

There are no studies comparing clinical or pharmacokinetic outcomes with different doses of clindamycin for surgical prophylaxis. Older pharmacokinetic studies show a good penetration of clindamycin into surgical tissues including bone [13–15]. Based on serum levels after intravenous administration, this suggests that commonly used doses of 600 mg or 900 mg should exceed the MIC of most relevant pathogens [1,15].

REFERENCES

- [1] Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt)*. 2013;14:73–156. doi:10.1089/sur.2013.9999.
- [2] Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. *Pharmacotherapy*. 2007;27:1081–1091. doi:10.1592/phco.27.8.1081.
- [3] Koopman E, Nix DE, Erstad BL, Demeure MJ, Hayes MM, Ruth JT, et al. End-of-procedure ceftazolin concentrations after administration for prevention of surgical-site infection. *Am J Health Syst Pharm*. 2007;64:1927–1934. doi:10.2146/ajhp070047.
- [4] Forse RA, Karam B, MacLean LD, Christou NV. Antibiotic prophylaxis for surgery in morbidly obese patients. *Surgery*. 1989;106:750–756; discussion 756–757.
- [5] Yamada K, Matsumoto K, Tokimura F, Okazaki H, Tanaka S. Are bone and serum ceftazolin concentrations adequate for antimicrobial prophylaxis? *Clin Orthop Relat Res*. 2011;469:3486–3494. doi:10.1007/s11999-011-2111-8.
- [6] Edmiston CE, Krepel C, Kelly H, Larson J, Andris D, Hennen C, et al. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? *Surgery*. 2004;136:738–747. doi:10.1016/j.surg.2004.06.022.
- [7] Swank ML, Wing DA, Nicolau DP, McNulty JA. Increased 3-gram ceftazolin dosing for cesarean delivery prophylaxis in obese women. *Am J Obstet Gynecol*. 2015;213:415.e1–e8. doi:10.1016/j.ajog.2015.05.030.
- [8] Grupper M, Kuti JL, Swank ML, Maggio L, Hughes BL, Nicolau DP. Population pharmacokinetics of ceftazolin in serum and adipose tissue from overweight and obese women undergoing cesarean delivery. *J Clin Pharmacol*. 2017;57:712–719. doi:10.1002/jcph.851.
- [9] Young OM, Shaik IH, Twedt R, Binstock A, Althouse AD, Venkataramanan R, et al. Pharmacokinetics of ceftazolin prophylaxis in obese gravidae at time of cesarean delivery. *Am J Obstet Gynecol*. 2015;213:541.e1–e7. doi:10.1016/j.ajog.2015.06.034.
- [10] Kheir MM, Tan TL, Azboy I, Tan DD, Parvizi J. Vancomycin prophylaxis for total joint arthroplasty: incorrectly dosed and has a higher rate of periprosthetic infection than ceftazolin. *Clin Orthop Relat Res*. 2017;475:1767–1774. doi:10.1007/s11999-017-5302-0.
- [11] Catanzano A, Phillips M, Dubrovskaya Y, Hutzler L, Bosco J. The standard one gram dose of vancomycin is not adequate prophylaxis for MRSA. *Iowa Orthop J*. 2014;34:111–117.
- [12] Crawford T, Rodvold KA, Solomkin JS. Vancomycin for surgical prophylaxis? *Clin Infect Dis*. 2012;54:1474–1479. doi:10.1093/cid/cis027.
- [13] Panzer JD, Brown DC, Epstein WL, Lipsen RL, Mahaffey HW, Atkinson WH. Clindamycin levels in various body tissues and fluids. *J Clin Pharmacol New Drugs*. 1972;12:259–262.
- [14] Nicholas P, Meyers BR, Levy RN, Hirschman SZ. Concentration of clindamycin in human bone. *Antimicrob Agents Chemother*. 1975;8:220–221.
- [15] Schurman DJ, Johnson BL, Finerman G, Amstutz HC. Antibiotic bone penetration. Concentrations of methicillin and clindamycin phosphate in human bone taken during total hip replacement. *Clin Orthop Relat Res*. 1975;142–146.



