Prophylactic antibiotics for massive endoprostheses in orthopaedic oncology: gaps in our understanding

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Background

Primary bone tumours (PBTs) are rare malignancies with wide biological and clinical heterogeneity. Age-specific incidence rates show a bimodal distribution, with osteosarcoma and Ewing sarcoma peaking between the ages of 15-19 and chondrosarcoma being more common in the middle and older age groups. For many patients, treatment involves limb-salvage surgery, usually with massive endoprosthetic replacement (EPR) of large segments of bone and joints. Osteosarcoma and Ewing sarcoma treatment also involves immunosuppressive chemotherapy regimens, with or without radiotherapy, whereas with a few exceptions, chondrosarcomas are treated with surgery alone. Approximately two-thirds of patients achieve long-term survival from their cancer[1]. Therefore, the durability of EPR is essential for maintaining limb function and quality of life. In addition to PBTs, EPRs are increasingly being used to treatment of Metastatic bone disease in selected cases.

Unfortunately, the risk of infection remains high, which can be devastating for patients, leading to pain, poor physical functioning, reduced quality of life, and even death, as [2–6]well as significant healthcare costs[2–6].

A recent systematic review demonstrated an overall pooled weighted deep infection rate of 10% (95% CI 8-11%) for oncology-related lower limb EPR[7]. This rate is much higher than total hip arthroplasty (between 0.8% and 1.2%) [8]. There are many reasons for this, including concomitant use of immunosuppressive chemotherapy, radiotherapy, pre-existing co-morbidities, and complex surgery, routinely requiring prolonged operation times, extensive tissue dissection, and large implants.

Antimicrobial prophylaxis is a critical infection prevention and control (IPC) measure recommended alongside skin decolonisation before surgery, antiseptic skin preparation, hand decontamination, environmental control, and wound care.

Antibiotic prophylaxis for EPR surgery

National and international guidelines recommend antibiotic prophylaxis for orthopaedic implant surgery. These guidelines do not recommend a specific antibiotic regimen. However, they do recommend that antibiotic(s) should meet specific criteria: be active against the most common pathogens; administered at an appropriate dose to ensure adequate serum and tissue concentrations at the operative site; administered at an appropriate time to maintain adequate concentration for the entire duration of surgery; be safe, and administered for the shortest effective period to minimise adverse effects[9–11]

The lack of clear evidence-based recommendations contributes to wide variation in practice. A 2012 audit sent to 38 members of the British Orthopaedic Oncology Society identified a wide range of antibiotic choices for EPR surgery in the UK, often extrapolated from conventional hip and knee arthroplasty. Of the 27 (response rate 71%) respondents reflecting the majority of UK centres, 24 preferred to give single-agent antibiotic regimens. The most common antibiotics were cefuroxime (55.5%), co-amoxiclav (11.1%), flucloxacillin (11.1%), vancomycin (7.1%) and teicoplanin (3.7%). The only combination regimen reported was flucloxacillin plus gentamicin (11.1%). This is consistent with a broader study of UK orthopaedic practice, showing that between 2005 and 2011, there was a gradual decline in the use of cephalosporins and a corresponding increase in the use of combination regimens including penicillin derivatives and teicoplanin, which carry a lower *Clostridioides difficile* infection (CDI) risk[12]. Half of the hospitals that changed prophylaxis stated CDI as the main reason in that study.

A recent international cross-sectional survey of international practice was sent to 96 sarcoma surgeons. Of the 72 respondents (75% response rate), 46% believed preoperative antibiotic administration was the most critical initial step to prevent postoperative infection[13]. This group had a greater consensus about antibiotic choice compared with the UK. 73% of respondents preferred Gram-positive cover alone, usually with cefazolin[13]. However, there was a wide variation in duration; 33.7% felt antibiotics should be stopped after 24 hours, whereas 41.4% thought they should be discontinued after removing suction drains[13].

Duration

The Prophylactic Antibiotic Regimens In Tumor Surgery (PARITY) trial investigated whether extending prophylaxis for EPR reduced infection rates [14]. In this international multicentre randomised trial, 611

patients undergoing massive endoprostheses for lower extremity bone tumours were randomised to either five days or 24 hours of cefuroxime. The study provided level 1 evidence that there was no benefit in extending the duration of prophylaxis in this population. Upper limb EPRs were excluded to reduce the sample size required to achieve adequate statistical power due to the lower infection rates at these sites. High overall event rates were seen in PARITY compared to previous reports, probably due to the prospective monitoring of patients for events and the broad definition of infection applied.

