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Chairmen:

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قسمت چهارم

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.²⁹⁻³² 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.³³ 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.³⁴ Teicoplanin is notable for having a long half-life (32-176 hours), low toxicity, and good tissue penetration, which allows it to achieve therapeutic concentrations in bone and surrounding soft tissues.^{33,35}

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 RCT, Periti et al. compared administration of a single dose of teicoplanin (400mg intravenous (IV) bolus at time of anesthesia) versus that of 5 doses of cefazolin over a 24 hour period (2g at induction and 1g every 6 hours postoperatively) as prophylaxis in patients undergoing TJA. They randomized 846 patients and noted that 6 patients (1.5%) in the teicoplanin group and 7 patients (1.7%) in the cefazolin group developed a surgical wound infection during

their hospital stay, which was a non-significant difference. Additionally, a non-significant difference in adverse events was recorded in the two groups, with 3 (0.7%) of the teicoplanin patients and 9 (2.1%) of the cefazolin patients.³²

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 (ceftazidime, cefepime, ceftazidime, cefprozil, cephalosporin, or cephadrine) should be avoided; first and second generation cephalosporins with different R1 side chains can be given.

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.³ Clindamycin is a 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.³⁶ However, clindamycin is a bacteriostatic agent. In addition vancomycin alone has a relatively poor activity against *Staphylococcus aureus* and clinical studies implicate that vancomycin as prophylaxis alone increases the risk for SSI. Therefore a second agent should be considered (levofloxacin, moxi-floxacin) in addition to vancomycin.⁸

Cross-reactivity between penicillin and cephalosporin is overestimated and much lower than reported in earlier studies. The 10% estimate of risk of 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.^{37,38} The high cross-reactivity found in earlier studies may be due in part to contamination of the study drugs with penicillin during the manufacturing process.^{39,40} 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.^{41,42} Skin testing in penicillin-allergic patients cannot reliably predict an allergic response to a cephalosporin, particularly to compounds with dissimilar side chains.⁴³ However, skin testing may be useful in determining whether a true allergy to penicillin exists.⁴⁴

Twenty-seven articles on the topic of the cross-reactivity of penicillin and cephalosporin were reviewed, of which 2 were meta-analyses, 12 were prospective cohorts, 3 were retrospective cohorts, 2 were surveys, and 9 were laboratory studies. The authors demonstrated that penicillin has a cross-allergy with first generation cephalosporins (OR 4.8; CI 3.7-6.2) and a negligible cross-allergy with second generation cephalosporins (OR 1.1; 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 approximately 1% and in those with a confirmed penicillin allergy 2.55%. For penicillin-allergic patients, the use of third or fourth generation

cephalosporin or cephalosporins (such as cefuroxime and ceftriaxone) with dissimilar side chains than the offending penicillin carries a negligible risk of cross allergy.⁴⁵

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).⁴⁶ The relative risk of an anaphylactic reaction to cephalosporin ranges from 1:1,000 to 1:1,000,000 and this risk is increased by a factor of 4 in patients with a history of penicillin allergy.⁴⁷

Based on an analysis of 9 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, CI 3.6-9.2) and all first generation cephalosporins plus cefamandole (OR 4.8, CI 3.7-6.2) were observed in penicillin-allergic patients; no increase was observed with second generation cephalosporin (OR 1.1, CI 0.6-2.1) or third generation cephalosporin (OR 0.5, CI 0.2-1.1).^{41,42}

In a retrospective cohort of 2,933 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.⁴⁸

In a large, retrospective review of 534,810 patients who received penicillin followed by a cephalosporin at least 60 days later, Apter et al. noted that a total of 3,877 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.⁴⁹

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 85 cases had an adverse drug reaction to cephalosporin compared to 5 (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 ($p=0.03$).⁵⁰

Question 6: What are the indications for administration of vancomycin?

Consensus: Vancomycin should be considered for patients who are current MRSA carriers or have anaphylactic allergy to penicillins.