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QUESTION 3: Is one dose of preoperative antibiotic adequate for patients undergoing total joint arthroplasty (TJA)?

RECOMMENDATION: Despite the current guidelines from the Centers for Disease Control and Prevention (CDC) advocating for a single dose of perioperative antibiotics, these studies are underpowered and primarily in specialties outside orthopaedics. From the limited evidence available, it appears that a single perioperative dose of antibiotics, compared to multiple doses, does not increase the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs). A randomized prospective study in patients undergoing elective arthroplasty is underway that should answer this question definitively.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Perioperative antibiotic prophylaxis remains an important strategy for minimizing one of the most devastating complications following TJAs, PJIs [1,2]. All current guidelines recommend the use of perioperative antibiotics [3–7] (Table 1). For arthroplasty, the costs and morbidities associated with PJIs have led to abundant research to reduce the rate of postoperative infections. To this end, perioperative antibiotics are widely used; however, hospital protocols vary from a single preoperative dose to several days of postoperative prophylaxis. Many surgeons administer antibiotics for a total of 24 hours as this is the maximum time period recommended by several current guidelines. However, there was a recent change in the guidelines provided by the World Health Organization (WHO) and CDC. They recommend against the administration of antibiotics in the postoperative period and that only a single preoperative antibiotic be administered, largely due to fears of increased bacterial resistance and side effects of unnecessarily prolonged antibiotics [4,5]. The 2017 CDC Guidelines issued this statement as a strong recommendation with high-quality evidence. However, the limited literature in arthroplasty cannot support this recommendation.

A recent systematic review and meta-analysis by Thornely et al. explored whether or not a single preoperative antibiotic dose is adequate for arthroplasty patients [8]. Their review returned four randomized controlled trials (RCTs) [9–12] with a total of 4,036 patients. In patients receiving postoperative prophylaxis, the infection rate was 3.1% (63/2055), compared to the rate (2.3%) of a single preoperative dose (45/1981). They concluded that postoperative antibiotics did not reduce the rates of infections; however, they reported that the quality of evidence was very low. Among the available RCTs, three include teicoplanin as a single dose treatment, which is currently unavailable in the United States [10,13,14]. Heydemann et al. randomized 211 patients to a single dose vs. 48 hours of nafcillin or ceftazolin; no deep infections were seen in either cohort [9]. Ritter et al. compared a single preoperative dose of cefuroxime to 24 hours of postoperative prophylaxis in a small RCT of 196 patients, and found no postoperative infections in either group [11]. Lastly, Wymenga et al., in a multicenter RCT of 3,013 patients, compared a single preoperative dose of cefuroxime to a group receiving 3 total doses and found no significant differences in infections between groups. These

authors, however, recognize that their sample sizes were too small to detect a difference given the infrequency of PJIs and recommended continued use of postoperative prophylaxis until larger studies could be performed [12]. Other literature has been retrospective in nature, including reviews by Tang et al. [15] and van Kasteren et al. [16], each of which had < 2,000 patients and found no differences in infection rates between groups. The largest retrospective review by Engesaeter et al. showed a significantly higher revision rate with a single dose compared to four doses given on the day of surgery. The higher revision rate was partially caused by infections [17]. While the majority of studies are underpowered, a retrospective study by Tan et al. demonstrated no differences in 90-day or 1-year PJIs in the 4,523 patients that received a single dose of antibiotics compared to 16,159 patients that received 24 hours of antibiotics. Throughout all preoperative risk groups, however, patients with 24 hours of antibiotics demonstrated a trend toward a higher rate of acute renal failure.

It is important to recognize the different antibiotics used in each study noted above, as well as the small sample sizes. Furthermore, the meta-analysis performed by the CDC predominantly includes surgical interventions of the trunk without hardware retention (including vascular surgery, cardiothoracic surgery, general surgery, as well as ear, nose and throat). For surgeries of the extremity with retained implants, however, the evidence is more limited and consists of small RCTs or retrospective reviews without sufficient power to detect a statistical differences [13,14,18–25]. Among them, Gatell et al. did find a significant reduction in the rates of infections compared to a single preoperative dose for patients with retained metal implants [24]. These studies were also performed predominantly in the 1990s and early 2000s and modern antibiotics may have a different result. Given the devastating outcomes of PJIs for patients, we neither agree nor disagree with the CDC recommendations that antibiotics should not be provided postoperatively until sufficiently powered evidence can be provided through a multicenter RCT that is adequately powered and is considering the low event rate of infection in total joint arthroplasty. While future studies may show that there are no differences in single versus multiple doses of perioperative antibiotic prophylaxis, the current literature does not support this strong conclusion.

