Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: April 30, 2024

Citation: Friedl S., et al., 2024. Selection of new pathogens during antibiotic treatment or prolonged antibiotic prophylaxis in orthopedic surgery. Medical Research Archives, [online] 12(4). https://doi.org/10.18103/mra.v12i4.5277

DOI: https://doi.org/10.18103/mra.v12i4.5277

ISSN: 2375-1924

REVIEW ARTICLE

Selection of new pathogens during antibiotic treatment or prolonged antibiotic prophylaxis in orthopedic surgery

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ABSTRACT

In orthopedic surgery regarding open or infected wounds, both the current antibiotic therapy as well as the perioperative antibiotic prophylaxis, may select new pathogens leading to iterative debridement and changing the antibiotic regimens targeting more resistant microorganisms.

The risk of finding new and more resistant pathogens is relatively high (5%-15%) and exceeds the incidence of primary surgical site infections (SSI) after elective orthopedic surgery with primary wound closures. Based on a narrative review of the current scientific literature, we summarize mechanisms and associations of such a pathogen selection by therapeutic or prophylactic agents and focus on the importance of an adequate initial debridement and on an effective antibiotic stewardship.

Keywords: antibiotic therapy; antibiotic prophylaxis; osteoarticular infection; selection pressure; new surgical site infections

Introduction

The selection of new pathogens by a current therapeutic antibiotic course, or due to antibiotic prophylaxis, undermines the management of orthopedic infections; including surgical site infections (SSI)[1,2]. Whenever selection occurs, these selected new pathogens are usually more antibiotic-resistant than the primary SSI pathogens after elective surgery[3,4]. Indeed, pathogens selected under current antibiotic therapies might belong to the naturally-resistant non-fermenting, gram-negative rods[3-6], or to the group of (methicillin-resistant) skin commensals[7]. To cite one example, Carrara et al. reported a significantly high prevalence of multidrug-resistant gram-negative rods after an inappropriately prolonged empirical antibiotic regimen in a pooled cohort of 73,595 orthopedic and non-orthopedic patients[8]. Besides the field of SSI, other reasons for resistant pathogen selections could be a prolonged hospital stay in case of nosocomial infections, a nursing home dependency, or the use of urinary catheters[9,10]. In a single center cohort study of 2480 adult and infected orthopedic patients (among them 1153 patients with osteoarticular infections) Wuarin et al. witnessed many pathogens resistant to ongoing antibiotic therapy upon a new surgical debridement for a persistent ulcer or wound problem. Ten percent of all their integrative surgeries revealed new bacterial SSIs with antimicrobial resistance to ongoing antibiotic agents in 7%[11].

The mechanisms for selection of new pathogens in orthopedic surgery are multiple. However, and most frequently, the persistence of an ulcer, postoperative wound dehiscence, or any other problem of a persistent skin breakdown, represents a gateway for an external contamination that the current antibiotic cannot kill or prevent[11]. Similarly, concomitant antibiotic administrations might alter the yield of the diagnosis performances. While a single-dose perioperative prophylaxis might not diminish the number of positive intraoperative microbiological samples[12,13], a prolonged preoperative therapy may alter the results[14,15]. In a cohort of 2612 adult and infected orthopedic patients, Al-Mayahi et al. noticed that prior therapeutic antibiotic exposure was significantly associated with negative culture results (odds ratio (OR) 2.8) and, moreover, the isolation of more antibiotic-resistant, unexpected pathogens (OR 2.8 for non-fermenting rods, and an OR of 3.0 for methicillin-resistant skin commensals)[14]. In this study, also the pre-incisional intravenous application of a single-dose of cefuroxime was equally associated with significantly higher risk of antibiotic-resistant pathogens, in particular more non-fermenting gram-negative rods[15,16] and gram-positive microorganisms[17], including for skin commensals[7,17]. In another Swiss study with 1840 orthopedic procedures, the preoperative antibiotic therapy was significantly associated with non-fermenting infections (124/194 with prior antibiotic use vs. 531/1456 without; $p<0.01$) [14].

These new SSI pathogens indicate a dilemma in terms of clinical decision making[11]. If the general and local evolution is satisfactory, and within the frame of which is expected, the responsible clinicians might interpret them as contamination, and continue with the current antibiotic treatment. But very frequently, the evolution has been unsatisfactory; hence the indication for re-debridement is made. Consequently, these new pathogens are

interpreted as a causative pathogen of persistent inflammation, which leads to a consecutive broadening of the antimicrobial spectrum and to a prolongation of the total antimicrobial therapy[11]. This frequent approach *per se* is not evidence-based (as there are no formal scientific data to underline it) and probably leads to an over-prescription of antimicrobial agents all over the world.