Consideration should be given to screening high risk patients such as:

- Patients in regions with a high prevalence of MRSA.
- Institutionalized patients (nursing home residents, dialysis-dependent patients, and those who have been in the intensive care unit).
- Healthcare workers.

Delegate Vote: Agree: 93%, Disagree: 7%, Abstain: 0% (Strong Consensus)

Justification: The AAOS recommendation 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.”⁵¹ Similarly, the consensus position of the Medicare National Surgical Infection Prevention Project’s SIPGWW meeting was that “for patients with known MRSA colonization, vancomycin should be considered the appropriate antimicrobial agent for prophylaxis.”⁵⁶ Additionally, the Society for Healthcare Epidemiology of America recently recommended routine surveillance cultures at the time of hospital admission for patients at high risk for carriage of MRSA.⁵²

Question 7: Is there evidence to support the routine use of vancomycin for preoperative prophylaxis?

Consensus: No. Routine use of vancomycin for preoperative prophylaxis is not recommended.

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

Justification: Current data suggest that the role of vancomycin in orthopaedic surgery prophylaxis should be limited. There is ample evidence that vancomycin is inferior against methicillin-sensitive strains of staphylococcal species when compared to cephalosporin and penicillinase-resistant penicillin.^{8,53}

Several systematic analyses concluded that no clear benefit in clinical or cost effectiveness has been demonstrated for the routine use of vancomycin compared with cephalosporin for prophylaxis. However, most of these studies were conducted before the

increasing prevalence of MRSA and may not accurately reflect the current environment. In some hospitals, community-associated MRSA (CA-MRSA) strains are now responsible for a significant portion of SSIs.^{54,55} However, there is no consensus about what constitutes a high prevalence of methicillin resistance and no evidence that routine use of vancomycin for prophylaxis in institutions with perceived high risk of MRSA infection results in fewer SSIs than the use of a cephalosporin. Although two RCTs have been conducted in institutions with a high MRSA prevalence, the differences in SSI rates and outcomes were conflicting. Similarly, several studies have utilized decision analysis models to calculate MRSA prevalence thresholds for which vancomycin would have clinical benefit and be more cost-effective than cephalosporin for surgical prophylaxis. However, these studies all suffer from the lack of randomization to provide baseline probabilities for the clinical effectiveness of each treatment at different rates of MRSA prevalence.

While there is a growing body of evidence to support the routine use of vancomycin for preoperative prophylaxis, this should be tempered by the fact that there is an increasing threat of colonization and infection with vancomycin-resistant *enterococci* (VRE)⁵⁶ and an increased prevalence of MRSA strains with reduced susceptibility to vancomycin.^{57,58}

The choice of drug prophylaxis should take into account the antibiotic resistance patterns in hospital systems. In a recent study by Fulkerson et al., the susceptibilities of *S. epidermidis* and *S. aureus* to cefazolin at two high-volume academic centers in New York and Chicago were only 44% and 74%, respectively.⁵⁹ Of the most common organisms infecting patients undergoing TJA at these hospitals, 26% to 56% were resistant to the standard recommended prophylactic agent. Thirty-three of the 194 infections were diagnosed within a month after the surgery. Of these, 8 were due to *S. epidermidis* and 16 were due to *S. aureus*. Of these, only 2 of the 8 (25%) of the *S. epidermidis* infections and 11 of the 16 (69%) of the *S. aureus* infections were sensitive to cefazolin. However, these infections were 100% susceptible to vancomycin.