REFERENCES

- [1] Hansen E, Belden K, Silibovsky R, Vogt M, Arnold WV, Bicanic G, et al. Perioperative antibiotics. *J Arthroplasty*. 2014;29:29–48. doi:10.1016/j.arth.2013.09.030.
- [2] Parvizi J, Shohat N, Gehrke T. Prevention of periprosthetic joint infection: new guidelines. *Bone Joint J* 2017;99-B:3–10. doi:10.1302/0301-620X.99B4-BJ-2016-1212.R1.
- [3] Anderson DJ, Podgorny K, Berrios-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35:605–627. doi:10.1086/676022.
- [4] World Health Organization. Global guidelines on the prevention of surgical site infection. 2016. <http://apps.who.int/iris/bitstream/handle/10665/250680/9789241549882-eng.pdf;jsessionid=70B2932526C4105C06D33FD6EB991151?sequence=1>.
- [5] Centers for Disease Control and Prevention. Guidelines library. Infection control. Updated Feb 28, 2017. <https://www.cdc.gov/infectioncontrol/guidelines/index.html>. Accessed November 19, 2017.
- [6] Leaper D, Burman-Roy S, Palanca A, Cullen K, Worster D, Gautam-Aitken E, et al. Prevention and treatment of surgical site infection: summary of NICE guidance. *BMJ*. 2008;337:a1924.
- [7] Parvizi J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. *Bone Joint J*. 2013;95-B:1450–1452. doi:10.1302/0301-620X.95B11.33135.
- [8] Thornley P, Evaniew N, Riediger M, Winemaker M, Bhandari M, Ghert M. Postoperative antibiotic prophylaxis in total hip and knee arthroplasty: a systematic review and meta-analysis of randomized controlled trials. *CMAJ Open*. 2015;3:E338–E343. doi:10.9778/cmajo.20150012.
- [9] Heydemann JS, Nelson CL. Short-term preventive antibiotics. *Clin Orthop Relat Res*. 1986;184:187.
- [10] Kanellakopoulou K, Papadopoulos A, Varvaroussis D, Varvaroussis A, Giamarellos-Bourboulis EJ, Pagonas A, et al. Efficacy of teicoplanin for the prevention of surgical site infections after total hip or knee arthroplasty: a prospective, open-label study. *Int J Antimicrob Agents*. 2009;33:437–440. doi:10.1016/j.ijantimicag.2008.10.019.
- [11] Ritter MA, Campbell E, Keating EM, Faris PM. Comparison of intraoperative versus 24 hour antibiotic prophylaxis in total joint replacement. A controlled prospective study. *Orthop Rev*. 1989;18:694–696.
- [12] Wymenga A, van Horn J, Theeuwes A, Muijtjens H, Slooff T. Cefuroxime for prevention of postoperative coxitis. *Acta Orthop Scand*. 1992;63:19–24. doi:10.3109/17453679209154842.
- [13] Periti P, Stringa G, Mini E, Surgery the ISG for AP in O. Comparative multicenter trial of teicoplanin versus cefazolin for antimicrobial prophylaxis in prosthetic joint implant surgery. *Eur J Clin Microbiol Infect Dis*. 1999;18:113–119. doi:10.1007/s100960050238.
- [14] Suter F, Avai A, Fusco U, Gerundini M, Caprioli S, Maggiolo F. Teicoplanin versus cefamandole in the prevention of infection in total hip replacement. *Eur J Clin Microbiol Infect Dis*. 1994;13:793–796. doi:10.1007/BF0211338.
- [15] Tang WM, Chiu KY, Ng TP, Yau WP, Ching PTY, Seto WH. Efficacy of a single dose of cefazolin as a prophylactic antibiotic in primary arthroplasty. *J Arthroplasty*. 2003;18:714–718.