Significantly more severe antibiotic-related complications were seen in the longer-duration group (5.1% vs 1.6%: HR 3.24, 95% CI 1.17-8.98; P=0.02). CDI was the most common antibiotic complication and occurred three times more frequently in the 5-day group (3.8% vs 1.3% in the 24-hour group) [14].

The lack of benefit and increased harm with extended antibiotic prophylaxis has been consistently demonstrated in multiple prospective studies across various surgical specialities. Nevertheless, PARITY conclusively answers this question in the bone tumour population.

Despite this excellent study, there is a lack of evidence that current antibiotic regimens meet the recommended criteria for implant surgery. These are fundamental to ensuring adequate intraoperative cover during the critical period of risk when the surgical site is exposed to contamination. Questions remain about the optimal antibiotic choice, specifically the spectrum of coverage, timing and dose requirements, and risk profiles.

The Spectrum of Antibiotic Coverage

Guidelines recommend that prophylactic antibiotics are active against the most common pathogens, but more data are required about EPR in orthopaedic oncology. A 2014 systematic review of infection rates in EPRs identified 48 studies[7]. Twenty-one included information on the antibiotic prophylaxis administered. Only 7 provided details of antibiotic choice, which influences the pathogen profile of infected cases by selecting pathogens resistant to the antibiotics used. All seven studies had small cohorts of primary procedures using a 1st, 2nd, or 3rd generation cephalosporin. The most common infecting organisms were *Staphylococcus aureus* and Coagulase-negative staphylococci (CoNS).

CoNS have a low prevalence of sensitivity to cephalosporins which therefore do not reliably cover these commonly infecting organisms [15]. Although glycopeptides provide more reliable coverage against CoNS, they were not found to be superior to cephalosporins in a recent systematic review and meta-

analysis of antibiotic prophylaxis in primary hip and knee arthroplasty[16]. 6 RCTs were identified, with 2886 participants receiving either a cephalosporin (1st or 2nd generation) or a glycopeptide, with teicoplanin in 5 of the 6 RCTs. The limitations included: significant unexplained heterogeneity among the studies; small sample sizes with low event rates limiting the statistical power to detect differences in infection rates; short (less than 12 months) follow-up in four of the RCTs, which may mean missing CoNS infections that glycopeptides may have covered; and that studies conducted in the 1980s and 90s were included when antibiotic resistance rates differed.

Furthermore, glycopeptides have poor activity against gram-negative bacilli (GNB) compared with cephalosporins; therefore, it is not possible to determine whether providing extended cover for gram-positive organisms alone by covering CoNS with glycopeptides reduces infection rates. More recently, a retrospective observational study in revision arthroplasty investigated extending gram-positive cover by adding cefazolin to vancomycin compared to vancomycin alone [17]. The study was conducted in a hospital with a high background rate of MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE) prosthetic joint infections. Targeted use of vancomycin and cefazolin among patients undergoing revision total knee arthroplasty (TKA) significantly reduced the rate of overall infections (7.89 to 3.13%, p = 0.046), particularly MRSA (4.21 to 0.89%, p = 0.049).

It is common practice to add a 2nd antibiotic to a glycopeptide to provide better GNB activity[18]. An observational study combining gentamicin or aztreonam with cefazolin decreased the rate of PJIs in patients undergoing primary hip but not in knee arthroplasty [19]. This is partly because in this study Gram-negative organisms caused 30% of the surgical site infections (SSI) following hip arthroplasty and only 10% of SSIs after knee arthroplasty. This was a retrospective study with numerous sources of bias and confounders. Therefore, results must be interpreted cautiously. The fixed doses of antibiotics in these studies may have led to underdosing of antibiotics rather than an inadequate spectrum of coverage. Recently, weight-based dosing for vancomycin has been recommended.

