

## مجموعه مقالات نشست بین‌المللی «هم‌رأیی» درباره عفونت مفاصل مصنوعی

رؤسای جلسه:

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### Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection

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#### قسمت هفتم

(Seventh Section)

#### Question 16: Should preoperative antibiotic doses be weight-adjusted?

**Consensus:** Preoperative antibiotics have different pharmacokinetics based on patient weight and should be weight-adjusted.

**Delegate Vote:** Agree: 95%, Disagree: 4%, Abstain: 1% (Strong Consensus)

**Justification:** Because of the relative unpredictability of pharmacokinetics in obese individuals, doses are best estimated on the basis of specific studies for individual drugs carried out in this population. Only a few antibiotics (aminoglycosides, vancomycin, daptomycin, and linezolid) have been studied in the obese population. AAOS recommendation for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, states that “timing and dosage of antibiotic administration should optimize the efficacy of the therapy. Dose amount should be proportional to patient weight; for patients >80 kg, the doses of cefazolin should be doubled.”<sup>2</sup>

The recommended dose of cefazolin is based on patient's body mass index (BMI), with 1.0g for people who weigh <80 kg and 2.0g for those who weigh >80 kg. The adult dose of cefuroxime is 1.5g. The recommended dose of clindamycin is 600 to 900mg.<sup>61</sup> The recommended dose of vancomycin, which is based on BMI, is 10-15mg/kg, up to a limit of 1g, in patients with normal renal function.<sup>149</sup> However, there is literature to support the use of higher doses of vancomycin, with emphasis that doses >4g/day have been associated with increased risk of nephrotoxicity. A trough level is obtained prior to the fourth scheduled dose and in certain occasions there may be a need to shorten dosing interval to maintain therapeutic trough level (eg q12h to q8h dosing).

Because 30% of adipose is water, an empirical approach is to use the Devine formula to calculate ideal body weight (IBW), to which is added a dosing weight correction factor (DWCF) of 0.3 times the difference between actual body

weight (ABW) and IBW ( $IBW + 0.3 \times [ABW - IBW]$ ) to arrive at a weight on which to base dosage of hydrophilic antibiotics. No studies confirm this approach for  $\beta$ -lactam drugs. Clinical studies suggest a DWCF of 0.4 for aminoglycosides and 0.45 for quinolones.<sup>150</sup>

For aminoglycosides, some suggest using ABW using a dosing correction factor,<sup>151,153</sup> while others suggest dosing based on lean body weight (LBW) with appropriate monitoring with the first dose.<sup>152</sup> Current guidelines for vancomycin administration are based on loading doses of vancomycin on the total body weight (TBW) of the patient and maintenance doses on the calculated creatinine clearance (CrCl) of the patient.<sup>153,154</sup> However, deciding whether to base CrCl calculations on ABW, IBW, or another measure is still to be determined. As a general rule, obese and morbidly obese patients require higher doses of cephalosporin to achieve similar outcomes; however, there are fewer absolute dosing recommendations. At least one study demonstrated that a dose of 2g of cefazolin should provide adequate levels for at least 4 hours, even in super morbid obesity (MO) ( $BMI \geq 50 \text{ kg/m}^2$ ).<sup>155</sup>

Other studies confirm that vancomycin should be given on the basis of ABW, with dosage adjustments based on serum concentrations<sup>156</sup> whereas aminoglycoside dosing requires calculation of adjusted body weight via a correction factor.<sup>157</sup>

Forse et al. conducted a prospective RCT in MO patients undergoing gastroplasty and found that the blood and tissue levels of cefazolin were significantly lower for all MO patients who received 1g cefazolin compared with the blood and tissue levels of the drug found in normal weight patients who received a similar dose of antibiotic. Moreover, the MO patients who only received 1g of cefazolin had antibiotic levels below the MIC of 2mcg/mL for gram-positive cocci and 4mcg/mL for gram-negative rods. The serum and tissue concentrations were adequate only when 2g of cefazolin were administered. Also, relative to 1g, the administration of cefazolin 2g decreased the wound infection rate from 16.5 to 5.6% in these MO patients.<sup>18</sup>

