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GENERAL ORTHOPAEDICS

Systemic antibiotic prophylaxis in arthroplasty – a narrative review of how many doses are optimal

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- Systemic antibiotic prophylaxis (SAP) is well-established in arthroplasty to prevent periprosthetic joint infection. However, the optimal duration and dosing of SAP remain a matter of debate, as evidenced by ongoing discordance between recommendations and clinical practice, reflected in the heterogeneity and imprecision of national and societal guidelines.
- The evidence currently available regarding the duration of SAP is summarised and discussed, specifically the postoperative repeated administration of antimicrobials within the first 24 h.
- The evidence available suffers from limitations, specifically deficiencies in outcome assessments in the available randomised controlled trials. Observational studies suggest that a short postoperative prolongation (<24 h) of SAP in arthroplasty may result in superior long-term outcomes compared to a single dose, and that an optimal dosing strategy, which warrants further prospective evaluation, may involve 'stacked dosing' in the early postoperative period, with re-administration every two half-lives when using commonly recommended beta-lactam antibiotics, instead of repetition at usual dosing intervals over 24 h. A stacked approach would also cover recognised indications for repetition, such as major blood loss and increased duration of operation, potentially simplifying prescribing protocols.
- Pharmacokinetic simulations are provided to illustrate the distinct concentration–time profiles associated with different prophylaxis regimens.
- Prolonging SAP beyond 24 h is not recommended.
- This review concludes by providing recommendations for further research, particularly a call to document SAP regimens with sufficient detail (choice of drug, dose regimen, and duration of administration) into established national arthroplasty registries, which should rapidly enable a significantly more nuanced understanding of these critical issues than permitted by the current literature.

Keywords: antibiotics; arthroplasty; postoperative; prolonged; prophylaxis; repeated dosing

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Introduction

The efficacy of systemic antibiotic prophylaxis (SAP) to prevent surgical site infection (SSI) in arthroplasty, and its effect on the occurrence of periprosthetic joint infection (PJI), was first clearly demonstrated in a multicentre study from the United Kingdom and Sweden published in 1984 (1). Subsequently, the benefits of SAP have become well-established in this type of surgery, as documented in various systematic reviews with meta-analyses (2, 3, 4, 5, 6). SAP has demonstrated a relative risk reduction (RRR) by approximately a factor of 5 and a number needed to treat of 13 compared to no antibiotic administration, making it one of the most efficient measures to prevent SSI, respectively PJI, in arthroplasty (2).

However, the optimal duration and dosing of SAP in arthroplasty remain a matter of debate (3, 5, 7, 8). As previous systematic reviews and meta-analyses were unable to demonstrate a benefit for postoperative prolongation of SAP (3, 5, 9, 10, 11), current guidelines recommend the administration of a single dose only (6, 12). Nonetheless, it remains common practice in many countries to extend SAP postoperatively after arthroplasty (3, 5, 7, 8, 9, 13, 14, 15, 16, 17). In particular, the Norwegian guidelines recommend a short postoperative extension of SAP (16, 18), based on data from the Norwegian arthroplasty registry (19, 20). In contrast, other guidelines explicitly prioritize explicitly reducing antibiotic use in line with general principles of antimicrobial stewardship (21).

The aim of this review was, therefore, to provide a detailed analysis of the evidence available regarding single-dose vs postoperatively prolonged SAP regimens. Particularly, the review also encompasses observational studies, as the randomised trials available suffer from important limitations, in our opinion. Furthermore, an analysis of antimicrobial pharmacokinetic–pharmacodynamic (PK–PD) factors relevant to surgical prophylactic dosing regimens is provided to better understand the potential efficacy of different SAP regimens, respectively, as well as the limitations of previous studies, and to prioritise SAP regimens for prospective evaluation. We conclude by presenting suggestions for further research that may resolve the ongoing uncertainty around postoperative prolongation of antimicrobials.

Methods

We have conducted a narrative review of the published evidence on the duration of SAP in arthroplasty. First, relevant publications are summarised and critically reviewed. The identification of the literature involved cross-referencing existing guidelines and reviews, along with a comprehensive literature search in PubMed and Google Scholar, using the keywords ‘arthroplasty’ and ‘antibiotic prophylaxis’. We then present evidence related to antimicrobial PK–PD relevant to arthroplasty prophylaxis. Pharmacokinetic simulations using literature-derived typical parameter values were conducted using Simulx 2023R1 (Lixoft, Antony, France) in order to illustrate the PK–PD implications of different dosing regimens. Graphical illustrations were created using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) within RStudio 2023.06.2.