Despite the significant limitations of the current data, the weight of evidence does not support extending the spectrum beyond 1st or 2nd generation cephalosporins for hip or knee replacement. However, the extent to which this can be extrapolated to EPR is unknown. There are no data for extended-spectrum antibiotic prophylaxis in the PBT population. Studying the epidemiology of infection associated with the help of an extended-spectrum antibiotic regimen would provide insight into the selection of antibiotic-

resistant pathogens in infected EPR cases. A large observational cohort study could compare pathogen profiles of EPRs implanted at different anatomical sites, such as pelvis vs knee, to determine which anatomic sites may benefit from extended-spectrum prophylaxis. This could inform an RCT comparing the efficacy of a 1st or 2nd-generation cephalosporin with other extended-spectrum antibiotic regimens.

Significant gaps exist in understanding the organisms causing infection and the implication for a defined spectrum of coverage, antibiotic dosing, and risk profile of different regimens. The pathogen profile of EPR infections remains poorly defined. Published series show that CoNS and *Staphylococcus aureus* are the most common pathogens. However, the relative contribution of Gram-negative pathogens requires further study. Retrospective studies have shown lower infection rates after switching to an extended-spectrum antimicrobial regimen in specific circumstances, i.e., for revision arthroplasty where infection rates are higher than primary hip and knee replacements or where the prevalence of Gram-negative pathogens or MRSE is high. These circumstances may apply to EPR, and these observations could form the bases for a prospective study to investigate whether extended-spectrum prophylaxis reduces infection rates compared to 1st or 2nd-generation cephalosporins.

Timing and Dose

Several studies have shown higher SSI rates where antibiotic prophylaxis is given too early or late relative to incision time[20–22]. They show a U-shaped curve relationship when plotting SSI rates against the timing of antibiotic administration relative to incision time. The lowest SSI rates are seen when antibiotics are given between 0-60 minutes pre-incision. Vancomycin and ciprofloxacin are exceptions due to the need to administer these as prolonged infusions[11].

The administered dose should achieve serum and tissue concentrations exceeding the minimum inhibitory concentration (MIC) against target pathogens for the duration of surgery. Indeed, multiple controlled studies have demonstrated lower infection rates in patients with detectable antibiotics in serum at the end of surgery than in patients whose antibiotic concentrations are below the MIC of the commonly infected organisms [23,24].

A recent observational study of oncology patients undergoing surgery correlated intraoperative cefazolin concentrations with infection risk[25].The study concluded that current practice for cefazolin might not provide adequate tissue concentrations and lead to higher infection rates. These are the only

PK data available in an orthopaedic oncology population. Dosing for alternative antimicrobials warrants further investigation.

Arthroplasty guidelines recommend intra-operative re-dosing based on the estimated half-life of the antibiotic[26,27]. The available data investigating the effect of intraoperative blood loss on antibiotic concentrations are shown in Table 1. Older pharmacokinetic (PK) studies demonstrate a significant reduction in antibiotic concentrations with increasing blood loss[28,29]. These studies measured antibiotic concentrations in serum and tissue at serial time points using a traditional 2-stage approach; the first stage involves calculating individual PK parameters (e.g., clearance and volume of distribution); the second stage consists of the analysis of these PK parameters using descriptive statistics, usually the mean and standard deviation. This type of analysis can detect associations between drug dosing and serum or tissue concentrations but does not identify the patient and surgical factors leading to pharmacokinetic variability between individuals. More recent studies use a model-based approach in which PK data from multiple subjects are analysed simultaneously. Significant covariates can be identified in different dosing scenarios in the model-building phase. In these studies, blood loss was not identified as a major covariate in PK modelling studies of cefazolin, cefuroxime, and gentamicin. However, these studies included patients undergoing blood loss ranging from 0.6 to 1.8 litres, which may not be generalisable to EPR procedures involving higher blood loss.

Ideally, a single induction dose would provide reliable antibiotic cover for EPR surgery and would not rely on re-dosing after blood loss[32]. PK data from PBT patients would be more representative of the patient population so that the effect of body weight and clearance can be evaluated. Estimates of PK parameters for the population can be used to simulate dosing recommendations by objectively assessing the probability of achieving adequate concentrations during surgery for different dosing and re-dosing scenarios. Additionally, these studies would help inform initial doses and re-dosing intervals that provide reliable cover, avoiding toxicity.