Van Kralingen et al. studied the influence of body weight measures and age on pharmacokinetic parameters and evaluated unbound cefazolin concentrations over time in obese patients. Twenty MO patients (BMI 38-79 kg/m<sup>2</sup>) were studied following the administration of 2g of cefazolin at induction of anesthesia. Blood samples were collected up to 4 hours post dosing to determine the total and unbound plasma cefazolin concentrations. Cefazolin clearance was 4.2±1.0 L /h (mean ± standard deviation) and showed a negative correlation with age (p=0.003) but not with body weight measures (p>0.05). In all patients, unbound cefazolin concentrations remained above 1mg/L (MIC 90) of MSSA until 4 hours post dosing.<sup>158</sup>

Ho et al. attempted to determine an optimal dosing regimen for cefazolin as a prophylactic antibiotic in surgery for patients with MO. Twenty-five patients undergoing elective surgical procedures were given a single dose of cefazolin: 10 with MO (BMI 40-50 kg/m<sup>2</sup>) received 2g via intravenous push (IVP), 5 with MO received 2g via 30 minute infusion, 5 with super morbid obesity (SMO, BMI >50 kg/m<sup>2</sup>) received 2g via infusion, and 5 with SMO received 3g via infusion. The protective

duration, determined using a pharmacodynamic target for fT>MIC of 70%, was 5.1 hours for MO2-IVP, 4.8 hours for MO2-INF, 5.8 hours for SMO2-INF, and 6.8 hours for SMO3-INF. The authors concluded that a single 2g dose of cefazolin appears to provide antibiotic exposure sufficient for most common general surgical procedures of <5 hr duration regardless of BMI.<sup>155</sup>

In contrast, Edmiston et al. concluded that 2g of cefazolin may not be sufficient for patients with a BMI >50 kg/m<sup>2</sup>, based upon measurements of total serum concentrations in morbidly obese patients undergoing gastric bypass. The authors assigned 38 patients to one of 3 BMI groups: A) BMI=40-49 kg/m<sup>2</sup> (n=17), B) BMI=50-59 kg/m<sup>2</sup> (n=11), and C) BMI>=60 kg/m<sup>2</sup> (n=10) and measured serum and tissue concentrations of cefazolin. They determined that therapeutic tissue levels were only achieved in 48.1%, 28.6%, and 10.2% in groups A, B, and C respectively. The authors measured concentrations in the serum skin, adipose tissue, and omentum, but did not evaluate unbound cefazolin concentrations, which may be expected to migrate across tissues rapidly.<sup>159</sup>

**Table. Recommended dosing of preoperative antibiotics by weight**

Antimicrobial	Actual Body Weight (ABW; kg)	Recommended Dose (mg)	Perioperative Redosing Schedule	Indication
Cefazolin	< 60	1000	every 4 hours	Primary Perioperative Prophylaxis
	60-120	2000	every 4 hours	
	> 120	3000	every 4 hours	
Cefuroxime	No adjustments	1500	every 4 hours	Primary Perioperative Prophylaxis
Vancomycin	Weight based dosing recommended	15 mg/kg (Maximum dose 2000 mg)	one dose pre-op, one dose 12 hours post-op, one dose 24 hours post-op	Perioperative Prophylaxis for current MRSA carriers and/or patients with β-lactam allergy
Clindamycin	No adjustments	900	every 3 hours	Perioperative Prophylaxis for patients with β-lactam allergy
Teicoplanin	No adjustments	400	NA	Perioperative Prophylaxis for current MRSA carriers and/or patients with β-lactam allergy

**Question 17A: What type of perioperative antibiotic prophylaxis is recommended for current MRSA carriers?**

**Consensus:** For current MRSA carriers, vancomycin or teicoplanin is the recommended perioperative antibiotic prophylaxis.

