Prophylactic Antibiotics: Administration and Timing before Operation Are More Important than Administration after Operation

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(See the article by van Kasteren et al. on pages 921–7)

Van Kasteren et al. [1] have published an interesting analysis of prospectively collected data regarding antibiotic prophylaxis among 1922 patients who underwent primary, nonemergency total hip arthroplasty at 1 of 11 hospitals in The Netherlands during 2000–2002. This work began as part of an effort on their part to standardize and improve prophylactic antibiotic administration to this group of patients. Infectious complications of total joint arthroplasty are associated with serious morbidity and high cost but are difficult to study, because the overall infection rate is relatively low; therefore, demonstrating statistically significant differences requires very large numbers of patients. The focus of the authors’ study was the influence of timing of the prophylaxis dose prior to operation, antibiotic-impregnated cement, and continuing prophylactic antibiotic treatment after the procedure had ended. Strengths of the study include the prospective design and data capture, the multicenter nature of the study, and the 1-year follow-up for all patients. Unfortunately, despite a good design and a large number of patients, most comparisons failed to demonstrate statistically significant differences. In univariate analysis, increases in age, National Nosocomial Infections Surveillance score [2], American Society of Anesthesiology score [3], and duration of operation were significantly associated with an increase in the rate of surgical site infection. In multivariate analysis, only duration of operation of >75th percentile was a significant risk of surgical site infection.

However, when one looks at the graph of infection rates that are correlated with time of prophylaxis administration, there is a rather compelling trend similar to that seen in the classic article on timing by Classen et al. [4]. Although the differences were not individually significant, there is a pronounced U-shaped curve, with the lowest infection rate for administration between 0 and 30 min before incision and increasing rates as the time before or after incision increases. The effect is more striking after incision than before. There are abundant existing references suggesting why this difference probably occurred. Studies of various operative procedures confirm that higher antibiotic levels during the operation [5, 6] and measurable levels at the end of the operation [6, 7] are associated with lower infection rates. In addition, repeating the administration of prophylactic antibiotics during prolonged operations reduces the infection rate [8, 9]. Current US guidelines recommend administration of prophylaxis within 120 min [4] or 60 min [10, 11] of incision, and European guidelines recommend administration of prophylaxis within 30 min [1, 12] of incision. In addition, studies demonstrate good tissue penetration and excellent levels of antibiotic in serum and tissue samples when administration of prophylaxis is very close to the time of incision [13, 14]. The number of patients who received antibiotic-impregnated bone cement are simply too few to provide a recommendation for or against this strategy; the univariate analysis suggests more infections, and the multivariate analysis suggests fewer infections, with a probability of >0.14 in each case.

Two areas in which surveyed practice patterns differ from current recommendations are the timely administration of prophylactic antibiotics, which occurs only 56% of the time, and the avoidance of prolonged postoperative antibiotics, which are given nearly 60% of the time [15]. Coordinating the administration of antibiotics during a tight time window be-
before operation can be difficult, and coordinated efforts involving multiple disciplines are necessary for success [16–19]. Some have questioned whether giving the antibiotic too close to the time of incision might have less efficacy [20], but the data of van Kasteren et al. [1] and others [13, 14] are reassuring in this regard. It is important to observe that, although there was no statistically significant difference between the results of administration of prophylaxis during the intervals of 30–60 min and 0–30 min before incision, the results during the 0–30 min interval actually showed a lower rate of surgical site infection, which lends no credence to the concern that administration of prophylaxis close to the time of incision might be less effective. However, for total hip arthroplasty, administration of prophylaxis during the 60 min before incision had equally good results. This may be because the average duration of operation was only 79 min, and thus, administration of prophylaxis even 1 h before incision would be expected to achieve therapeutic levels of antibiotics throughout the duration of operation. The longer the operation, the more benefit is achieved by administration of prophylaxis as close as possible to the time of incision.