There is good consensus on the timing of prophylaxis administration, but the extent to which current regimens adequately cover EPR procedures needs to be clarified. Antibiotic dosing has not been studied in EPR surgery, and the extrapolation of practice from conventional arthroplasty has not considered the pharmacokinetic implications. Standard dosing and re-dosing advice may not be sufficient in oncology patients. Pharmacokinetic studies are required so that dosing regimens are

appropriate for the oncology population, and pharmacokinetic modelling should be used to inform population-level dosing recommendations. The practicalities of dose and timing need to be considered for EPR surgery which is routinely prolonged and may involve substantial blood loss. Re-dosing is often performed inconsistently in practice and has been associated with higher infection rates in observational studies[30–32]. The heterogeneity of the primary bone tumour population (renal function and body weight) may warrant prophylactic antibiotics with a long half-life that reliably cover EPR surgery with a single dose at induction. PK studies will also help manage the risks of unnecessarily higher doses and subsequent toxicity, particularly with aminoglycosides in osteosarcoma and Ewing sarcoma patients receiving neo-adjuvant nephrotoxic chemotherapy.

Unintended consequences of broader cover

Any regimen will carry risks. The toxicity of single doses includes acute kidney injury (AKI) and anaphylaxis. In contrast, longer-term therapy may be associated with other toxicities such as anaemia, skin reactions and hepatic dysfunction.

Anaphylaxis

Commonly used prophylactic antibiotics can cause life-threatening anaphylactic reactions. The 6th National Audit Project (NAP6) analysis provides the incidence rate of anaphylaxis for common prophylactic antibiotics[33]. In one year, there were 266 reports of perioperative anaphylaxis after an estimated 3,126,067 anaesthetics were administered in UK hospitals. Antibiotics were identified as causing 48% of probable or definite anaphylactic events. All anaphylactic reactions were graded as 3 to 5 in severity, i.e., potentially life-threatening. Four of ten deaths in NAP6 were thought to be caused by an antibiotic. Estimates of anaphylaxis incidence per 100,000 were highest for teicoplanin (16.4), followed by co-amoxiclav (8.7), vancomycin (5.4), cefuroxime (0.9), flucloxacillin (0.9) and gentamicin (0.5). It is concerning that an observational study estimated a three times higher rate of teicoplanin anaphylaxis than NAP6 — between 1:2088 and 1:1655, which may reflect underreporting of anaphylaxis in the audit[34]. Gram-negative active agents such as gentamicin and ciprofloxacin were generally associated with a lower risk of anaphylaxis.

The NAP6 audit highlights the considerable range in the incidence of anaphylaxis with commonly administered prophylactic agents, which is an essential consideration in assessing the risk of a particular prophylactic regimen.

Acute Kidney Injury

First-generation cephalosporins appear attractive due to their low risk of toxicity, like beta-lactams. AKI is well-known risk with repeated doses of aminoglycosides and is associated with a high morbidity. The PARITY trial only compared different durations of the same antibiotics, so there are no prospective studies evaluating the rates of AKI between different regimens in patients with PBTs. The seven observational studies reporting EPR infection rates with different prophylactic regimens used cephalosporins. Observational studies of other types of orthopaedic surgery have shown an association between gentamicin and AKI. A single-centre pre-and post-implementation study comparing AKI rates after cefuroxime to those after flucloxacillin plus gentamicin used in two consecutive periods found higher rates of AKI among patients with the combined regimen[35]. There are limited data on the risk of AKI with teicoplanin for prophylaxis in orthopaedic [41].A cardiac surgery study found teicoplanin associated with similar rates of AKI to vancomycin. However, teicoplanin is generally associated with a lower risk of AKI than vancomycin[36].

Observational studies are helpful, but it is impossible to attribute AKI risk to the antibiotic or account for baseline risk. These analyses may not be generalisable to PBTs patients who commonly receive concurrent nephrotoxic chemotherapy and may therefore be at increased risk.

Clostridium difficile risk

CDI is more common among paediatric oncology than non-oncology patients. Several factors may contribute, such as increased exposure to antibiotics during neoadjuvant chemotherapy (for treatment or prophylaxis), an immunocompromised host, frequent hospitalisations, and proton pump inhibitors[37].