**Delegate Vote:** Agree: 86%, Disagree: 12% Abstain: 2% (Strong Consensus)

**Question 17B: Should patients with prior history of MRSA be re-screened? What should the choice of perioperative prophylactic antibiotics be in these patients?**

**Consensus:** Patients with prior history of MRSA should be re-screened preoperatively. If patients are found to be negative for MRSA, we recommend routine perioperative antibiotic prophylaxis.

**Delegate Vote:** Agree: 76%, Disagree: 23%, Abstain: 1% (Strong Consensus)

**Justification:** Implementation of a MRSA prevention program may significantly reduce MRSA SSIs. However, it is unlikely that any single MRSA-specific intervention (such as adding or switching to vancomycin) can optimally prevent SSIs. Several studies provide convincing data on the clinical effectiveness of vancomycin in preventing SSIs when MRSA prevalence is high.<sup>69,70,79</sup> Further research is needed to determine which components of a MRSA prevention program are essential in successfully preventing MRSA SSIs.<sup>160</sup> It is uncertain whether decontamination should alter the type of antibiotic prophylaxis, as few studies have retested patients' MRSA status immediately prior to surgery.

The AAOS recommendations for the use of IV antibiotic prophylaxis in primary TJA, recommendation 2, states that "vancomycin may be used in patients with known colonization with MRSA or in facilities with recent MRSA outbreaks."<sup>1</sup> Additionally, the Society for Healthcare Epidemiology of America recently recommended routine surveillance cultures at the time of admission to the hospital for patients at high risk of MRSA.<sup>52</sup>

Walsh et al. implemented a comprehensive MRSA program in which vancomycin was added to the routine cefazolin prophylaxis regimen for patients who tested positive for nasal MRSA carriage. Other components of the program included decolonization of all cardiothoracic staff who screened positive for nasal MRSA carriage, application of nasal mupirocin ointment for 5 days in all patients starting one day before surgery, application of topical mupirocin to exit sites after removal of chest and mediastinal tubes, and rescreening of patients for MRSA colonization at the time of hospital discharge. This program resulted in a significant reduction in the SSI rate (2.1% vs 0.8%,  $p < 0.001$ ) as well as a 93% reduction in postoperative MRSA wound infections (from 32 infections/2,767 procedures during the 3 year pre-intervention period to 2 infections/2,496 procedures during the 3 year postintervention period). The data suggest that a bundled approach to preventing MRSA SSIs may be more critical than a single intervention.<sup>79</sup>

Pofahl et al. published on the impact of introducing MRSA screening programs and treatment of subsequent MRSA SSIs. After a MRSA surveillance program was instituted, the rate of MRSA SSI decreased from 0.23% to 0.09%, with the most pronounced reduction seen in TJA procedures (0.30% to 0%,  $p = 0.04$ ). However, the authors note that changes in perioperative antibiotics in MRSA-positive patients was at the discretion of the attending surgeon.<sup>161</sup>

**Question 18: What is the recommended prophylaxis in patients undergoing major orthopaedic reconstructions for either tumor or non-neoplastic conditions using megaprosthesis?**

**Consensus:** Until the emergence of further evidence, we recommend the use of routine antibiotic prophylaxis for patients undergoing major reconstruction.

**Delegate Vote:** Agree: 93%, Disagree: 6%, Abstain: 1% (Strong Consensus)

**Justification:** Deep infection has been reported as being one of the most common complications following endoprosthetic replacement of large bone defects, ranging between 5%-35% in some series.<sup>162-166</sup> Reinfection rates after revision surgery for endoprosthetic infection have been reported as high as 43%.<sup>165</sup> Despite this there is insufficient evidence to suggest that a different perioperative antibiotic regimen is warranted. Recently a multicenter, blinded, randomized, controlled trial, using a parallel two-arm design has been set up that will evaluate 920 patients from Canada and the USA who are undergoing surgical excision and endoprosthetic reconstruction of a primary bone tumour. The patients will receive either short (24 h) or long (5 days) duration postoperative antibiotics. The primary outcome will be rates of deep postoperative infections in each arm. Secondary outcomes will include type and frequency of antibiotic-related adverse events, patient functional outcomes and quality-of-life scores, reoperation and mortality.<sup>167</sup>