In this narrative review, we summarize the literature regarding the selection of new pathogens under prophylactic and therapeutic antibiotic regimens; and discuss measures to reduce selection risk in orthopedic surgery and traumatology.

Methods

We performed a scientific literature review in English and German language in the PubMed database searching for the following MeSH terms: "bone diseases" AND "bacterial infections", "anti-bacterial agents administration and dosage", "anti-bacterial agents therapeutic use", AND "antibiotic prophylaxis" AND "reoperation".

Concerning the subgroups , MESH terms "joint diseases", "fractures open", "prosthesis related infections" surgical wound infection", "osteomyelitis" AND "complications" AND "therapy" AND "epidemiology" AND "prevention" AND "control" as well as the above mentioned terms.

We included almost all types of studies reporting a detailed use of systemic antibiotic therapies or prophylaxes for orthopedic infections in adult patients. Hence, we included studies and case series in adult patients with more than ten patients and hand-searched their references for additional citations. In contrast, we excluded articles written in different languages than English or German, series with less than ten cases, papers without abstracts or without detailed information regarding antibiotic use. We equally excluded cases using week-long acting antibiotic agents such as dalbavancin or oritavancin[18], or with the use of topical[19], intraosseous[20], and spacer-(cement)-related antibiotics solely. As we expected a very high heterogeneity of the retrieved articles concerning results, study population, microbiology and methodology, we renounced on statistical analyses and displayed the key findings in Tables 1-3. Table 1 links the preoperative antibiotic therapies, or prophylaxes, to the results of intraoperative samples in the orthopedic literature. Table 2 specifically focuses on prosthetic joint infections (PJI) and Table 3 resumes the epidemiology of selection in open fractures and trauma-related infections.

At database closure on 31 July 2023, we had retrieved 2590 articles. Of them, we excluded 2562 for lack of detailed information and finally display 28 in the Tables.

Results

Selection under prophylactic antibiotic use

According to our review, the selection of (antibiotic-resistant) pathogens might theoretically also occur with a single-dose prophylaxis in elective surgery and immediate wound closure. Arguments in favor are the high proportion of cephalosporin-resistant (or methicillin-resistant) skin commensals in adult orthopedic surgery, when all other preventive measures correspond to the state-of-the-art. Usually, at least 20%-30% of all orthopedic SSI

pathogens are resistant to the prophylaxis correctly administered during the index surgery[21,22]. Unsurprisingly, in many tertiary centers, today the incidence of SSI with methicillin-resistant coagulase-negative staphylococci is higher[22] than with methicillin-susceptible, or methicillin-resistant, S. aureus[23]. Data published in the United States National Nosocomial Infections Surveillance System report stated up to 65% of coagulase-negative staphylococci have become resistant to methicillin during the past two decades[24]. The high proportion of methicillin-resistant primary SSI bears the possibility of selection during the effects of an antibiotic prophylaxis based on beta-lactam agents such as second-generation cephalosporins[2]. At least, this possibility cannot be ruled out. A formal testing of this hypothesis is lacking in orthopedic surgery. In other medical disciplines, the (transient) selecting effect of a single dose of an antibiotic agent has been investigated. For example, Khalil et al.detected isolated colonies of penicillin-V- and amoxicillin-resistant viridans streptococci before antibiotic administration in twenty one percent of healthy controls and noticed an increased streptococcal fraction with reduced susceptibility to amoxicillin after short time substance exposition, even without further selective factors present[25].

Importantly, we ignore which proportion of the SSI pathogens after a routine perioperative prophylaxis are true selections and which are not (i.e. that are resistant to the prior prophylaxis by chance). Methodologically speaking, we would need a prospective trial randomizing between a cephalosporin-prophylaxis and a placebo, and compare the antimicrobial susceptibilities of eventual SSI microorganisms in both arms. Such a clinical trial cannot take place because of major ethical concerns. To circumvent this, there has been attempts to broad the perioperative prophylaxis. However, almost all of them failed to reveal a superiority compared to the classical recommended prophylaxes. To give a usual example, the routine vancomycin-prophylaxis (which practically is the universal gram-positive coverage) regularly fails to show any benefit, when research groups investigate all patients[26]. To our knowledge, all international guidelines advocate against broad-spectrum prophylaxes for routine surgical procedures.