Evidence from non-randomised studies

Observations from the Norwegian arthroplasty registry (19) provide key information regarding the duration of SAP, as it is the only source combining data about the choice of SAP and long-term outcomes in total hip arthroplasty (THA). While no significant difference was identified depending on the SAP regimen regarding revision for PJI among the 22 170 THA included, a major difference was observed in the long-term revision risk for all causes, particularly for aseptic loosening (Fig. 1). Administration of four doses of beta-lactam antibiotics within the first 24 h was associated with a RRR of 3.5 times (95% CI: 2.1–5.8, $P < 0.001$) at 10 years for revision for all causes compared to a single-shot SAP, after adjusting for potential confounders such as age, gender, duration of operation, type of ventilation in the operating room, type of prosthesis fixation, cement type, and addition of antibiotics within the cement. Based on these findings, the Norwegian guidelines recommend the administration of four doses of a first-generation cephalosporin as SAP in arthroplasty (16, 18).

Notably, the relative magnitude of the effect of repeated administration over 24 h was similar to the benefit of administration of any SAP compared to no prophylaxis at all (1, 2). Even if such a high RRR represents a strong argument (22) in favour of a postoperative prolongation of SAP, this aspect should be examined in greater detail. As only 46 revisions for PJI were reported (19), the power of any subgroup analysis is greatly limited when solely this reason for revision is analysed. A well-known limitation of arthroplasty registries is the registration of the reason leading to revision. Typically, the case report form is filled out at the end of the operation, whereas the final diagnosis may not be available until later. This is particularly true for PJI, as results of microbiological cultures are available only several days later (23, 24, 25, 26). For this reason, the International Prosthesis Benchmarking Working Group recommends analysing the global revision rate rather than focussing solely on a single reason for revision, as many diagnoses overlap or may not have been appropriately recognised (27). These arguments, however, increase the weight of the findings regarding all-cause revision rates. In the Norwegian arthroplasty registry, the 10-year revision rate for all reasons was 2.3% in the subgroup receiving four doses of SAP within the first day, compared to 8.8% in the single-shot group (Fig. 1) (19). For aseptic loosening, the 10-year revision rates were 1.5% vs 5.9%. At 15 years of

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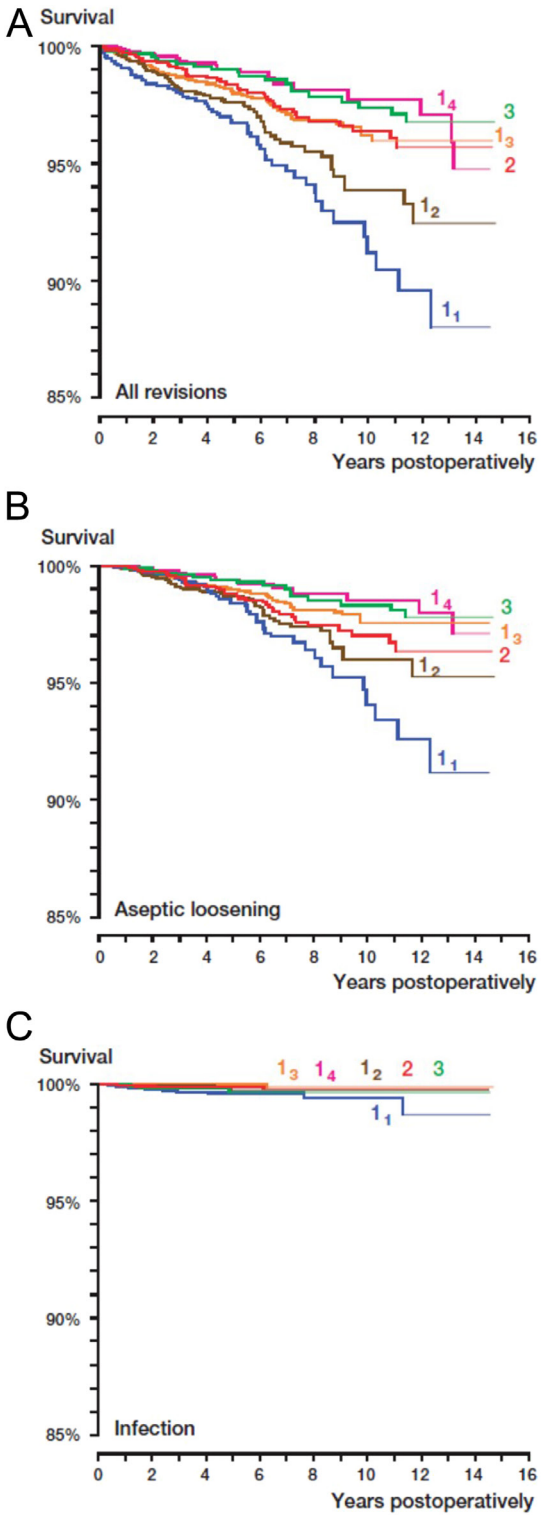