Another area of development involves silver coating of foreign materials, such as heart valves, cardiac catheters, and urinary catheters that has shown the ability to reduce the infection rate of medical devices; therefore, a logical extension of this work was to translate this concept to the field of endoprosthetics.<sup>168,169</sup> Both basic science and clinical research suggests a decreased incidence of SSI and PJI in endoprostheses coated with silver. Recently iodine-supported titanium implants have been also effective for preventing and treating infections after major orthopaedic surgery.<sup>170,171</sup>

In a rabbit study, the infection rate of silver-coated versus noncoated prostheses after inoculation with *Staphylococcus aureus* was determined and the silver concentrations in blood, urine, and organs with possible toxic side effects were documented. The authors convincingly demonstrated that megaprosthesis coated with silver showed a significantly lower infection rate (7% vs 47%,  $p < 0.05$ ) in comparison with a titanium group.<sup>173</sup> Furthermore, measurements of C-reactive protein, neutrophilic leukocytes, rectal temperature, and body weight showed significantly lower ( $p < 0.05$ ) signs of inflammation in the silver group. In a second study, authors analyzed the potential toxicological side effects of these implants and found that the silver concentration in blood (median 1.883 parts per billion (PPB)) and in organs (0.798-86.002 PPB) showed elevated silver concentrations, without

pathologic changes in laboratory parameters and without histologic changes of organs.<sup>172</sup>

In a prospective observational study, Harges et al. compared the infection rate in 51 patients with sarcoma (proximal femur, n=22; proximal tibia, n=29) who underwent placement of a silver-coated megaprosthesis to 74 patients (proximal femur, n=33; proximal tibia, n=41) in whom an uncoated titanium megaprosthesis was used. The authors reported a substantial reduction in the infection rate from 17.6% in the titanium group compared to 5.9% in the silver group (p=0.06). Furthermore, while 38.5% of patients ultimately underwent amputation when PJI developed, this was not necessary in any case in the study group. However, the authors note that the operating time required for the proximal tibia replacement was significantly shorter in the silver-coated prosthesis group (p=0.034) and that prolonged operating time was associated with a higher rate of PJI (p=0.025).

The same group reported a lack of toxicological side effects of silver-coated megaprotheses in 20 patients with bone metastases.<sup>173</sup> They reported that silver levels in the blood did not exceed 56.4 PPB and can be considered non-toxic. They further excluded significant changes in liver and kidney function based on laboratory values; and histopathologic examination of the periprosthetic environment in two patients showed no signs of foreign body granulomas or chronic inflammation, despite effective silver concentrations up to 1,626 PPB directly related to the prosthetic surface.<sup>173</sup>

Tsuchiya et al reported that iodine-supported implants were used to prevent infection in 257 patients with compromised status. Acute infection developed only in 3 tumor cases and one diabetic foot among the 257 patients. Abnormalities of thyroid gland function were not detected. None of the patients experienced loosening of the implant. Excellent bone ingrowth was found around all hip and tumor prostheses. The results indicate that iodine-supported titanium has favorable antibacterial activity, biocompatibility, and no cytotoxicity.<sup>170</sup>

Gosheger reviewed 197 patients with megaprotheses and discovered that those with cobalt chrome implants had more infections than those with titanium implants.<sup>176</sup>

Reviewing 197 patients (77 patients with a cobalt chrome alloy system and 120 patients with a titanium alloy system) who underwent lower extremity reconstruction with a megaprosthesis, the authors reported a 31.2% infection rate in the cobalt chrome group compared to 14.2% in the titanium group (p<0.01). When they performed a secondary analysis matching two identical subgroups, the cobalt chrome group was still associated with a significantly higher infection rate, with 5 infections of 26 megaprotheses vs one infection of 36 titanium megaprotheses (p<0.05).<sup>174</sup>

**Question 19: Should antibiotic prophylaxis be different in patients who have reconstruction by bulk allograft?**

**Consensus:** We recommend the use of routine antibiotic prophylaxis in patients who have reconstruction by bulk allograft.