In a study of deep infections following hip and knee arthroplasty over a 15-year period at The Royal Orthopaedic Hospital and Queen Elizabeth Hospital in England, 22 of 75 hip and knee infections (29%) were caused by microorganisms that were resistant to the antibiotic used for prophylaxis (cefuroxime). These included all 3 MRSA infections, all 3 *Pseudomonas aeruginosa* infections, and 11 coagulase-negative staphylococcus infections.^{60,61} Wiesel and Esterhai recommend administration of vancomycin in institutions where the prevalence of MRSA is greater than 10% to 20%.⁶² In a hospital with a high prevalence of MRSA, Merrer et al. conducted a prospective, observational study comparing the incidence of SSI after vancomycin or cefazolin prophylaxis before femoral neck fracture

surgery, as well as the impact of antibiotic prophylaxis on the emergence of VRE and *Staphylococcus aureus*. The authors found no significant difference in the rate of SSI, as a total of 8 (3%) occurred, 4% in the cefazolin group and 2% in the vancomycin group ($p=0.47$). At one week after surgery, there were a total of 6 patients (2%) who had hospital-acquired MRSA, corresponding to 0.7% in the cefazolin group and 5% in the vancomycin group ($p=0.04$), none of which were resistant to glycopeptides. Additionally, 3 patients (1%) acquired VRE, all of which were in the cefazolin group ($p=0.27$).⁶³ Cranny et al. used a combination of systematic reviews and economic modeling in order to answer questions about whether there is a level of MRSA prevalence at which a switch from non-glycopeptide to glycopeptide antibiotics for routine prophylaxis is indicated in surgical environments with a high risk of MRSA infection. The effectiveness reviews identified 16 RCTs with a further 3 studies included for adverse events only. They found no evidence to support that glycopeptides are more effective than non-glycopeptides in preventing SSI. Most of the trials did not report either the baseline prevalence of MRSA at the participating surgical units or MRSA infections as an outcome. The cost-effectiveness review included 5 economic evaluations of glycopeptide prophylaxis. Only one study incorporated health-related quality of life and undertook a cost-utility analysis. In conclusion, the authors indicate that there is currently insufficient evidence to determine whether there is a threshold prevalence of MRSA at which switching from non-glycopeptide to glycopeptide antibiotic prophylaxis might be cost effective.⁶⁴

Bolon et al. performed a meta-analysis of 7 RCTs published in the cardiothoracic surgery literature that compared SSIs in subjects receiving glycopeptide prophylaxis with those who received β -lactam prophylaxis. While neither agent proved to be superior for prevention of the primary outcome, occurrence of SSI at 30 days (RR 1.14, 95% CI 0.91-1.42), vancomycin prophylaxis was superior for the prevention of SSI caused by methicillin-resistant gram-positive bacteria (RR, 0.54; 95% CI 0.33-0.90) at 30 days after surgery.⁶⁵

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."¹ The Hospital Infection Control Practices Advisory Committee guideline also suggests that a high frequency of MRSA infection at an institution should influence the use of vancomycin for prophylaxis but acknowledges that there is no consensus about what constitutes a high prevalence of methicillin resistance.⁶⁶

Two prospective RCTs have evaluated antibiotic prophylaxis in hospitals with a high prevalence of MRSA. Tacconnelli et al. randomized patients undergoing surgery for cerebrospinal shunt placement to receive either vancomycin or cefazolin. The prevalence of MRSA in 2001 for a 1700-bed university hospital was

reported as one new case of MRSA infection per 100 hospital admissions. Shunt infections developed in 4% of patients receiving vancomycin (4/88) and 14% receiving cefazolin (12/88, RR, 0.22; 95% CI 0.11-0.99, $p=0.03$). The infecting pathogen was MRSA in 2 of 4 patients (50%) receiving vancomycin and 9 of 12 (75%) patients receiving cefazolin.⁶⁷ Finkelstein et al. randomized 855 patients undergoing cardiothoracic surgery to either a vancomycin or cefazolin group. The prevalence of new cases of MRSA infection in the cardiac surgery ward was reported to be 3.0 and 2.6 per 100 admissions in 1995 and 1996 respectively. The overall rates of SSI were similar in both groups (9.5% for vancomycin and 9.0% for cefazolin). A trend toward more methicillin-resistant gram-positive infections was observed in the cefazolin group (4.2% vs 2.0%; $p=0.09$), while more methicillin-sensitive staphylococcus infections were seen in patients receiving vancomycin (3.7% vs 1.3%; $p=0.04$).⁶⁸