Concern about CDI associated with cephalosporins is the primary driver for changing prophylactic regimens in the UK. More data are required to evaluate the association of CDI with different prophylactic antibiotic regimens in orthopaedics. In the PARITY Trial, CDI rates with mostly cefazolin, were 1.3% in

the 24-hour group and 3.8% in the 5-day group[14]. Two studies suggest that cefuroxime use may be associated with an increased risk of CDI compared with other prophylactic regimens. The first study in trauma patients found that switching from cefuroxime to gentamicin plus flucloxacillin or teicoplanin reduced the incidence of C difficile infection from 8% to 3%[38]. A second study of hip fracture patients found an 80% risk reduction (6.9% to 1.5%) in CDI after switching surgical prophylaxis from cefuroxime to co-amoxiclav[39]. In both studies, the retrospective observational nature means that it is impossible to show that the reduction in CDI was solely due to the change in antibiotic prophylaxis, changes in stool sample collection rates or general changes in IPC measures. These studies report incidences as high as 7.1%, likely reflecting an older patient group with more predisposing risk factors for CDI.

When CDI occurs among oncology patients, the clinical outcomes are poorer than non-oncology patients. Two large double-blind trials found the cure rate for CDI was significantly lower among oncology patients compared with others (n = 922; 79.2% *v* 88.6%; $P < 0.001$, respectively) and the median time to resolution of diarrhoea was delayed (100 hours *v* 55 hours; $P < 0.001$, respectively). CDI can lead to significant delays in surgical and chemotherapy treatment.

The risk-benefit of these regimens has not been formally considered using risk profiling. There are many potential antibiotic options, but manufacturers have yet to pursue marketing authorisation for their use as antibiotic prophylaxis proactively. There are often minimal data to support their use. This is particularly the case for using alternative agents to cephalosporins, such as glycopeptides, that have increasingly been used due to concerns of CDI.

The benefits of any antibiotic regimen should be balanced against the risks and the adverse effects of antibiotics, such as anaphylaxis, AKI, and CDI. Whilst there has been a shift from cephalosporins to alternatives, including combination regimens to reduce the incidence of CDI in arthroplasty, data suggest higher risks for acute kidney injury and anaphylaxis while infection rates are unchanged. However, the higher infection rate and devastating consequences of infected EPR warrant further evaluation.

Future research

This review identifies gaps of knowledge to set future research priorities. The focus should be on understanding on which factors to consider when optimising antibiotic regimens. Currently we do not know whether the prophylactic needs of this patient population can be met with a 'one-size fits all' approach, or whether certain information should be used to individualise prophylaxis.

Dosing is essential to achieving adequate prophylactic cover. Pharmacokinetic studies are required to understand the variability in local tissue concentrations for commonly used antibiotics to define the dosing requirements in this patient population. We recommend that expertise in antibacterial pharmacology is integrated into the design of future studies.

RCTs comparing SSI rates with different regimens are required to determine optimal choice. Previous RCTs have been conducted in orthopaedic surgery but none in this specific patient population and all have significant methodological limitations. Although PARITY compared duration rather than choice, it has shown completing an adequately powered RCT in this patient population is feasible with international collaboration.

Other factors need to be taken into consideration when choosing a prophylactic regimen. The efficacy of a specific regimen to reduce deep infection rates needs to be balanced against the risks of broad-spectrum antibiotic use, therefore future studies should evaluate drug toxicity and the impact on antibiotic resistance.

The potential clinical implications of this research include fewer EPR infections, fewer antibiotic-related complications, and a deeper understanding of infection prevention in this vulnerable and complex group of patients.

Conclusion

PARITY has been a landmark study in antibiotic prophylaxis in orthopaedic oncology patients. However, many critical questions remain around antibiotic choice and dose. Further research in this area is warranted to identify and optimise antibiotic regimens, including a randomised, controlled trial assessing the effects on SSI, drug toxicity, and antimicrobial resistance.

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Competing interests

The authors declare no competing interests.

1. Muella P, Belot A, Morris M, Rachet B. *Net Survival and the Probability of Cancer Death from Rare Cancers*.; 2013.

2. Jeys LM, Grimer RJ, Carter SR, Tillman RM. *Periprosthetic Infection in Patients Treated for an Orthopaedic Oncological Condition*.; 2005.