**Delegate Vote:** Agree: 93%, Disagree: 5%, Abstain: 2% (Strong Consensus)

**Justification:** The periprosthetic area is inherently a locus minoris resistance. Bulk allograft is in essence is a large foreign body and therefore represents a nidus for deep infection following surgery, apart from the prosthetic components. Additionally, bulk allografts are used most often in the setting of revision arthroplasty when there is frequently additional local soft tissue and vascular compromise, which compounds the risk for infection. Therefore, it would seem reasonable to want to modify the perioperative antibiotic protocol to protect these reconstructions. Unfortunately, there is insufficient literature to support altering antibiotic regimens, as most studies on the use of bulk allograft do not indicate or detail the antibiotic regimens utilized. Even if this data were available, it would not be accurate to properly compare the infection rates of different clinical series based on their perioperative antibiotic protocols because of the heterogeneity of patient populations. However, there is a growing body of literature to support the use of antibiotic-impregnated allograft in the revision setting as a means of decreasing infection rates. In addition, there are several reports of using antibiotic-impregnated graft substitute or grafts as a way to fill bony defects and promote bony ingrowth while delivering supratherapeutic doses of antibiotics to the local environment in cases of osteomyelitis. While there is no current literature applying this technology to the use of bone defects in infected revision arthroplasty, it may be a promising technique.

Witso et al. used netilmicin-impregnated allografts for reconstruction in revision hip and knee surgery and found no adverse effects.<sup>175</sup> Buttaro et al. favorably used vancomycin-supplemented cancellous grafts for reconstruction after infected THA.<sup>176,177</sup> Michalak et al. and Khoo et al. impregnated segmental allografts with gentamicin and flucloxacillin respectively.<sup>178,179</sup> However, all these groups used antibiotic impregnated grafts only in the second stage of a two-stage revision, after resolution of clinical and laboratory evidence of infection.

Winkler et al. performed 37 one-stage uncemented revision THAs using cancellous allograft bone impregnated with antibiotics and noted a 92% success rate, defined as recurrent infection at a mean follow-up of 4.4 years (range 2-8 years). In addition, no adverse effects were seen and the incorporation of bone graft was comparable to unimpregnated grafts.<sup>180</sup>

In a similar series, Buttaro analyzed the incidence of infection after one-stage aseptic revision hip reconstruction using acetabular and/or femoral vancomycin-impregnated impacted bone allograft and a

THA fixed with cement containing no antibiotic. In 75 consecutive patients (80 hips), followed for a mean of 36 months (range 24-59 months), deep infection occurred in one patient for an incidence of infection of 1.25%, which occurred 2 years after the index procedure and was thought to be hematogenous in origin.<sup>181</sup>

Cancellous bone allograft can store and release high initial local amounts of vancomycin without compromising incorporation of the graft, and some favorable results have been published following two-stage revision of infected THA with this technique.<sup>176,177,182-184</sup>

**Question 20: Do patients with poorly controlled diabetes, immunosuppression, or autoimmune disease require a different perioperative antibiotic prophylaxis?**

**Consensus:** No. Routine antibiotic prophylaxis is recommended in these patients.

**Delegate Vote:** Agree: 90%, Disagree: 9%, Abstain: 1% (Strong Consensus)

**Justification:** Several studies have demonstrated that diabetes mellitus (DM), especially uncontrolled DM, is a risk factor for postoperative infection in THA and TKA.<sup>185-188</sup> A recent retrospective cohort study within the Kaiser Healthcare system found no significant increase in risk of revision or deep infection or revision whether patients had controlled (HbA1c<7%) or uncontrolled diabetes (HbA1c>7%). Specifically, compared with patients without DM, there was no association between controlled DM and risk of revision (OR 1.32; 95% CI 0.99-1.76). Similarly, compared to patients without DM, there was no association between uncontrolled DM and risk of revision (OR 1.03; 95% CI 0.68-1.54).<sup>189</sup>