Selection under therapeutic antibiotic use

Therapeutic regimens may select new SSIs, especially when the (surgical) wounds remain open (absence of primary wound closure; open fractures[27,28] or during surgical re-interventions, e.g. second looks, iterative debridement, postoperative wound dehiscence[29] (Table 1). The Wuarin study[11] assessed the impact of interactive debridement on the occurrence of new, secondary SSIs during antibiotic administration and found a global risk of approximatively 10%[11], with an antibiotic resistance to ongoing agents in 7%. The median delay between two surgical interventions was 16 days. In the entire study population, 1617 infection episodes (65%) were debrided once, compared to 705 cases with multiple debridement (35%); of which 510 a second time and 195 a third time. The pathogens of these new SSIs were distributed among the entire gram-positive and -negative spectra[11]. The authors failed identifying a specific microbiological pattern to tailor a specific prophylaxis regimen, but were almost unanimous regarding the therapeutic consequences of their findings. The responsible

clinicians very often broadened the antimicrobial spectrum to cover concomitantly the new and old pathogens believed to be causative of the actual infection; and they equally prolonged the therapy[11]. In literature, we see this sort of adaptation to new findings also in the hallmark of orthopedic surgeries, regarding prosthetic joints and their infections (PJI) (Table 2). Many clinicians confirm that the pathogens during the re-implantation are, in the majority of cases different from the index pathogens, and likely to be resistant to the therapeutic agents that have been administered during several weeks in the interval between the removal and the re-implantation of prosthesis. Even if the infection recurs in terms of timing and anatomical localization, these so-called "persistent or recurrent PJI" after a two-stage exchange, frequently are new infections or selections[35,42,43] in micro-biological terms. Many solid data underline the link between a systemic antibiotic pre-treatment and the occurrence of multi-resistant PJIs, especially after second stage during a two-stage exchange[35,36,42]. In terms of epidemiological consequences on a larger scale, Benito et al. noticed an increasing proportion of PJI caused by gram-negative bacilli, while the proportion of multidrug-resistant bacteria rose to 15.8%[36].

Alteration of pathogens because of antibiotic treatment prior to surgery

Unfortunately, the proportion of orthopedic infections, admitted to hospital with empirical systemic antibiotic treatment remain substantial, despite decade-long efforts to withhold antibiotics until the intraoperative samples. In Geneva, Switzerland, the proportion of adult orthopedic patients admitted with empirical antibiotic treatment was as high as 43%[14]. Importantly, the majority of the patients was perfectly stable and could have afforded the delay of antibiotic administration until the first surgery. Among 3840 osteoarticular infections, Levy et al reported that 9% were culture-negative cases, of which one-third were related to unnecessary prior antibiotic exposure[44]. In another series of PJIs, the overall incidence of culture-negative cases was 7%, half of which were patients who had received a prior course of antimicrobial therapy[12].

Open fractures

In the orthopedic field, the two hallmarks for pathogen selection are open fractures[27,28] (Table 3) and surgery in infected diabetic foot ulcers[19]. While the microbiologic spectrum of SSI in elective patient cohorts is reported to be resistant to the prior prophylaxis in 20%-30%, in open fractures, these numbers may exceed 50%[27]. The corresponding surgeries are accompanied by a high proportion of (multi-resistant) gram-negative pathogens. Dunkel et al. documented in a retrospective study of 1492 open fractures that in 71% of all pathogens of clinical infections (mostly Enterobacteriacae and Pseudomonas spp.) were intrinsically resistant to the empirical antibiotic regimen used. Among them were 44% Gustilo and Anderson grade I, 24,8% Gustilo and Anderson grade II and 20.8% grade III fractures, while 10% were non-classifiable[27]. The median duration of prophylaxis was three days and the median number of surgical interventions was two. Grade III fractures and vascular injuries with secondary skin breakdown were significantly associated with SSIs caused by resistant pathogens, whereas the duration or the choice of the prophylaxis did not alter the overall fate of developing an infection[27].