Figure 1

Cox-risk-adjusted Kaplan–Meier survival curves from the Norwegian arthroplasty registry of cemented THA implanted from 1987 to 2001, for any revision (A), for revision due to aseptic loosening (B), and for revision for PJI (C) as endpoints (reproduced from reference (19)). Age, gender, duration of operation, ventilation type of the operating room, risk factors related to cement type and component type, as well as the administration of SAP and antibiotics in the cement, were included in the risk adjustment. Data presentation was broken down into the various groups of SAP. The main number indicates the duration of SAP in days, whereas the number in subscript indicates the number of doses administered within the first 24 h postoperatively.

follow-up, as may be extracted from the Kaplan–Meier analysis, the rates were 4.2% vs 11.9% for all-cause revision and 2.9% vs 8.8% for aseptic loosening (Fig. 1) (19). Despite no significant effect on the revision rate for PJI, the effect on global revision rates and revision rates for aseptic loosening was substantial. It cannot be argued that the revision rates in the best subgroup are simply low for historical reasons, as a 10-year overall revision rate of 2.2% corresponds to the best results currently observed in the Australian arthroplasty registry, also for THA with cemented stems (28).

As results from 1987 to 2001 are reported, major changes in diagnostic microbiological practices implemented since then must be considered (19, 29). At that time, microorganisms with low virulence were not recognised as being pathogenic (30). These microorganisms could not even be consistently identified, as necessary optimisations of microbiologic culture methods were established only at a later time (23, 25, 26, 31, 32, 33). In particular, systematic collection at revision of microbiologic samples in sufficient numbers and with the necessary quality later became the standard of care, including the replacement of swabs with tissue biopsies (34, 35, 36, 37). The reported revision rate over time in the group receiving a single-shot SAP was also surprisingly high for THA with cemented stems, particularly in the short-term follow-up, in comparison to observations from other national arthroplasty registries and despite considerations of improvements in revision rates in THA over time (28, 38). The reported revision rate for PJI of only 0.3% (46 PJI among 14 465 THA in the group with SAP) (19) is also very low compared to the rate of 1% observed in THA in studies matching data from contemporary registries (39, 40, 41). Thus, it can be speculated that many of the so-called aseptic revisions described had been unrecognised PJI of low virulence, thus providing a potential causal explanation for the influence of the various regimes of SAP (Fig. 1) (19). Improved awareness and diagnostics may well explain the increasing PJI rates observed in the Norwegian arthroplasty registry between 1987 and 2007 (42).

Two large studies from other arthroplasty registries also addressed the question of the duration of SAP (15, 43). Although both studies failed to identify any effect regarding the repetition of SAP, both considered only revisions for PJI, as opposed to revisions for all causes, and limited follow-up to 12 months only. Thus, as argued above, these studies may have been incapable of detecting any potential effect of SAP duration, due to

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inadequate outcome measurement. The first of these studies, a retrospective single-centre study of a mixed population of 20 682 THA and total knee arthroplasty (TKA), examined the PJI rate at 12 months follow-up and reported a non-significant odds ratio of 0.755 (95% CI: 0.489–1.166, $P = 0.205$) of single-dose vs 24 h of cefazolin or vancomycin in a multivariable analysis (43). Patients in the single-dose group were those who were discharged on the day of the operation, whereas the standard of care was repeated administration of SAP for 24 h. This potentially induces a bias, with healthier patients being in the outpatient group. Notably, the subgroup with postoperatively prolonged SAP had significantly more patients with obesity, more comorbidities, and a more frequent administration of vancomycin as SAP. Vancomycin is associated with a higher SSI rate than beta-lactam antibiotics (44). Furthermore, the study combined THA and TKA, despite the latter having up to twice the revision rates for PJI as THA (39, 40, 41). Together, these issues raise the possibility of incomplete adjustment for potential confounders, which may have led to a biased estimate of the treatment effect. The second study, from the Dutch arthroplasty registry, investigated the rate of complete component exchanges for PJI at 12 months follow-up in a mixed population of 242 179 THA and TKA (15). Group attribution was determined by the standard of care in the treating hospital, as the Dutch arthroplasty registry does not register SAP at the patient level. While the publication concludes that there is no effect, analysing THA and TKA separately, it may be noted that an adjusted hazard ratio of 2.21 (1.12–4.38) was found for cefazolin single dose vs multiple dose in THA, although this effect was not identified for cefuroxime nor in TKA. Finally, a substantial proportion of revisions for PJI are likely to have been missed in this study, as only complete component exchanges were considered, whereas prosthesis-retaining treatments would be indicated most frequently in early postoperative PJI (45, 46, 47). Arguing in favour of such a bias would be the very low rate of revision for PJI reported, of only 0.3% (399 of 130 712 THA and 303 of 111 467 TKA) (15).