TABLE 1. Guidelines for perioperative antibiotic prophylaxis

Recommendation from Guidelines	Organization										
	BOA 2012	AAOS 2014	SAOA 2016	ACS 2016	SCIP 2011	IHI 2012	ASHP 2013	SIGN 2014	WHO 2016	CDC 2017	NICE 2017
Appropriate antibiotic selection	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Administration within 1 hr before surgical incision	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Discontinuation after incision closure	–	–	–	No	–	–	–	–	✓	✓	–
Discontinuation within 24 h	Debatable	✓	✓	Unknown	✓	✓	Debatable	–	–	–	–

BOA, British Orthopaedic Association [1]; AAOS, American Academy of Orthopaedic Surgeons [2]; SAAO, South African Orthopaedic Association [3]; ACS, American College of Surgeons [4]; SCIP, Surgical Care Improvement Project [5]; IHI, Institute for Healthcare Improvement [6]; ASHP, American Society of Health-System Pharmacists [7]; SIGN, Scottish Intercollegiate Guidelines Network [8]; WHO, World Health Organization [9]; CDC, Centers for Disease Control and Prevention [10]; NICE, The National Institute for Health and Care Excellence [11]

- [16] van Kasteren MEE, Manniën J, Ott A, Kullberg BJ, de Boer AS, Gyssens IC. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. *Clin Infect Dis*. 2007;44:921-927. doi:10.1086/512192.
- [17] Engesaeter LB, Lie SA, Espehaug B, Furnes O, Vollset SE, Havelin LI. Antibiotic prophylaxis in total hip arthroplasty: effects of antibiotic prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0-14 years in the Norwegian Arthroplasty Register. *Acta Orthop Scand*. 2003;74:644-651. doi:10.1080/00016470310018135.
- [18] Backes M, Dingemans SA, Dijkgraaf MGW, van den Berg HR, van Dijkman B, Hoogendoorn JM, et al. Effect of antibiotic prophylaxis on surgical site infections following removal of orthopedic implants used for treatment of foot, ankle, and lower leg fractures: a randomized clinical trial. *JAMA*. 2017;318:2438-2445. doi:10.1001/jama.2017.19343.
- [19] Buckley R, Hughes GN, Snodgrass T, Huchcroft SA. Perioperative cefazolin prophylaxis in hip fracture surgery. *Can J Surg J Can Chir*. 1990;33:122-127.
- [20] Garcia S, Lozano ML, Gatell JM, Soriano E, Ramon R, Sanmiguel JG. Prophylaxis against infection. Single-dose cefonicid compared with multiple-dose cefamandole. *J Bone Joint Surg Am*. 1991;73:1044-1048.
- [21] Garotta F, Pamparana F. Antimicrobial prophylaxis with ceftizoxime versus cefuroxime in orthopedic surgery. *Ceftizoxime Orthopedic Surgery Italian Study Group*. *J Chemother*. 1991;3:34-35.
- [22] Hellbusch LC, Helzer-Julian M, Doran SE, Leibrock LG, Long DJ, Puccioni MJ, et al. Single-dose vs multiple-dose antibiotic prophylaxis in instrumented lumbar fusion - a prospective study. *Surg Neurol*. 2008;70:622-627; discussion 627. doi:10.1016/j.surneu.2007.08.017.
- [23] Liebergall M, Mosheiff R, Rand N, Peyser A, Shaul J, Kahane Y, et al. A double-blinded, randomized, controlled clinical trial to compare cefazolin and cefonicid for antimicrobial prophylaxis in clean orthopedic surgery. *Isr J Med Sci*. 1995;31:62-64.
- [24] Gatell JM, Garcia S, Lozano L, Soriano E, Ramon R, SanMiguel JG. Perioperative cefamandole prophylaxis against infections. *J Bone Joint Surg Am*. 1987;69:1189-1193.
- [25] Karachalios T, Lyritis GP, Hatzopoulos E. Antibiotic prophylaxis in the surgical treatment of peritrochanteric fractures: a comparative trial between two cephalosporins. *Chemotherapy*. 1990;36:448-453. doi:10.1159/000238803.
- [26] American Association of Hip and Knee Surgeons. Position Statement on CDC Guideline: Post-operative prophylactic antibiotics. 2017. <http://www.aahks.org/newsroom/press-releases/aahks-position-statement-on-cdc-guideline-post-operative-prophylactic-antibiotics/>.
- [27] McDonald M, Grabsch E, Marshall C, Forbes A. Single- versus multiple-dose antimicrobial prophylaxis for major surgery: a systematic review. *Aust N Z J Surg*. 1998;68:388-396.
- [28] Mauerhan DR, Nelson CL, Smith DL, Fitzgerald RH, Slama TG, Petty RW, et al. Prophylaxis against infection in total joint arthroplasty. One day of cefuroxime compared with three days of cefazolin. *J Bone Joint Surg Am*. 1994;76:39-45.



