Prevention

1.1. PREVENTION: ANTIBIOTIC PROPHYLAXIS

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QUESTION 1: Is there a correlation between operative time and the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing tumor resection and endoprosthetic reconstruction? If so, should postoperative antibiotics be prolonged in these patients?

RECOMMENDATION: Based largely on the arthroplasty literature, there is considerable evidence that prolonged operative time is associated with an increased risk for postoperative infection. However, there is insufficient evidence to suggest that a prolonged postoperative antibiotic regimen can mitigate this risk. Therefore, there is no evidence to support prolonged postoperative antibiotics in orthopaedic oncology patients undergoing surgeries of prolonged duration. If the duration of the procedure exceeds two half-lives of the prophylactic antimicrobial, intraoperative redosing is needed to ensure adequate serum and tissue concentrations of the antimicrobial.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A thorough literature search was conducted using PubMed, Google Scholar and the Cochrane database. Search terms included "infection," "surgical duration," "surgical time," "operative duration," "orthopaedic," "resection," "reconstruction," "endoprosthesis," "antibiotic duration" and "postoperative antibiotic" in various combinations. The majority of articles found did not specifically focus on orthopaedic oncology patients.

Several studies support the hypothesis that prolonged surgical time was associated with increased risk of postoperative SSI. In a systematic review conducted by Cheng et al. [1], 4343 studies initially identified were narrowed down to 81, many of which demonstrated nearly double the infection risk in cases that exceeded cutoff times of 1-4 hours, and almost threefold the risk in surgeries exceeding 5 hours. When all included studies were pooled, the authors observed the risk of SSI to increase by 5% for every 10 minutes of surgery, 13% for every 15 minutes, 17% for every 30 minutes, and 37% for every 60 minutes. Based on the seven orthopaedic-specific studies included in their review, they found a statistically significant association between operative duration and infection with an 84% increased likelihood of SSI when operative time exceeded different cut-off points ($p = 0.0003$).

In the arthroplasty literature, although some articles have demonstrated an association between prolonged operative time and increased risk of postoperative infection, it remains controversial whether increased operative time is an independent risk for SSI/PJI. Previous studies using administrative or registry databases have linked increased operative time to periprosthetic infection after total joint arthroplasty (TJA) with statistical significance [2–6]. However, the findings of these studies were limited by the significant heterogeneity of their samples and varying definitions for PJI as well as the definitions for operative time. Using data from a single institution, Peersman et al. [7] observed the risk of infection to increase significantly in total knee arthroplasty if the surgery took longer than 2.5 hours. They also investigated the impact of 24 vs. 48 hours of postoperative antibiotics on mitigating this increased risk and found no difference in the two antibiotic regimens. An epidemiological study of over 2,000 patients who underwent orthopaedic surgery in China also demonstrated that surgical time longer than three hours was an independent risk factor for development of SSI, with an odds ratio of 3.633 [8]. Pulido et al. corroborate these findings, showing that on univariate analysis longer operative time had statistically significant association with periprosthetic infection in 9,245 hip and knee replacement patients, but multivariate analysis adjusted for confounding factors revealed that operative time was not an independent predisposing factor for PJI [9]. In contrast, there are studies that failed to demonstrate such a correlation and even found an inverse relationship between operative time and PJI [10–14].

In the orthopaedic oncology patient, risks are even higher considering that patients are often immunocompromised and tumor resection can create a large dead space contributing to development of infection. The overall incidence of SSI in cases of malignant musculoskeletal tumors is reported as greater than 12% in some studies [15] and approximately 10% according to a large systematic review and meta-analysis [16]. Nagano et al. [15] demonstrated in their series of 457 patients with benign or malignant musculoskeletal tumors that duration of surgery is a significant risk factor in acquiring SSI (using threshold of 355 minutes), with an odds ratio of 6.06. Li et al. [17] reviewed a series of 53 patients with osteogenic sarcoma who underwent resection and segmental replacement, demonstrating a postoperative infection rate of 7.5%, much higher than primary arthroplasty. They utilized an antibiotic regimen consisting of three days of intravenous antibiotics followed by five days of oral antibiotics for all of the patients, and the authors were unsure whether this made a meaningful difference. In patients undergoing allograft reconstructions, the infection rate is also high: Tann and Mankin demonstrated a 9% infection rate in their series with the duration of the operative procedure to significantly increase the infection rate [18].