Obesity has also been associated with a significant increase in rate of postoperative infection following TJA.<sup>190-192</sup>

Human immunodeficiency virus (HIV) has also been associated with an alarming rate of postoperative complications, including infection. Parvizi et al. reported on 6 deep infections in 21 HIV-positive patients undergoing TJA. The authors remarked that the immune status of the patients was related to their risk of deep PJI, in that 5 of the 6 patients ultimately developed Acquired Immune Deficiency Syndrome (AIDS) and the CD4 count was significantly lower at 239±112μL at latest follow-up for patients who developed infection compared to 523±171μL for the study population as a whole (p<0.001). In this study the authors reported using prophylactic antibiotics (cephalosporins) preoperatively and 3 doses postoperatively and added antibiotic powder (vancomycin and tobramycin) to the cement in 2 patients thought to be at high risk for infection.<sup>193</sup>

Similarly, Ragni et al. found a very high postoperative infection rate (26.5%) in 34 TJA in HIV-positive hemophiliacs, all of whom had CD4 counts less than 200/μL at time of surgery.<sup>194</sup> Haberman et al. noted an infection rate of 12.7% in their cohort of 41 patients with

HIV undergoing TJA, but did not identify any difference in the outcomes relating to CD4 count.<sup>195</sup> Their perioperative antibiotic protocol was a 5 day course of cefuroxime and in all procedures antibiotic-containing cement (Palacos R, Zimmer, Warsaw, IN) was used. In a smaller series of 6 HIV-infected patients undergoing TJA, Wang et al. noted no infectious or other complications. The authors again used antibiotic (vancomycin)-impregnated bone cement in all cemented cases.<sup>196</sup> Unger et al. evaluated the results of 26 TKAs in HIV-positive hemophiliacs and found no cases of deep infection, but it is interesting to note that the average CD4 count of these patients was 463μL.<sup>197</sup>

Hemophilia has historically been considered a risk factor for PJI, due in part to its relation to HIV and AIDS, but also as an independent risk factor. An article by Silva et al. reviewed the long-term results of primary TKA in patients with hemophilia and noted an overall prevalence of PJI of 16% with a rate of infection in HIV-positive and HIV-negative patients of 17% and 13% respectively (p=0.5). The authors' perioperative protocol included 3 to 5 days of prophylactic antibiotics and antibiotic cement was not used.<sup>198</sup> In contrast, Rodriguez-Marchan reported an infection rate of only 3% of 35 TJA in hemophiliac patients, but used antibiotic-laden bone cement and 2 days of perioperative antibiotic prophylaxis.<sup>199</sup>

Asplenic patients are at increased risk of infection by encapsulated bacteria; and although there is evidence to support vaccinations and penicillin prophylaxis in patients under 16 and over 50 years of age, there is no consensus on the appropriate perioperative management of these immunocompromised patients. In a single case report by Shaarani et al. of an asplenic patient who underwent a TKA, the patient ultimately developed a MRSA infection. In this case standard polymethylmethacrylate (PMMA) was used for cementing components and the patient received intravenous prophylactic dose of second generation cephalosporin preoperatively.<sup>200</sup>