Methodological arguments

Randomised controlled trials (RCTs) have been placed at the top of the hierarchy of evidence – commonly visualised as the 'pyramid of evidence' – as this study design permits a direct and (statistically) unbiased estimate of the treatment effect in the population from which the individuals in a study are recruited. Conversely, due to the risk of confounding in non-randomised designs, observational studies have been relegated to the lower tiers (48, 49). However, as many authors have pointed out, simply ranking study designs in this uniaxial manner, while ignoring the specific strengths and weaknesses of relevant studies along other axes of evidence (for example generalisability, methods of outcome assessment), may be misleading (49). Conversely, causality may well be strongly suggested by observational studies if the totality of the evidence supports this conclusion, particularly in the setting of large relative risks persisting after confounder adjustment (22, 50). A classic example would be the relation between smoking and lung cancer, with causality being accepted based on a chain of arguments and sufficient relative risk, without the requirement for proof by RCT (51). The exact relative risk sufficiently strong to dominate theoretical concerns around residual confounding risk is a matter of debate, but values of 5–10 have been suggested. Even if not that solid from a statistical point of view, a relative risk of 2 may already be enough to have causality being accepted in a lawsuit (52). Rare events occurring at a late interval following an exposure/intervention of interest may be better investigated by observational designs, such as register-based cohort or case–control studies (53). PJI is a rare event, affecting approximately 1% of THA and up to 2% of TKA (39, 40, 41). The additional difficulties in diagnosing PJI have already been discussed above, leading to an underestimation in any study. Diagnosis of PJI can be delayed, occurring more than 1 year postoperatively, and made only following revision (39, 40, 41, 54). Thus considering the overall revision rate in arthroplasty registry studies is recommended as a better option than focussing on single reasons for revision (27). Many years of follow-up are required, a timeframe realistically recorded only in national registries, particularly as revision may happen in other institutions than primary care. Therefore, considering only randomised trials is a major shortcoming that affects the systematic reviews performed to date (2, 3, 4, 5, 6, 9). Indeed, few would support the position that SAP should not be administered at all in arthroplasties performed on joints other than the hip, simply on the basis that there is no RCT evidence of a benefit over placebo available for other joints (4). To withhold postoperatively prolonged SAP based solely on the fact that no RCT, nor any meta-analysis limited to RCTs, has proven an advantage over single-dose SAP is similarly flawed.

A recently published study comparing repeated SAP with single-shot SAP combined with topical vancomycin (55) illustrates well the limitations of the randomised trials available. With only 165 cases included, the study was underpowered to investigate a complication affecting roughly 1% (39, 40, 41). Results numerically favoured repeated SAP, with 0 of 85 (0%) vs 3 of 80 (3.8%) PJI, despite topical vancomycin having a probable effect in preventing PJI in both hip and knee primary as well as revision arthroplasty, as shown by various recent systematic reviews with meta-analyses of the literature (56, 57, 58, 59). This led to prematurely stopping the trial after an intermediate analysis, but proceeding thus may have induced another methodological (type 2) error (60). The rather high PJI rate in the group of single-shot SAP with topical vancomycin also indicates some other, hidden perioperative issues (39, 40, 41). Some RCTs are planned or ongoing to compare single

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shot with prolonged SAP (ClinicalTrials.gov Identifier NCT03283878 and NCT04297592). However, we are concerned that these studies may fail to identify a difference between the regimens due to the relatively short follow-up periods. The planned duration of follow-up may be insufficient to identify implant loosening caused by low-virulence organisms that may take many years to manifest.