Surgeons have attempted to mitigate infection rates in high-risk patients by administering postoperative antibiotics for a prolonged period; largely, the efficacy of this strategy is not borne out in the literature. Aponte-Tinao et al. [19] report an overall infection rate of 9% in their series of 673 patients who underwent massive allograft reconstruction after tumor resection. Interestingly, a longer period of postoperative antibiotics was found to be a risk factor in development of infection. In the arthroplasty literature, there has also been no benefit associated with prolonged postoperative antibiotic use: Nelson et al. [20] argue that the optimal duration of antibiotics after surgery is 24 hours, as the risk of SSI did not decrease in their randomized controlled trial comparing that to a 7-day regimen. International Consensus Meeting on Periprosthetic Infections in 2013 recommended the use of 1 dose preoperatively and 24 hours of coverage postoperatively [21]. Although the Centers for Disease Control and Prevention recently released their 2017 Guideline for the Prevention of Surgical Site Infection [22], which recommends against the use of postoperative prophylactic antibiotics, including patients undergoing total joint arthroplasty, the American Association of Hip and Knee Surgeons (AAHKS) does not agree with this recommendation [23]. At this time, the AAHKS recommends postoperative antibiotics be continued for 24 hours and supports further research to determine whether shorter duration antibiotic treatment is safe and effective. Both the Board of Counselors and Board of Specialty Societies of the AAOS have endorsed this AAHKS recommendation through an advisory opinion; the American Academy of Orthopaedic Surgeons' Board of Directors adopted that advisory opinion in June 2017 [23]. In their comprehensive publication of clinical practice guidelines for antimicrobial prophylaxis in surgery, Bratzler et al. [24] recognize that duration of surgery is a risk factor for SSI but maintain the recommendation that the duration of postoperative antibiotics for orthopaedic procedures should be less than 24 hours. In cardiothoracic procedures in particular, the exception is made for a recommendation of up to 48 hours. Orthopaedic oncology patients undergoing prolonged surgical resection and reconstruction are not listed as an exception, despite their increased risks as outlined above. An ongoing large international randomized controlled trial, the Prophylactic Antibiotic Regimens in Tumor Surgery (PARITY) has published its feasibility pilot [25] and is scheduled to complete enrolment of 600 patients by the end of 2019 (NCT01479283). The study will determine if five days of postoperative antibiotics reduces infection rates compared to one day of postoperative antibiotics in the orthopaedic oncology population.

Although a longer period of postoperative antibiotics is not recommended by the guidelines [22–24], intraoperative redosing is needed to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the antimicrobial or there is excessive blood loss (i.e., > 1,500 mL). The redosing interval should be measured from the time of administration of the preoperative dose, not from the beginning of the procedure.

REFERENCES

[1] Cheng H, Chen BP, Soleas IM, Ferko NC, Cameron CG, Hinoul P. Prolonged operative duration increases risk of surgical site infections: a systematic review. Surg Infect. 2017;18:722–735.

[2] Peersman G, Laskin R, Davis J, Peterson MGE, Richart T. Prolonged operative time correlates with increased infection rate after total knee arthroplasty. HSS J. 2006;2:70–72. doi:10.1007/s11420-005-0130-2.

[3] Bozic KJ, Ward DT, Lau EC, Chan V, Wetters NG, Naziri Q, et al. Risk factors for periprosthetic joint infection following primary total hip arthroplasty: a case control study. J Arthroplasty. 2014;29:154–156. doi:10.1016/j.arth.2013.04.015.

[4] Pugely AJ, Martin CT, Gao Y, Schweizer ML, Callaghan JJ. The incidence of and risk factors for 30-day surgical site infections following primary and revision total joint arthroplasty. J Arthroplasty. 2015;30:47–50. doi:10.1016/j.arth.2015.01.063.

[5] Zhu Y, Zhang F, Chen W, Liu S, Zhang Q, Zhang Y. Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. J Hosp Infect. 2015;89:82–89. doi:10.1016/j.jhin.2014.10.008.