3. Hardes J, Gebert C, Schwappach A, et al. Characteristics and outcome of infections associated with tumor endoprostheses. *Arch Orthop Trauma Surg*. 2006;126(5):289-296. doi:10.1007/s00402-005-0009-1

4. Flint MN, Griffin AM, Bell RS, Wunder JS, Ferguson PC. Two-Stage Revision of Infected Uncemented Lower Extremity Tumor Endoprostheses. *Journal of Arthroplasty*. 2007;22(6):859-865. doi:10.1016/j.arth.2006.11.003

5. Grimer R J, Belthur M, Chandrasekar C, Carter S R, Tillman R. Two-Stage Revision for Infected Endoprostheses Used in Tumor Surgery. *Clin Orthop Relat Res*. 2002;395.

6. Sigmund IK, Gamper J, Weber C, et al. Efficacy of different revision procedures for infected megaprostheses in musculoskeletal tumour surgery of the lower limb. *PLoS One*. 2018;13(7). doi:10.1371/journal.pone.0200304

7. 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(6):2017-2027. doi:10.1007/s11999-013-2842-9

8. McPherson EJ, Woodson C, Holtom P, Roidis N, Shufelt C, Patzakis M. Periprosthetic total hip infection: outcomes using a staging system. *Clin Orthop Relat Res*. 2002;403:8-15.

9. Intercollegiate Guidelines Network S. *Scottish Intercollegiate Guidelines Network Antibiotic Prophylaxis in Surgery*.; 2008. www.sign.ac.uk/guidelines/published/numlist.html.

10. Berriós-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg*. 2017;152(8):784-791. doi:10.1001/jamasurg.2017.0904

11. Bratzler DW, Houck PM. *Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project*. https://academic.oup.com/cid/article/38/12/1706/304336

12. Aujla RS, Bryson DJ, Gulihar A, Taylor GJ. Trends in orthopaedic antimicrobial prophylaxis in the UK between 2005 and 2011. *Ann R Coll Surg Engl*. 2013;95(7):495-502. doi:10.1308/003588413X13629960047038

13. Hasan K, Racano A, Deheshi B, et al. Prophylactic antibiotic regimens in tumor surgery (PARITY) survey. *BMC Musculoskelet Disord*. 2012;13. doi:10.1186/1471-2474-13-91

14. Ghert M, Schneider P, Guyatt G, et al. Comparison of Prophylactic Intravenous Antibiotic Regimens after Endoprosthetic Reconstruction for Lower Extremity Bone Tumors: A Randomized Clinical Trial. *JAMA Oncol*. Published online 2022. doi:10.1001/jamaoncol.2021.6628

15. Malhas AM, Lawton R, Reidy M, Nathwani D, Clift BA. Causative organisms in revision total hip & knee arthroplasty for infection: Increasing multi-antibiotic resistance in coagulase-negative Staphylococcus and the implications for antibiotic prophylaxis. *Surgeon*. 2015;13(5):250-255. doi:10.1016/j.surge.2014.04.002

16. Siddiqi A, Forte SA, Docter S, Bryant D, Sheth NP, Chen AF. Perioperative antibiotic prophylaxis in total joint arthroplasty: A systematic review and meta-analysis. *Journal of Bone and Joint Surgery - American Volume*. 2019;101(9):828-842. doi:10.2106/JBJS.18.00990

17. Liu C, Kakis A, Nichols A, Ries MD, Vail TP, Bozic KJ. Targeted use of vancomycin as perioperative prophylaxis reduces periprosthetic joint infection in revision TKA knee. In: *Clinical Orthopaedics and Related Research*. Vol 472. Springer New York LLC; 2014:227-231. doi:10.1007/s11999-013-3029-0

18. Aujla RS, Bryson DJ, Gulihar A, Taylor GJ. Trends in orthopaedic antimicrobial prophylaxis in the UK between 2005 and 2011. *Ann R Coll Surg Engl*. 2013;95(7):495-502. doi:10.1308/003588413X13629960047038