Pharmacokinetic–pharmacodynamic considerations

Knowledge of the PK–PD factors influencing SAP efficacy is critical to a rational evaluation of the literature and to evaluate generalisability. First- or second-generation cephalosporins (e.g. cefalotin, cefazolin, and cefuroxime), along with anti-staphylococcal penicillins (e.g. cloxacillin), are usually recommended for SAP in arthroplasty due to their antibacterial spectrum and low risk of toxicity (3, 6, 7, 8, 12, 14, 16, 61, 62, 63). The PK–PD index best-describing beta-lactam efficacy is the time of exposure of the free (unbound) drug above the minimal inhibitory concentration of the target microorganism (fT>MIC) (63, 64, 65, 66, 67, 68, 69, 70, 71). Classical observations performed in historical (neutropenic) animal models initially established a PK–PD target of 40–50% fT>MIC (63, 64, 65, 66, 67, 68, 69, 70, 71). Conversely, more recent publications argue for optimal bacterial killing at concentrations maintained permanently above 4–6 × MIC (63, 69, 72). Some national intensive care guidelines have been adapted accordingly (73). As only some hundreds of bacteria are sufficient to cause implant-related infections (74, 75), high PK–PD targets may well be preferred (on a risk-benefit basis) in arthroplasty SAP, particularly during the early postoperative period (first few hours), even if no strong clinical evidence is available. Thus, it is useful to explore the potential implications, with respect to PK–PD target attainment, of different dosing regimens. For the purposes of illustrating cephalosporin and penicillin dosing regimens in arthroplasty, a simple one-compartment model describing plasma concentrations is a useful starting point and physiologically justified, as diffusion of these highly hydrophilic drugs into the extracellular space is fast and broadly reflected by serum concentration (71, 76, 77, 78). Note that historical studies describing concentrations in homogenised bone (i.e. containing all components of bone tissue) are misleading (79), as bacteria do not invade osteoid but remain in the extracellular space (disregarding intracellular persisters relevant in established infection), even if invading bone canaliculi (80, 81).

Using PK parameters derived from the literature (Table 1), various typical serum concentration–time profiles were simulated for an 80 kg individual with normal renal function for cloxacillin, cefalotin, cefazolin, and cefuroxime (Fig. 3). As the simulations consider total (bound + unbound) drug, and because only the unbound fraction is microbiologically active (65, 82), the target concentration has been adjusted according to typical protein binding (PB) according to

$$\text{target concentration}\left[\text{mg}/\text{L}\right] = \text{MIC}_{\text{ECOFF}} / \left(1 - \left(\text{PB}\left[\%\right]/100\right)\right)$$

where $\text{MIC}_{\text{ECOFF}}$ corresponds to the epidemiological cut-off MIC for *Staphylococcus aureus* (87). These simulations illustrate the potential implications of different dosing regimens: (i) single-dose SAP, (ii) multi-dose SAP at standard dosing intervals, and (iii) stacked multi-dose SAP, where the antimicrobial is re-dosed at every two (typical) half-lives of the drug for a total of four doses, as recommended in the Norwegian guidelines (16, 18). Considering the very high susceptibility of implants to infection (74, 75), a more aggressive PK–PD target of 5 × MIC is investigated, in addition to the classical 1 × MIC threshold. Finally, the serum elimination half-life must be considered in any analysis of dosing regimens, as PK–PD target attainment differs greatly for drugs with a very short half-life (e.g. cloxacillin, approximately 22–36 min) vs those with modestly longer

Table 1 Summary of the pharmacokinetic parameters of the antibiotic drugs most commonly recommended for SAP in arthroplasty. Values are indicated for healthy adults. Values may differ in the case of obesity and disease, as well and particularly in the case of severe renal failure. The majority of candidates for arthroplasty are, however, to be considered healthy enough for these values to be transposed in this patient population for illustrative purposes. Sources of the pharmacokinetic parameters are indicated.

Drug	References	AVD, L/kg	Protein binding, %	EH-L, min	Clearance, L/h	MIC*, mg/L	PBA MIC, mg/L
Cloxacillin	72, 78, 87, 88, 89, 90, 91, 92, 93	0.10	94	22–36	9.2	0.5	8.3
Cefalotin	94, 95, 96, 97, 98	0.07–0.20	65–80	30–54	11.1	1	4.0
Cefazolin	83, 94, 96, 97, 99, 100, 101, 102	0.10–0.15	80–90	84–120	4.6	2	13.3
Cefuroxime	77, 94, 103	0.17–0.20	20–50	80	8.3	4	5.0
Ceftriaxone	84, 85, 97	0.08–0.25	67–96	348–870	0.96	8	200
Clindamycin	86, 104, 105, 106	0.79	62–94	120–180	16.2	0.25	1.67

*MIC for *S. aureus* from reference 83.
AVD, apparent volume of distribution; EH-L, estimated half-life; MIC, minimum inhibitory concentration; PBA, protein binding adjusted.