[6] Namba RS, Inacio MC, Paxton EW. Risk factors associated with deep surgical site infections after primary total knee arthroplasty: an analysis of 56,216 knees. J Bone Joint Surg Am. 2013;95:775–782. doi:10.2106/JBJS.L.00211.

[7] Peersman G, Laskin R, Davis J, Peterson M. Infection in total knee replacement: a retrospective review of 6489 total knee replacements. Clin Orthop Relat Res. 2001;392:15–23.

[8] Li G, Guo F, Ou Y, Dong G, Zhou W. Epidemiology and outcomes of surgical site infections following orthopedic surgery. Am J Infect Control. 2013;41:1268–1271.

[9] Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res. 2008;466:1710–1715. doi:10.1007/s11999-008-0209-4.

[10] Boer ASD, Geubbels ELPE, Wille J, Groot AJM-D. Risk assessment for surgical site infections following total hip and total knee prostheses. J Chemother. 2001;13:42–47. doi:10.1179/joc.2001.13.Supplement-2.42.

[11] Wymenga AB, Horn JR van, Theeuwes A, Tmuytjens HL, Slooff TJJH. Perioperative factors associated with septic arthritis after arthroplasty. Acta Orthop Scand. 1992;63:665–671. doi:10.1080/17453679209169732.

[12] Suzuki G, Saito S, Ishii T, Motojima S, Tokuhashi Y, Ryu J. Previous fracture surgery is a major risk factor of infection after total knee arthroplasty. Knee Surg Sports Traumatol. Arthrosc. 2011;19:2040–2044. doi:10.1007/s00167-011-1525-x.

[13] Crowe B, Payne A, Evangelista PJ, Stachel A, Phillips MS, Slover JD, et al. Risk factors for infection following total knee arthroplasty: a series of 3836 cases from one institution. J Arthroplasty. 2015;30:2275–2278. doi:10.1016/j.arth.2015.06.058.

[14] Naranje S, Lendway L, Mehle S, Gioe TJ. Does operative time affect infection rate in primary total knee arthroplasty? Clin Orthop Relat Res. 2015;473:64–69. doi:10.1007/s11999-014-3628-4.

[15] Nagano S, Yokouchi M, Setoguchi T, Sasaki H, Shimada H, Kawamura I, et al. Analysis of surgical site infection after musculoskeletal tumor surgery: risk assessment using a new scoring system. Sarcoma. 2014;2014:645496.

[16] Racano A, Pazionis T, Farrokhyar F, Deheshi B, Ghert M. High infection rate outcomes in long-bone tumor surgery with endoprosthetic reconstruction in adults: a systematic review. Clin Orthop Relat Res. 2013;471:2017–2027. doi:10.1007/s11999-013-2842-9.

[17] Li X, Moretti VM, Ashana AO, Lackman RD. Perioperative infection rate in patients with osteosarcomas treated with resection and prosthetic reconstruction. Clin Orthop Relat Res. 2011;469:2889–2894. doi:10.1007/s11999-011-1877-z.

[18] Tan MH, Mankin HJ. Blood transfusion and bone allografts: effect on infection and outcome. Clin Orthop Relat Res. 1997;340:207–214.

[19] Aponte-Tinao LA, Ayerza MA, Muscolo DL, Farfalli GL. What are the risk factors and management options for infection after reconstruction with massive bone allografts? Clin Orthop Relat Res. 2016;474:669–673.

[20] Nelson CL, Green TG, Porter RA, Warren RD. One day versus seven days of preventive antibiotic therapy in orthopedic surgery. Clin Orthop Relat Res. 1983:258–263.

[21] 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.

[22] Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017;152:784–791. doi:10.1001/jamasurg.2017.0904.

[23] Yates AJ. Postoperative prophylactic antibiotics in total joint arthroplasty. Arthroplast Today. 2018;4:130–131. doi:10.1016/j.artd.2018.01.003.

[24] Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery. Surg Infect. 2013;14:73–156. doi:10.1089/sur.2013.9999.

[25] PARITY Investigators. Prophylactic antibiotic regimens in tumour surgery (PARITY): a pilot multicentre randomised controlled trial. Bone Joint Res. 2015;4:154–162. doi:10.1302/2046-3758.49.2000482.