. published results on 368 patients treated with a two-stage revision for infected TKA. Of this cohort, 58 (15.8%) developed reinfection and a causative organism was identified in 47/58 (81%) of patients.[135]

In a retrospective review of 117 patients who underwent two-stage exchange arthroplasty for PJI of the knee, 33 of 117 patients (28%) required reoperation for infection. At the time of reimplantation, antibiotic-laden bone cement (1.2g tobramycin and 1g vancomycin per 40g of cement) was used for fixation of the prosthesis, but there was no note of the parenteral or perioperative antibiotics utilized at the second stage.[136]

Question 15: For surgeries of longer duration, when should an additional dose of antibiotic be administered intraoperatively?

Consensus: An additional dose of antibiotic should be administered intraoperatively after two half-lives of the prophylactic agent. The general guidelines for frequency of intraoperative antibiotic administration are provided. We recommend that re-dosing of antibiotics be considered in cases of large blood volume loss (>2000 cc) and fluid resuscitation (>2000cc). As these are independent variables, re-dosing should be considered as soon as the first of these parameters are met.

Delegate Vote: Agree: 94%, Disagree: 5%, Abstain: 1% (Strong Consensus)

Justification: In cases of large blood volume loss and fluid resuscitation there is a remarkable loss of the prophylactic agent that can result in levels below the MIC. The same is true for longer surgeries that extend beyond the half-life of the agent. Thus, additional antibiotic treatment is needed to re-establish antibiotic levels that exceed the MIC. An additional dose of antibiotic has been shown to reduce SSI rates in cardiac patients and should be administered intraoperatively after two half-lives of the prophylactic agent.[3,74,75]

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, states that "timing and dosage of antibiotic administration should be such to optimize the efficacy of the therapy."[1] Both the IDSA and AAOS state that "Additional intraoperative doses of antibiotic are advised when the duration of the procedure exceeds one to two times the antibiotic's half-life or when there is significant blood loss during the procedure." The general guidelines for frequency of intraoperative antibiotic administration are as follows: cefazolin every 2-5 (4) hours, cefuroxime every 3-4 hours, clindamycin every 3-6 hours, isoxazoyl penicillin every 3 hours, and vancomycin every 6-12 hours.[2,137,138]

In a prospective multicenter study exploring the relationship between timing, duration, and intraoperative redosing of surgical antimicrobial prophylaxis and the risk of SSI, Steinberg et al. determined that intraoperative dosing was associated with a lower infection risk only when the preoperative antibiotic was given in the recommended time frame. In 1,062 (24%) cases, the surgical procedure lasted for at least 4 hours. Because of a longer half-life and the reduced need for redosing, cases that received vancomycin or fluoroquinolones were excluded from the analysis of the impact of redosing on infection risk (n=372). Intraoperative redosing was given in 21% of 690 of these long operations. Of the group that had a surgical procedure with a duration of >4 hours and who received the preoperative dose within one hour, 2 of 112 (1.8%) patients who were redosed intraoperatively developed infection, compared to 22 of 400 (5.5%) of those who were not re-dosed (OR 3.08, p=0.06).[10]

Scher et al. randomized 801 patients undergoing clean contaminated operations to one of three antibiotic regimens: 1g of cefazolin preoperatively, 1g of cefazolin preoperatively and another dose 3 hours later, and 1g of cefotetan

preoperatively. While all regimens demonstrated similar wound infection rates for surgeries lasting less than 3 hours, for those that exceeded 3 hours, the group that only received the single preoperative cefazolin dose had a statistically significant higher wound infection rate than those who received the second cefazolin dose (6.1% vs 1.3%, p<0.01).[139]
Shapiro et al. performed a placebo-controlled RCT to test the efficacy of perioperative cefazolin in preventing infection after abdominal or vaginal hysterectomy. The authors sub-analyzed the effect of surgery duration on the efficacy of perioperative prophylaxis by calculating adjusted relative odds of infection with and without prophylaxis for different durations of surgery and found that the efficacy of prophylaxis diminishes rapidly with increasing length of surgery; by 3 hours, 20 minutes prophylaxis had no measurable effect (OR=1).[140]
Polk et al. prospectively analyzed the antibiotic levels of 3 cephalosporins (cefazolin, cephaloridine, and cephalothin) given as a single preoperative dose and found that acceptable concentrations of cefazolin were maintained near the incision site until 3 hours post-administration, whereas cephalothin did not maintain wound levels consistent with effective antimicrobial activity.[141]
Ohge et al. prospectively examined the pancreatic tissue concentrations of cefazolin in 10 patients undergoing pancreatectomy and determined the optimal intraoperative time to repeat the dose of cefazolin. Based on their results, the authors recommended a second dose of kefzol be given 3 hours after first administration in order to maintain adequate levels of antibiotic activity. They measured MIC for 4 bacterial species, namely 360 isolates of MSSA, 204 isolates of *K. pneuomoniae*, 314 isolates of *E. coli*, and 30 isolates of streptococci species; and measured tissue levels of cefazolin. Antibiotic concentrations in adipose tissue and peritoneum 3 hours after administration of kefzol were lower than the MIC 80 for *K. pneumoniae*, *E. coli*, and streptococcal species.[142]
In a retrospective review of 131 patients with primary colorectal cancer in prolonged operations exceeding 4 hours, the surgical wound infection rates were 8.5% and 26.5% respectively for those with (n=47) and without (n=49) intraoperative repeated dosing, which were significantly different based on both a univariate (p=0.031) and a multivariate analysis (p=0.008).[143]
Zanetti et al. retrospectively compared the risk of SSIs in 1,548 patients who underwent cardiac surgery lasting >240 minutes after preoperative administration of cefazolin prophylaxis. The overall risk of SSI was similar among patients with (43 (9.4%) of 459) and without (101 (9.3%) of 1089) intraoperative redosing (OR 1.01, 95% CI 0.7-1.47). However, redosing was beneficial in procedures lasting >400 minutes; infection occurred in 14 (7.7%) of 182 patients with redosing and in 32 (16.0%) of 200 patients without (adjusted OR 0.44, 95% CI 0.23-0.86). Intraoperative redosing of cefazolin was associated with a 16% reduction in the overall risk for SSI after cardiac surgery, including procedures lasting >240min.[74,75]