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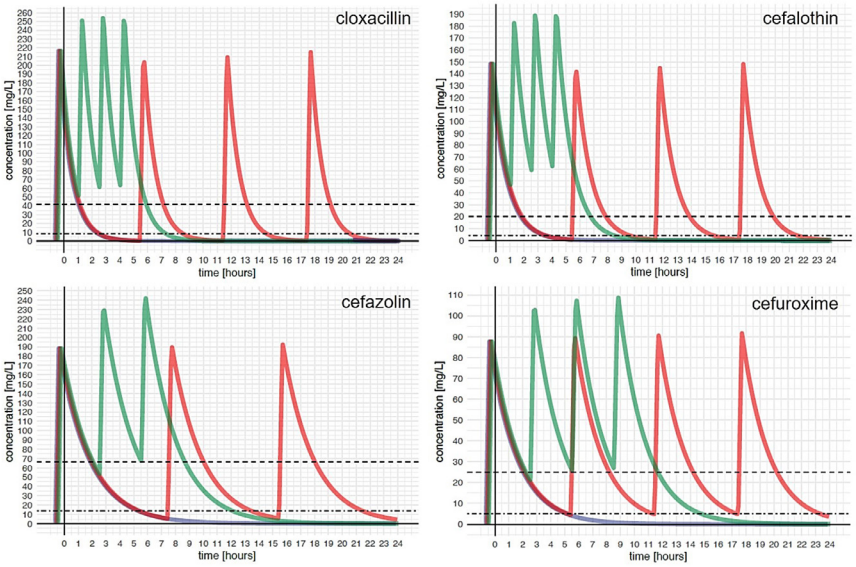

Figure 2

Pharmacokinetic simulations of antibiotic drugs typically administered for SAP in arthroplasty. A one-compartment model was used, with the pharmacokinetic parameters derived from the literature (Table 1), applied for a healthy 80 kg individual. The lower dashed line corresponds to a target concentration of 1× MIC, whereas the upper dashed line corresponds to 5× MIC. The blue curve corresponds to a single dose. The red curve corresponds to regular intermittent administration for antibiotic treatment. Please note that the usual administration of cefuroxime would be every 8 h, as for cefazolin, but may be increased to every 6 h, as illustrated. The green curve corresponds to stacked administration, one dose every two half-lives of the drug. Stacked administration provides the best coverage during the period of interest, particularly for drugs with a very short half-life, such as cefalotin or cloxacillin, and also offers the shortest exposure to antibiotics.

half-lives (e.g. cefazolin, approximately 84–120 min). Any analysis lumping together these regimens risks obscuring important differences related to the duration of effective antimicrobial concentrations.

If drugs with such short elimination half-lives are applied more than 60 min before incision, half or more of the drug already has been eliminated before surgery starts. Consequently, increased infection rates are observed in the case of administration >60–120 min before incision (17, 44). Contrary to common belief, infection rates may not increase significantly if the SAP is administered within 60 min after incision (17, 44). Nevertheless, SAP does not lose its positive effect even if applied with a delay, with the application of a tourniquet, of course, creating an exception (76). The administration of additional doses at short intervals during the procedure and in the hours that follow ensures optimal concentrations without drops below desired thresholds (Fig. 2). Considering that biofilm requires approximately 1 day to start forming (108, 109), it should not be surprising that a favourable effect of SAP may be observed during the early postoperative phase, when microorganisms are still in planktonic form, highlighting the need for targeting high antibiotic concentrations during this critical period. Systematically repeated administration has the advantage of overcoming the loss of efficacy in case of increased delay until incision and would be more robust to specific situations potentially compromising effective antimicrobial concentrations during the critical period, such as longer operation times or greater blood loss, where repeated dosing usually is recommended anyway. As cefazolin and cefuroxime have a relatively longer half-life, the same number of doses may not be necessary to cover the same duration as for cefalotin and cloxacillin. Some authors mention the apparent volume of distribution (AVD) as a pharmacokinetic parameter to be considered, specifically to justify dose increases in the case of obesity (7, 68, 83, 110). However, it is crucial to understand that increasing the dose of these antibiotics primarily influences peak concentration (Cmax). For antibiotics used in orthopaedic prophylaxis, Cmax, however, is not decisive for the bactericidal effect, as they belong to the class of beta-lactams, with a time-dependent effect (64, 65, 66, 67, 68, 71). A more efficient strategy for maintaining time above an effective concentration is to administer further doses, rather than increasing the dose. Toxicity associated with beta-lactams should not be an issue, particularly with short administration, even in the case of stacked administration (63, 73, 84).