Prolonged postoperative administration, which is another habit that is not supported by the study of van Kasteren et al. [1] or by any other publication, increases the number of resistant bacteria recovered from surgical patients [7, 21–24]. Whenever this has been examined, longer durations of antibiotic treatment beyond the duration of the operation do not result in lower rates of surgical site infection [25, 26]. Recently, the American Academy of Orthopedics published guidelines that suggest a lack of benefit from postoperative doses and recommend that administration not be prolonged for longer than 24 h [27].

The causes of surgical site infection are multifactorial and include patient factors; technical aspects of the operation, for which there are no verified parameters of measurement; blood loss; and perioperative management, including temperature levels, glucose level control, oxygenation, and prophylactic antibiotic administration. The critical aspects of prophylactic antibiotic administration are giving an appropriate antibiotic, giving an adequate dose, achieving proper timing before incision, and maintaining therapeutic levels of antibiotic throughout the operation. Achieving the proper timing and redosing when necessary are dependent on the multidisciplinary organization of the hospital and operating room. Postoperative doses do not add benefit and may increase the incidence of resistant pathogens in subsequent nosocomial infections.

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References


In an article published in the 1 April 2007 issue of the journal (Dellinger EP. Prophylactic antibiotics: administration and timing before operation are more important than administration after operation. Clin Infect Dis 2007;44:928–30), an error appeared in the first sentence. The sentence should read “Van Kasteren et al. [1] have published an interesting analysis of prospectively collected data regarding antibiotic prophylaxis among 1922 patients who underwent primary, nonemergency total hip arthroplasty at any one of 11 hospitals in The Netherlands during 2000–2002” (not “Van Kasteren et al. [1] have published an interesting analysis of prospectively collected data regarding antibiotic prophylaxis among 1922 patients who underwent primary, nonemergency total hip arthroplasty at 1 of 11 hospitals in The Netherlands during 2000–2002”). The journal regrets this error.

In an article published in the 15 April 2007 issue of the journal (Goossens H, Ferech M, Coenen S, Stephens P, and the European Surveillance of Antimicrobial Consumption Project Group. Comparison of outpatient systemic antibacterial use in 2004 in the United States and 27 European countries. Clin Infect Dis 2007;44:1091–5), an error appeared in figure 1. The colors indicated in the legend for macrolides, lincosamides, and streptogramins (MLS), tetracyclines, and quinolones are incorrect. Orange (not purple) indicates MLS, purple (not pink) indicates tetracyclines, and pink (not orange) indicates quinolones. The corrected figure appears below. The authors regret this error.

Figure 1. Total outpatient antibacterial use in the United States and 27 European countries in 2004 (total use for Greece, Iceland, and Bulgaria, 2002 data for Poland, and 2003 data for Italy). DDD, defined daily dose; MLS, macrolides, lincosamides, and streptogramins; TMP, trimethoprim. *Includes amphenicols (J01B), aminoglycosides (J01G), combinations of antibacterial agents (J01R), and other antibacterial agents (J01X).
Two errors appeared in the In the Literature section of the 15 March 2007 issue of the journal. The first article featured was published in 2007 (not 2006). The correct reference is as follows: Pai MP, Turpin RS, Garey KW. Association of fluconazole area under the concentration-time curve/MIC and dose/MIC ratios with mortality in nonneutropenic patients with candidemia. Antimicrob Agents Chemother 2007; 51:35–9. Also, in the first paragraph of the same feature, a reference citation is missing at the end of the third sentence. The sentence should read “A study involving 32 patients with candidemia confirmed the importance of the choice of fluconazole dose, finding that a ratio of dose to MIC >50 was associated with a 74% success rate, whereas the success rate among individuals with a lower ratio was only 8% [1]” (not “A study involving 32 patients with candidemia confirmed the importance of the choice of fluconazole dose, finding that a ratio of dose to MIC >50 was associated with a 74% success rate, whereas the success rate among individuals with a lower ratio was only 8% [1]”). The journal regrets these errors.