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QUESTION 4: Should patients undergoing outpatient total joint arthroplasty (TJA) receive additional postoperative prophylactic antibiotics?

RECOMMENDATION: Despite the current guidelines from the Centers for Disease Control and Prevention (CDC) advocating for a single dose of perioperative antibiotics, the studies utilized to form these guidelines are underpowered and primarily in specialties outside orthopaedics. The limited evidence suggests that a single perioperative dose of antibiotics, compared to multiple doses, does not increase the rates of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs). A randomized prospective study in patients undergoing elective arthroplasty is underway, which should help answer this question definitively.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Administration of prophylactic antibiotics during TJA surgery has been demonstrated to be an important step in the prevention of SSIs and PJIs. During the early years of arthroplasty, prophylactic antibiotics for a few days postoperatively was routine. Over the last decade or so, there has been a movement towards reducing the amount of prophylactic antibiotics administered to TJA patients. Currently, antibiotics are administered to patients undergoing primary TJA for a period of 24 hours. The number of doses of antibiotics that need to be administered to TJA patients is not known.

In recent years, and with the increase in popularity of outpatient TJA, many patients undergoing primary TJA may only receive a single dose of antibiotics. It is not known if a single dose of antibiotics may predispose these patients to higher incidences of SSIs/PJIs. Recent guidelines for prevention of SSIs issued by the World Health Organization (WHO) and the CDC recommend against the administration of additional postoperative antibiotics [1-3]. The recommendation by these organizations is in an antibiotic stewardship practice intended to limit liberal use of antibiotics that can result in the emergence of antimicrobial resistance and also expose patients to adverse effects associated with administration of prolonged antibiotics [2,4,5]. Although the CDC Guidelines issued this statement as a strong recommendation with high quality evidence, there is limited literature in arthroplasty to support this recommendation.

A systematic review and meta-analysis by Thornley et al. has examined the issue of number of doses of antibiotic prophylaxis following TJA. The analyses revealed that the incidence of infections was 3.1% (63/2055) in patients receiving multiple doses of antibiotics compared to an infection rate of 2.3% (45/1981) in patients receiving a single dose of antibiotics [6]. They concluded that postoperative antibiotics did not have additional benefits in reducing the rate of infections. The authors of the systematic review did acknowledge that the quality of evidence related to this subject in TJA is low. Of the four available randomized controlled trials, three include teicoplanin which is currently unavailable in the United States [7-9]. Furthermore, studies are usually underpowered with one randomized trial enrolling only 196 patients when comparing a single dose of cefuroxime to 24 hours of prophylaxis [10]. In addition, Wymenga et al. compared a cohort of patients who received a single preoperative dose of cefuroxime to a cohort who received 3 total doses in 3,013 patients and found no significant differences in infections between the two groups [11]. However, the authors recognized that their sample size was too small to detect a difference given the infrequency of PJI and recommended continuing the use of postoperative prophylaxis until larger studies could be performed [11]. Additionally, in a national registry study, Engesaeter et al. demonstrated higher revision rates in patients receiving a single dose of antibiotics compared to four doses given on the day of surgery [12].