Finally, yet importantly, the only RCT available regarding SAP in the internal fixation of closed fractures is worthwhile to be mentioned (111). This study proved a substantial reduction in SSI for SAP with ceftriaxone (5 of 1105 cases) compared to placebo (41 of 1090 cases). While this publication is a milestone for SAP in internal fracture fixation, it often is discarded arbitrarily in discussions about SAP in arthroplasty. However, the pathomechanisms of infection and the spectrum of microorganisms are similar between fracture fixation devices and joint replacements (112, 113). Particularly interesting is the fact that ceftriaxone is an antibiotic drug with a long half-life usually requiring administration only once a day (84). These results may well be explainable by the long half-life of ceftriaxone, which ensures adequate postoperative exposure, in contrast to first and second-generation cephalosporins (114, 115, 116). This RCT, in fact, studied SAP effective for more than 24 h. A single dose of a drug with a

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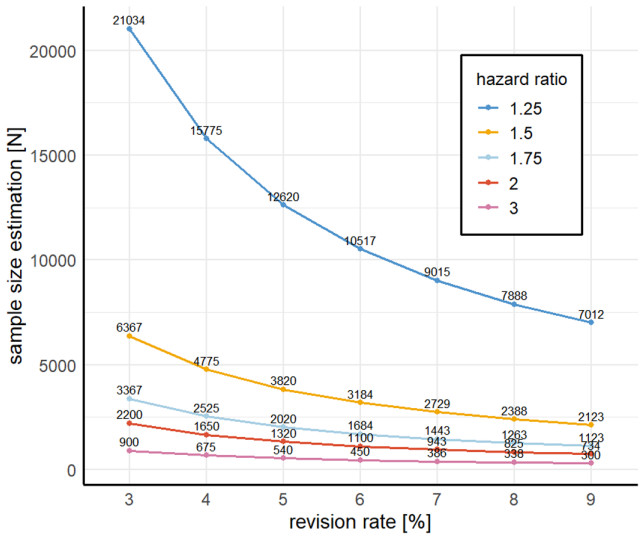

Figure 3

Graphical illustration of a power analysis, considering an alpha-error of 0.05 and a beta-error of 0.2 (power 0.8), as well as considering only half of the revisions (aseptic loosening and PJI) to be possibly influenced by modifications of the SAP. Considering a 10-year revision rate of 6%, commonly identified in national arthroplasty registries, only 5000 THA would be necessary in each group to identify a difference as small as 25% in the revision rate. The sample size needed corresponds to half the number of THA performed each year in a small country such as Switzerland. The sample size would increase the more risk factors have to be considered. Nevertheless, established national arthroplasty registries would be able to provide relevant case numbers within a rather small number of years if SAP would be incorporated among the collected parameters.

short half-life may not be considered equivalent from a pharmacokinetic point of view. Due to elevated protein binding, ceftriaxone is sometimes not considered a drug of choice for the treatment of staphylococcal infections, despite the fact that the activity of beta-lactams correlates to the concentration of the unbound drug (65, 84, 85, 117, 118, 119). Accordingly, cefalotin also has a high protein binding, and may thus be affected similarly, despite its recognised adequacy for SAP, supporting the notion that pharmacokinetic-pharmacodynamic assessments are required both *in vitro* and *in vivo* to appropriately predict SAP efficacy (16, 18, 120).

Alternatives to beta-lactams

In cases of allergy to beta-lactam antibiotics or in cases of high prevalence of methicillin resistance, alternatives such as clindamycin and vancomycin are mainly recommended (7, 8, 86, 121, 122, 123). From a PK point of view, their longer half-life would allow a less stringent timeframe for administration. However, from a PD viewpoint, they may be less advantageous due to less rapid bacterial killing (124). Indeed, some studies associated clindamycin and vancomycin with an increased PJI risk (3, 44, 61, 62). In the case of vancomycin, the combination of (i) limited safe rate of administration (125, 126, 127), (ii) delayed and incomplete distribution into third compartments such as bone (119, 127, 128), and (iii) inherently reduced bactericidal activity against staphylococci (124, 129, 130, 131) renders it a poor option compared to beta-lactams in settings where these first-line options can be safely and effectively deployed. Regarding clindamycin, there is, to the best of our knowledge, very limited literature available. An increased risk for PJI in cases of allergy to beta-lactam antibiotics may be largely explained by the use of second-line antibiotics (132, 133). This issue, however, complicates any analysis. While the Norwegian arthroplasty registry reported no increased risk for revision for PJI after primary TKA for clindamycin in a recent publication, the Swedish knee arthroplasty registry had observed some years earlier an RR of 1.5 (95% CI: 1.2–2.0; $P = 0.001$) (61, 134). The increased risk may potentially be explained by resistance to clindamycin and particularly by C. acnes infections, as observed in an American shoulder arthroplasty registry study (135).

