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Letter to Editor

Microbiology Section

Cefuroxime Prophylaxis in Total Joint Arthroplasty: Need for Antibiotic Stewardship

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To the Editor,

The efficacy of prophylactic antibiotics for Total Joint Arthroplasty (TJA) has been well established. Perioperative antimicrobial prophylaxis for TJA has been shown to reduce the risk of Prosthetic Joint Infection (PJI) by more than 80% [1]. The selection of prophylactic antibiotics requires an understanding of the common microorganisms causing PJIs. The most prevalent causative organisms involved in PJIs are *Staphylococcus aureus* and coagulase negative staphylococci [2]. Gram-negative bacilli are involved to a much lesser extent (< 10%) [2]. According to the American Academy of Orthopaedics Surgeons (AAOS, 2004) the preferred antimicrobial prophylaxis for TJA is cefazolin or cefuroxime [3]. In recent years, Methicillin resistant *Staphylococcus aureus* (MRSA) and Gram-negative bacilli that are resistant to antibiotics are increasingly being reported as nosocomial pathogens [4,5]. Thus, the use of antimicrobial agents effective against these microorganisms is necessary in the prophylaxis for prosthetic orthopaedic surgeries. Although antimicrobial resistance is a pertinent problem in India, there is a paucity of microbiological data from periprosthetic joint infections [6]. This prompted us to prospectively study all joint arthroplasties complicated by infections to determine the bacteria involved in these infections and their antimicrobial susceptibility profile.

This prospective study was conducted over a period of two-years (from June 2013 to June 2015). Patients admitted to orthopedic inpatient department of All India Institute of Medical Sciences, New Delhi, scheduled for primary Total Hip Arthroplasty (THA) or Total Knee Arthroplasty (TKA) were included. The study protocol was approved by Institute's ethical committee and the written informed consent was obtained from all the participants. PJI was defined according to the Musculoskeletal Infection Society (MSIS) criteria [7]. During the study period, perioperative antibiotic prophylaxis was cefuroxime 1.5 g administered, 30 minutes before incision during the induction of anesthesia. Specimens from suspected cases of infected arthroplasties were processed in accordance with recognized standard operating procedures [8,9]. Antibiotic susceptibility to amikacin (30µg), amoxicillin-clavulanic acid (20/10µg), cefotaxime (30µg), ceftazidime (30µg), cefuroxime (30µg), clindamycin (2µg), ciprofloxacin (5µg), erythromycin (15µg), imipenem (10µg), levofloxacin (5µg), meropenem (10µg), netilmycin (30µg), teicoplanin (30µg)and vancomycin (30µg) was determined by Kirby- Bauer disk diffusion method and the results were interpreted in accordance with Clinical Laboratory Standards Institute (CLSI) guidelines [10]. Following suture removal, an initial visit of the patient after 4 weeks and thereafter the subsequent visits at 3, 6 and 12 months were monitored.

A total of 759 patients were enrolled. There were 439 (58%) TKAs and 320(42%) THAs. Follow-up was available for all the patients. Fifteen patients (1.97%) were diagnosed with PJI. Of the 15 infected arthroplasties, 11(73%) & 4(27%) were THA and TKA respectively. Eleven of the infections (73%) occurred within 3 months of the index arthroplasty; the remaining four infections (27%) occurred between 3 to 12 months.

Sixteen isolates were cultured from intraoperative specimens obtained at the time of debridement of the 15 infected arthroplasties. Of the total 16 isolates, 9(56%) were Gram-positive [*Staphylococcus aureus*, 5 (56%); *Enterococcus* species, 3(33%); *Staphylococcus haemolyticus*, 1(11%)] and 7(44%) were Gram-negative {*Escherichia coli*, 4(57%); *Klebsiella pneumoniae*, 2(29%); *Pseudomonas aeruginosa*, 1(14%)}. Of the total 12 isolates from early infections, nine (75%) were resistant to cefuroxime, whereas of the four isolates from delayed infections, 3 (75%) were resistant. Only 44% of Gram-positive isolates were susceptible to cefuroxime. Methicillin-resistance was noted in 33 % Gram-positive isolates. Of the Gram-positive isolates, 100% were sensitive to vancomycin and teicoplanin, 83% were sensitive to amikacin, netilmycin and amoxicillin-clavulanic acid, 67% were sensitive to levofloxacin, 57% were sensitive to ciprofloxacin, and 44% were sensitive to erythromycin and clindamycin. All the Gram-negative isolates were uniformly resistant to cefuroxime. Of the Gram-negative isolates, 86% were sensitive to imipenem, 57% were sensitive to amikacin and netilmycin, 43% were sensitive to levofloxacin and meropenem, 29% were sensitive to amoxicillin-clavulanic acid and 14% were sensitive to ceftazidime and cefotaxime.

Contrary to the published reports [1,6] where there is a predominance of Gram-positive organisms in PJIs, we observed that the incidence of Gram-positive and Gram-negative organisms was nearly equal. Though there was a predominance of Gram-positive organisms, it is interesting to note that the proportion of Gram-positive bacteria was lower than reported in other studies [2,6]. As suggested by Norton *et al.*, this low proportion could be attributed to the emergence of resistant Gram-negative organisms as pathogens responsible for PJIs [11].

The eleven early PJIs could be attributed to the failure of perioperative cefuroxime prophylaxis. However, the four delayed PJIs were most likely hematogenous and hence cannot be attributed to the ineffectiveness of cefuroxime. Of note, all the Gram-negative isolates were resistant to cefuroxime, raising the concern that this agent may not provide adequate prophylaxis. Trish *et al.,* and Phillips et al., have also reported resistance of organisms infecting patients with joint replacements to recommended prophylactic antibiotic agents at their hospitals [12,13]. The findings of our study suggest that combination therapy with cefuroxime and amikacin or levofloxacin would be more effective than therapy with cefuroxime alone for perioperative prophylaxis of TJA. The findings of this study have been shared with the treating unit and their perioperative antimicrobial prophylactic policy for TJA is under review for modification.

To date the cephalosporins (cefazolin and cefuroxime) have been the preferred antimicrobials, with proven success for prophylaxis of TJA [1]. However, methicillin-resistant staphylococcal infections and the increasing proportions of Gram-negative resistant organ-

isms have created a scenario whereby cefuroxime or cefazolin alone might not comprise the appropriate prophylaxis in TJA [11-14]. Hence, continuous monitoring of local epidemiology of PJI combined with extensive research to evaluate the effectiveness of current recommended perioperative prophylactic agents in TJA is highly recommended. The findings of our study might add to the growing evidence for the need of antimicrobial stewardship for more effective surgical prophylaxis.

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