Three other clinical studies have used pre- and post-intervention periods to assess the effect of switching to vancomycin for surgical prophylaxis in patients undergoing cardiothoracic or orthopaedic surgery. Garey et al. demonstrated that a change from cefuroxime to vancomycin prophylaxis decreased the average monthly SSI rate by 2.1 cases/100 coronary artery bypass graft (CABG) procedures when compared with patients undergoing cardiac valve replacement surgery. This was attributed to a lower rate of infections caused by MRSA and CNS during this 4-year study of nearly 6,500 patients.⁶⁹ Similarly, Spelman et al. reported a decrease in SSI rates from 10.5% to 4.9% ($p<0.001$) after switching the antibiotic prophylaxis regimen from cefazolin to vancomycin plus rifampin in 1,114 CABG procedures. This was attributed to a decrease in the incidence of MRSA infections from 67% during the one year pre-intervention period to 0% in the one year post-intervention period.⁷⁰ Smith et al. retrospectively reviewed total and MRSA PJI in 5,036 primary TJAs as well as the cure rate of PJI in a 2 year pre-intervention period when cefazolin was the antibiotic prophylaxis of choice to the 2 year post-intervention period when vancomycin was the antibiotic prophylaxis of choice. They found that with the use of vancomycin the total rate of PJI was significantly reduced (1.0% vs 0.5%, $p=0.03$) and the rate of MRSA PJI was also reduced (0.23% vs 0.07%, $p=0.14$). Furthermore, PJIs were more successfully treated with irrigation and debridement only, not requiring antibiotic spacers (76.9% vs 22.2%, $p=0.002$).⁷¹

A study published on Australian Surveillance Data (Victorian Healthcare Associated Surveillance System) of over 20,000 cardiac and arthroplasty procedures identified 1,610 case in which vancomycin was administered as compared to 20,939 cases in which a β -lactam was used. The adjusted OR for an SSI with methicillin-sensitive *Staphylococcus aureus* (MSSA) was 2.79 (95% CI 1.6-4.9) when vancomycin prophylaxis was administered ($p<0.001$), whereas the unadjusted OR

for an SSI with MRSA was 0.44 (OR 0.19-1.004; p=0.05).⁷²

Several recent studies have developed decision analysis models to determine the threshold of MRSA prevalence at which vancomycin would minimize the incidence and cost of SSI. For CABG surgery, the authors of two studies have recommended a MRSA prevalence threshold of 3% among infections caused by *S. aureus*.⁷³⁻⁷⁵ Miller et al. suggested that lower rates of MRSA prevalence (eg 3%-10%) were within the error of their model and that surgical prophylaxis with vancomycin would have a modest effect in reducing the incidence of SSI. For vascular surgery, a MRSA prevalence of 50% was suggested before a β -lactam agent is replaced with vancomycin for surgical prophylaxis.⁷⁶ The authors also suggested that an aminoglycoside should be added to the

prophylactic regimen once the prevalence of MRSA reaches 10%, which is in agreement with the recent guidelines from the British Society of Antimicrobial Chemotherapy.⁷⁷ Elliot et al. developed an economic model to explore the cost-effectiveness of vancomycin and/or cephalosporin for surgical prophylaxis in patients undergoing THA. Vancomycin was recommended when the rate of MRSA SSIs is $\leq 0.15\%$ and the rate of non-MRSA SSIs is $\geq 0.1\%$, or when the rate of MRSA infections is $\leq 0.2\%$ and the rate of other infections is $> 0.2\%$.⁷⁸ Each of these decision analysis studies noted that their biggest limitation was the lack of available evidence from RCTs, with a high prevalence of MRSA infections as one of the most important factors that influenced modeling assumptions.

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