Systemic antibiotic prophylaxis beyond 24 h

Although two systematic reviews in cardiac surgery indicate an advantage for prolonging SAP up to 48 h postoperatively to decrease the risk of SSI compared to shorter regimes (136, 137), a phenomenon not detected by any individual study, there is no evidence supporting this in arthroplasty. As discussed above, the study from the Norwegian arthroplasty registry did not demonstrate any advantage regarding the risk of revision in THA for SAP prolonged beyond 24 h (19). Moreover, extending the SAP beyond 24 h postoperatively does not provide any reduction in PJI risk in aseptic revision THA and TKA (13, 138). Prolonging SAP beyond 24–48 h drastically increased the incidence of antibiotic-related complications in a large, retrospective study from Veterans Affairs, with a number needed to harm of less than 10 (139). Additionally, administering SAP for 48 h leads to a detectable induction of resistances among the skin flora (140, 141). Even a short course of antibiotics has a major impact on the diversity of the gut microbiome, taking up to 6 months and more to recover, with potentially persistent diversity depletion (142, 143, 144, 145, 146, 147). Disturbance of the gut microbiome is the underlying pathomechanism for the development of antibiotic-associated diarrhoea and the promotion of antimicrobial resistance (144, 146). Certain conditions, such as Alzheimer's disease, even have been linked to alterations in the gut microbiome (148). Thus, limiting the duration of SAP, provided this does not compromise efficacy, should remain a guiding principle.

Financial arguments

Total treatment costs for hip and knee PJI have been estimated to be approximately USD 75 000 to 95 000 in

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the year 2009, representing an increase of more than 25% compared to 2001, and have probably increased further since (149). Cost comparison from one country to another, however, is limited by differences in tariffs and billing systems, and as other studies limited the analysis to the hospitalisation, but costs are always high (150, 151, 152, 153). When considering lifelong costs, the financial burden may also be even higher, as revision for PJI is associated with functional impairment and thus increased long-term socioeconomic costs (154, 155, 156). While the effect of optimised SAP may not be as pronounced as demonstrated in the publication from the Norwegian arthroplasty registry, due to currently lower revision rates (19, 28, 38, 157), the potential benefits of even a minor reduction in PJI rates far outweigh the supplementary costs of implementing short repeated SAP protocols with first- or second-generation cephalosporins (68, 150, 152).

Suggestions for future research

While it would not be wise to establish recommendations based solely on data published 20 years ago from a single source (19), it is worth noting that this publication merely confirmed observations made previously in the Norwegian arthroplasty registry (20). Available national arthroplasty registries could easily expand data acquisition and provide useful results within some years of observation. The 10-year overall revision rate in THA is approximately 6% throughout registries (158). Approximately half of the revisions are due to PJI and aseptic loosening (28, 38, 158). Only this group of diagnoses would potentially be accessible to influence from optimised SAP. A power analysis with a type I error rate of 5% and a type II error rate of 20% reveals that including two groups of only 5000 procedures each would suffice to determine a difference of 25% in the revision risk (Fig. 3). To put this into perspective, this number is equivalent to half the annual THA procedures performed in a smaller country like Switzerland (159). If the effect is larger, and this may be expected from the data of the Norwegian arthroplasty registry (19), fewer patients would be necessary. However, as the reported revision rates were higher than current revision rates observed in other national arthroplasty registries, the effect of prolonged SAP may be less pronounced, and more cases are needed (19, 28, 38, 158, 160). As discussed above, significant advancement in our understanding of SAP regimens would be afforded by this approach, without the need for large randomised trials, as had been advocated by some authors (5). Registries would also allow further risk stratification, considering implants, surgical approach, experience of the surgeon and other known risk factors for revision, while permitting the ongoing evaluation of prophylaxis strategies in the face of evolving antimicrobial resistance patterns.

Conclusion

SAP is a well-established and effective measure in preventing PJI and SSI in arthroplasty. As illustrated and discussed, there is a chain of arguments indicating the Norwegian recommendations, with SAP prolonged postoperatively but stacked over the first hours (16, 18), may well be the best option when using beta-lactam antibiotics and should be evaluated prospectively. This approach would also have the advantage of covering recognised needs for the repetition of SAP, such as major blood loss or longer duration of operation, without requiring specific intervention from the treating team. However, prolonging SAP beyond 24 h is not beneficial and thus not recommended. In our opinion, available RCTs and meta-analysis arguing against postoperative prolongation of SAP suffer from relevant methodological weaknesses or mistakes. To advance our understanding of SAP in arthroplasty, national arthroplasty registries are encouraged to collect data regarding SAP administration, including the necessary granularity regarding timing and dosing. This approach has the potential to provide decisive data within a medium-term observation period, helping to optimise SAP practice.

ICMJE Conflict of Interest Statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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