19. Bosco JA, Tejada PRR, Catanzano AJ, Stachel AG, Phillips MS. Expanded Gram-Negative Antimicrobial Prophylaxis Reduces Surgical Site Infections in Hip Arthroplasty. *Journal of Arthroplasty*. 2016;31(3):616-621. doi:10.1016/j.arth.2015.09.051

20. Classen DC. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med* . 1992;326:281-286.

21. Dellinger EP. Prophylactic antibiotics: Administration and timing before operation are more important than administration after operation. *Clinical Infectious Diseases*. 2007;44(7):928-930. doi:10.1086/512198

22. Hawn MT, Richman JS, Vick CC, et al. Timing of surgical antibiotic prophylaxis and the risk of surgical site infection. *JAMA Surg*. 2013;148(7):649-657. doi:10.1001/jamasurg.2013.134

23. Zelenitsky SA, Ariano RE, Harding GKM, Silverman RE. Antibiotic pharmacodynamics in surgical prophylaxis: An association between intraoperative antibiotic concentrations and efficacy. *Antimicrob Agents Chemother*. 2002;46(9):3026-3030. doi:10.1128/AAC.46.9.3026-3030.2002

24. Goldman D. Cephalothin prophylaxis in cardiac valve surgery. *J Thorac Cardiovasc Surg* . Published online 1977:470-479.

25. Byers IS, Turner NA, Levine NL, et al. Antibiotic Prophylaxis for Megaprosthetic Reconstructions: Drug and Dosing May Matter More than Duration. *Antimicrob Agents Chemother*. 2022;66(10):e0014022. doi:10.1128/aac.00140-22

26. Bratzler DW, Houck PM. *Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project*. https://academic.oup.com/cid/article/38/12/1706/304336

27. Intercollegiate Guidelines Network S. *Scottish Intercollegiate Guidelines Network Antibiotic Prophylaxis in Surgery*.; 2008. www.sign.ac.uk/guidelines/published/numlist.html.

28. Markantonis SL. Effects of blood loss and fluid volume replacement on serum and tissue gentamicin concentrations during colorectal surgery. *Clin Ther*. 2004;26(2).

29. Swoboda SM, Merz C, Kostuik J, Trentler B, Lipsett PA. *Does Intraoperative Blood Loss Affect Antibiotic Serum and Tissue Concentrations?* http://archsurg.jamanetwork.com/

30. Kasatpibal N, Whitney JD, Dellinger EP, Nair BG, Pike KC. Failure to Redose Antibiotic Prophylaxis in Long Surgery Increases Risk of Surgical Site Infection. In: *Surgical Infections*. Vol 18. Mary Ann Liebert Inc.; 2017:474-484. doi:10.1089/sur.2016.164

31. Wolfhagen N, Boldingh QJJ, De Lange M, Boermeester MA, De Jonge SW. Intraoperative Redosing of Surgical Antibiotic Prophylaxis in Addition to Preoperative Prophylaxis Versus Single-dose Prophylaxis for the Prevention of Surgical Site Infection. *Ann Surg*. 2022;275(6):1050-1057. doi:10.1097/SLA.0000000000005436

32. Bertschi D, Weber WP, Zeindler J, et al. Antimicrobial Prophylaxis Redosing Reduces Surgical Site Infection Risk in Prolonged Duration Surgery Irrespective of Its Timing. *World J Surg*. 2019;43(10):2420-2425. doi:10.1007/s00268-019-05075-y

33. Cook TM, Thomas M, Harper NJN. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th national audit project. *Br J Anaesth*. 2018;121(1):159-171.

34. Azamgarhi T, Shah A, Warren S. Teicoplanin anaphylaxis associated with surgical prophylaxis. *Br J Clin Pharmacol*. 2018;84(5). doi:10.1111/bcp.13506

35. Bell S, Davey P, Nathwani D, et al. Risk of AKI with gentamicin as surgical prophylaxis. *Journal of the American Society of Nephrology*. 2014;25(11):2625-2632. doi:10.1681/ASN.2014010035

36. Olsson DP, Holzmann MJ, Sartipy U. Antibiotic prophylaxis by teicoplanin and risk of acute kidney injury in cardiac surgery. *J Cardiothorac Vasc Anesth*. 2015;29(3):626-631. doi:10.1053/j.jvca.2014.08.010

37. Bishop KD, Castillo JJ. Risk factors associated with Clostridium difficile infection in adult oncology patients with a history of recent hospitalization for febrile neutropenia. *Leuk Lymphoma*. 2012;53(8):1617-1619. doi:10.3109/10428194.2012.654472

38. Al-Obaydi W, Smith CD, Foguet P. *Changing Prophylactic Antibiotic Protocol for Reducing Clostridium Difficile-Associated Diarrhoeal Infections*. Vol 18.; 2010.