Blood Loss: Swoboda et al. attempted to determine the effect of intraoperative blood loss on prophylactic cefazolin and gentamicin serum and tissue concentration in a prospective study of elective spinal surgical procedures with expected large blood loss. At 60 minutes after the incision, blood loss correlated with cefazolin tissue concentrations (r=-0.66, p=0.05) and the clearance of gentamicin from the tissues (r=0.82, p=0.01). Based on their measured pharmacokinetic values, additional doses of cefazolin should be administered when the operation exceeds 3 hours and blood loss is greater than 1500mL. A dose of gentamicin greater than 1.8mg/kg should be administered more than 30 minutes prior to the surgical incision.[144]
Blood Loss/Volume Replacement: Markantonis et al. investigated the effects of surgical blood loss and fluid volume replacement on gentamicin concentrations in serum and in 3 tissue types (subcutaneous fat, epiploic fat, and colonic wall) in patients in undergoing colorectal surgery. Gentamicin was administered at a standard dose of 2 mg/kg and blood and tissue samples were obtained concurrently at specific times throughout each procedure. The mean concentration at first surgical incision was 7.83 (0.82) μg/mL and decreased to 2.60 (0.28) μ/mL at skin closure, resulting in borderline effectiveness even for susceptible gram-negative microorganisms (MIC-1.0). A strong negative correlation was found between the intravenously-administered fluids and gentamicin concentrations in serum and tissues (p≤0.04).[145]
Klekamp et al. prospectively studied orthopaedic patients with either large or small blood loss who also received vancomycin prophylaxis to determine the effect of intraoperative volume shifts on serum vancomycin concentrations. There were 6 index patients in the large blood loss group (greater than 2L) and 7 in the control group (less than 2L), with mean estimated blood loss for index and controls was 4.4L and 1.0L; and the mean intraoperative fluid resuscitation, excluding blood products, was 12.4L and 5.1L respectively. There was a modest inverse correlation between blood loss and the intraoperative serum half-life of vancomycin. Although controls maintained slightly higher intraoperative vancomycin concentrations at each time point, there was no statistically significant difference between the groups with regard to absolute concentrations or rate of decline. After 8 hours, the serum concentration of vancomycin exceeded the MIC-90 for *S. aureus* by approximately eightfold in all but one case patient, who was morbidly obese and had massive blood loss. Thus blood loss during orthopaedic procedures has a minimal effect on the intraoperative kinetics of vancomycin and administering vancomycin every 8 to 12 hours seems appropriate for most patients.[146]
Two well-controlled studies of surgical prophylaxis with cefazolin similarly demonstrated minimal effects of blood loss on drug concentrations during THA and spine fusion procedures. Meter et al. examined the effect of intraoperative blood loss and volume resuscitation during

THA on serum levels of cefazolin in 18 patients. At 4 hours after administration, the serum level of cefazolin was 45 mcg/mL, which far exceeded the MIC for *S. aureus* (0.5mcg/mL), despite an average intraoperative blood loss of 1137±-436 mL. This led the authors to conclude that even with blood losses of 2L, it is not necessary to redose cefazolin any earlier than 4 hours in order to maintain the MIC for most common infecting organisms.[147] The authors repeated the study in 19 patients undergoing instrumented posterior spinal fusion and found that there was no significant difference between preoperative and intraoperative cefazolin clearance and there was no correlation between blood loss and cefazolin level.[148]

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