Renal disease (including renal failure, dialysis dependence, and renal transplant) has been implicated as increasing the risk of PJI. McCleery et al. analyzed the Scottish Arthroplasty Registry in order to determine the rates of PJI in patients with renal failure, those undergoing dialysis, and those with a renal transplant. They found that patients with renal failure had a significantly increased risk of early infection (1.6%, RR 1.52, p=0.02) and late infection (4.47%, RR 2.2, p<0.001). Patients on dialysis had a significantly increased risk of late infection (8.0%, RR 3.99, p<0.001) and early revision (3.7%, RR 4.4, p<0.001). Renal transplant patients had a significantly increased risk of late infection, despite whether the transplantation occurred before TKA (9.1%, RR 4.5, p=0.03) or at any time (8.0%, RR 4.0, p=0.05).<sup>201</sup> Lieberman et al. documented a deep infection rate of 19% in 16 chronic renal dialysis patients and more favorable outcomes in renal transplant patients.<sup>202</sup> Sakalkale et al. reported a

deep infection rate of 13% in 12 patients with end-stage renal failure on dialysis who underwent THA. In this study, perioperative prophylactic antibiotics were administered for 2 to 5 days.<sup>203</sup> In contrast, other authors have reported no increased rate of infection in patients on chronic hemodialysis undergoing THA.<sup>204,205</sup>

Similarly, liver disease has been associated with increased morbidity following TJA. Pour et al. performed a case control study of 71 non-cirrhotic patients with hepatitis C undergoing TJA and found that this cohort had higher rates of wound drainage following THA when compared to matched controls (15 vs 3.8%,  $p=0.03$ ).<sup>206</sup>

Orozco et al. recently published a case control study to analyze the effect of fibrosis and thrombocytopenia on the diagnosis of hepatitis C and clinical outcomes. Analyzing 72 patients (77 joint replacements), the authors found that fibrotic hepatitis C patients had higher deep infection rates (21% vs 0%,  $p=0.047$ ) and rates of cellulitis (21% vs 0%,  $p=0.047$ ), while thrombocytopenia showed a trend towards greater infection.<sup>207</sup>

Solid organ transplant (SOT) is a risk factor for PJI due to the need for chronic use of immunosuppressant medications. Vergidis et al. performed a case control study of patients with SOT who developed PJI and compared them to non-infected controls matched by transplant type, prosthetic joint type, and order of organ transplantation or joint implantation. Of 367 patients with both a joint replacement and SOT, there were 12 cases of PJI, of which 8 were renal transplants, 3 were liver transplants, and 1 was a heart transplant patient. Eight infections were caused by gram-positive organisms, 2 were caused by nontuberculous mycobacteria, and the remaining 2 were culture-negative. Of note, patients received perioperative cefazolin, or in cases of colonization or prior infection with MRSA, vancomycin.<sup>208</sup> Tannenbaum et al. reported results on 35 TJA in 19 patients with renal or liver transplant and documented an infection in 5 patients who had the joint replacement after the transplantation. There were no infections in patients who had TJA before the organ transplantation. In this series, prophylactic antibiotics were administered for at least 48 hours or until the drains were removed and bone cement when used was not impregnated with antibiotics.<sup>209</sup>

#### **Question 21A: Should preoperative antibiotics be different for primary and revision TJA?**

**Consensus:** No. Perioperative antibiotic prophylaxis should be the same for primary and uninfected revision arthroplasty.

**Delegate Vote:** Agree: 89%, Disagree: 10%, Abstain: 1% (Strong Consensus)

#### **Question 21B: Should preoperative antibiotics be different for hips and knees?**

**Consensus:** Perioperative antibiotic prophylaxis should be the same for hips and knees.

**Delegate Vote:** Agree: 99%, Disagree: 1%, Abstain: 0% (Strong Consensus)

**Justification:** Patients undergoing revision TJA are at higher risk of developing PJI than primary arthroplasty and those undergoing revision knee procedures are at even highest risk.<sup>210-212</sup> One recent study has effectively demonstrated targeting infection prevention programs at high-risk surgical patients that take into account an institution's local epidemiology and antibiogram.<sup>213</sup>

Liu et al. determined the impact of adding vancomycin to cefazolin as antimicrobial prophylaxis in 414 patients undergoing revision TKA based on a notable increase in PJI in revision TKA patients, with many being methicillin-resistant. Following introduction of vancomycin to the routine preoperative antibiotic prophylaxis, the infection rate decreased from 7.89% to 3.13% ( $p=0.046$ ). In particular, a significant reduction in PJI resulting from methicillin-resistant organisms over this time period was seen (4.2% to 0.9%,  $p=0.049$ ).<sup>219</sup>

#### **Question 22: What is the best antibiotic prophylaxis to choose in patients with colonization by carbapenem resistant enterobacteriaceae or multi-drug resistant (MDR)-Acinetobacter spp?**

**Consensus:** There is insufficient data to recommend expanded antibiotic prophylaxis in patients known to be colonized or recently infected with MDR pathogens.