402 39. Gulihar A, Nixon M, Jenkins D, Taylor GJS. Clostridium difficile in hip fracture patients:
403 Prevention, treatment and associated mortality. *Injury*. 2009;40(7):746-751.
404 doi:10.1016/j.injury.2008.12.004

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407 **Table**

Table I. Summary of covariates identified in pharmacokinetic modelling studies for commonly used prophylactic antibiotic regimens.

Study/Setting	Drug, dose, and timing	Major covariates	Effect of covariates	Effect of blood loss	Clinical relevance
Swoboda et al[31] (1996) Spinal surgery N = 11	Cefazolin Dose: 1 g (range 9 to 24 mg/kg) Timing: 15 to 30 mins pre-incision	No pharmacokinetic modelling	Unable to identify covariates	Antibiotic concentration correlated with blood loss.	Blood loss is significantly associated with low antibiotic concentrations in serum and tissue.
Naik et al[32] (2017) Major urological and spinal surgery N = 20	Cefazolin Dose: 2 g Intermittent infusion or continuous infusion Timing: 15 to 60 mins pre-incision	Renal function, body weight	Cefazolin clearance = ¼TVCL*(Cr_{Cl}/80) Cefazolin central volume of distribution = ¼TVVc*(WT/80) *0.75	Not a significant covariate Measured blood loss: Intermittent group – mean 0.67 L (SD 0.40) Continuous group – median 1.04 L (SD .75)	Renal function and body weight were significant covariates for cefazolin levels. Earlier re-dosing intervals of 2 to 3 hours increased the likelihood of adequate intraoperative cover, with continuous infusions superior at a lower total dose.
Asín-Prieto et al[33] (2015) Colorectal surgery N = 63	Cefuroxime Dose: 1.5 g Timing: 30 mins pre-incision	Renal function	CL (L/h) = θ_{CL}+(CL_{Cr}–4.8) x θ_{CLcr} If (CL_{Cr} ≥ 4.8 L/h): CL(L/h) = θ_{CL} Where θ_{CL} = 8.77 and θ_{CLcr}= 1.71	Not measured	A 1.5 g dose should be administered every 2 hours to provide adequate coverage. This is sooner than the 4-hour re-dosing interval recommended in the guidelines.
Markantonis et al[30] (2004) Colorectal surgery N = 16	Gentamicin Dose: 2 mg/kg Timing: 30 mins pre-incision	No pharmacokinetic modelling	Unable to identify covariates	Antibiotic concentrations in serum and tissues correlated with blood loss.	A 2 mg/kg dose of gentamicin, associated with significant intraoperative blood loss requiring significant fluid replacement, did not achieve concentrations of the drug above MICs for Gram-negative microorganisms throughout the procedure in either serum or tissue.
da Silva Neto et al[34] (2021) Colorectal surgery N = 20	Gentamicin Dose: 5 mg/kg Timing: 30 mins pre-incision	Renal function	CL (L/h) = 0.0449 x AJBW + 0.0195 x CL_{CR}	Not a significant covariate Measured blood loss ranged from 0.2 to 1.8 L	In patients with creatinine clearance > 50 ml/min, 5 mg/kg gentamicin (with an additional 2.5 mg/kg in prolonged surgery at 6 hrs) maintained PTA targets for > 10 hrs.

AJBW, adjusted body weight; CL, clearance in litres per hour; CrCl, creatinine clearance in millilitres per minute; IBW, ideal body weight AJBW = IBW + 0.4%(TBW-IBW)]; MIC, minimum inhibitory concentration; PTA, probability of target attainment; SD, standard deviation; TBW, total body weight; TVCL, typical value of cefazolin clearance; TVVc, typical value of cefazolin central volume of distribution; WT, weight in kilograms.

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