**Delegate Vote:** Agree: 76%, Disagree: 8%, Abstain: 16% (Strong Consensus)

**Justification:** There is an increasing awareness of the threat posed by *K. pneumoniae* strains with decreased susceptibility to carbapenems worldwide.<sup>214</sup> This resistance is conferred by *K. pneumo carbapenemase* (KPC), which is a  $\beta$ -lactamase that also confers resistance to broad-spectrum cephalosporins, as well as commercially available  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations.<sup>215</sup> As there are few antimicrobial options, prevention of *K. pneumo carbapenemase K. pneumoniae* (KPC-KP) has become a major priority of those studying nosocomial infections.<sup>216</sup>

While there is no evidence on the management of surgical antimicrobial prophylaxis in a patient with past infection or colonization with a resistant gram-negative pathogen, it is logical to provide prophylaxis with an agent active against MRSA for any patient known to be colonized with this gram-positive pathogen who will have a skin incision; specifically, prophylaxis for a resistant gram-negative pathogen in a patient with past infection or colonization with such a pathogen may not be necessary for a purely cutaneous procedure.

In a literature review, KPC-producing microbes are resistant to many non- $\beta$ -lactam molecules. Most isolates are resistant to fluoroquinolones, aminoglycosides, and co-trimoxazole. Some isolates are susceptible to

amikacin and gentamicin and most are susceptible to colistin and tigecycline.<sup>214,217-219</sup>

In a prospective RCT, De Smet et al. studied the elimination of colonization with MDR organisms using selective oropharyngeal and/or digestive tract decontamination (SOD/SDD) in a multicenter crossover study using cluster randomization of 5,939 intensive care unit patients in the Netherlands. SOD included 4 days of intravenous cefotaxime and topical application of tobramycin, colistin, and amphotericin B in the oropharynx and stomach. SDD consisted of oropharyngeal application only of the same antimicrobials. Using a random effects logistic regression analysis, the OR for death at day 28 in the SOD and SDD group, as compared with the standard care group, were 0.86 (95% CI 0.74-0.99) and 0.83 (95% CI 0.72-0.97) respectively.<sup>220</sup>

Perez et al. used a mouse model to examine the effect of antibiotic treatment on the establishment and elimination of intestinal colonization of KPC-KP. They administered 3 days of antibiotics (clindamycin, zosyn, tigecycline, ertapenem, cefepime, and ciprofloxacin) before KPC-KP

was administered orogastrically. The authors reported that of the 4 antibiotics with minimal activity against the KPC-KP strain (MIC >16mcg/mL), those that suppressed total anaerobes and Bacteroides (ie clindamycin and zosyn) promoted colonization by KPC-KP (p<0.001), while agents that did not suppress total anaerobes and bacteroides (ie ciprofloxacin and cefepime) did not (p=0.35). Of the antibiotics with moderate activity against KPC-KP, ertapenem (MIC 4mcg/mL) did not promote colonization by KPC-KP, while tigecycline (MIC 3mcg/mL) did (p<0.001), despite not reducing levels of total anaerobes and bacteroides. Orgogastric administration of gentamicin and polymyxin E suppressed KPC-KP to undetectable levels in the majority of mice. The authors posited that antibiotics that disturb the intestinal anaerobic microflora lack significant activity against KPC-KP promote colonization, while the administration of non-absorbed oral antibiotics may be an effective strategy to suppress colonization with this microorganism.<sup>221</sup>

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