Additionally, a broader-spectrum prophylaxis failed to reduce the overall SSI risk, or at least the proportion of multi-resistant SSI's. In a study of 134 patients with Anderson Grade III fractures, Patanwala et al. noted no benefit of a broad gram-negative antibiotic coverage[52]. Also, Redfern et al. found no difference in grade-III fractures undergoing a prophylaxis with either cefazolin plus gentamicin (32%) versus piperacillin/tazobactam (31%) alone[53]. Moreover, exceeding the perioperative prophylaxis beyond 72 hours after surgery in 500 patients with long-bone open fractures was even associated with an increased rate of (multi-resistant) SSI (odds ratio 1.11 [95% confidence interval, 1.04-1.19][54]. In line with these results, Velmahose et al. identified in 117 trauma patients in whom a prolonged prophylaxis was an independent risk for bacterial resistance among future SSI microorganisms[47]. Several other studies equally failed to prove better outcomes in patients treated with broad-spectrum prophylaxis[52,53,55], while noticing increasing numbers of resistant bacterial strains throughout their healthcare facilities.

Special condition – orthopedic tumor surgery

The SSI incidence in orthopedic tumor surgery in adults is recognized higher than in non-oncologic orthopedic surgery[56]. Importantly, their causative microorganisms and antibiotic susceptibilities are also different from the non-oncologic cases[57]. The incidence of orthopedic oncologic SSI is reported considerably higher (i.e., 4% to 38%[56,58]) compared to SSI rates in non-oncologic orthopedic surgery (i.e., 0.1% to 4%[2,56]). Postoperative wound complications in orthopedic tumor surgery are equally high, ranging from 16% to 56%[59,60]. The reasons for these higher SSI incidences are considered to be multi-factorial: extensive soft tissue dissections and large remaining cavities, long operating times, mega-implants, radiotherapy, immune-suppression with oncologic treatments and iterative surgeries (e.g., plastic coverage of large defects[56]). Additionally, the irradiated skin might enhance the SSI risk[56,59].

Orthopedic tumor patients usually lack a long history of therapeutic antibiotic exposure. It is rather the external and internal skin alteration, that predisposes them to more and multi-resistant SSI. However, in oncologic surgery, antibiotic prophylaxis is often prolonged for several days with amoxicillin/clavulan-acid administered orally[56]. The higher proportion of multi-resistant pathogens might be influenced via selection due to prolonged prophylaxis after surgery in a delicate operative terrain. In our review, we renounce on displaying the epidemiological links between the perioperative antibiotic prophylaxis and antibiotic-resistant SSIs after tumor surgery, because of the particular setting and our own publications regarding this specific topic[56,57].

Discussion

Although the majority of clinicians witness similar personal experiences concerning "selection" (new SSI pathogens during iterative debridement for infections or multi-resistant samples that have been taken under the influence of systemic antibiotic therapies), only few articles address the epidemiology of this frequent phenomenon. We estimate the occurrence at a minimum of 5%-15% in the orthopedic field [11, Tables 1-3]. This epidemiology might be different in other surgical disciplines, which we, however, ignore. The selection of new pathogens is not a mere

laboratory issue, but has practical consequences. Only very experienced surgeons might dare to continue with the current antibiotic therapy, when new and resistant wound pathogens are detected. Probably a majority would succumb to switch to new antibiotic regimens broader in spectrum and prolong the total duration of antimicrobial therapy. Both approaches are comprehensible, but work against the global efforts for a better antibiotic stewardship[61].

Of note, it seems not to be the past antibiotic treatment that acts the main promotor of selection[62], but one or a combination of the following: current antibiotic therapy continuing without any antibiotic free-window, prior to surgical debridement and an open wound that was not, or could not be closed during the first intervention. In this setting, the current systemic antibiotics may select new pathogens by killing the susceptible ones, and pass the resistant ones that continuously arrive through the open skin. Often, these new pathogens appear to be more resistant than the prior ones[11].

There are no easy countermeasures to reduce pathogen "selection", but general basic principles could improve the management of SSI. From a surgical perspective, this would be an effort to perform a definitive surgery during the first and only intervention, and to avoid wound dehiscence and cavities[29].

Regarding diagnostics of SSIs, taking intraoperative samples only for control reasons, especially if there is a good clinical evolution during the infection for this reason ought to be scrutinized more frequently. Intraoperative microbiological samples may induce unnecessary changes in antibiotic treatments, ending in subsequent selection of multi-resistant pathogens. Control sampling should be preserved only for cases with a clear indication (i.e., upon wound worsening despite a targeted antibiotic treatment).

We would also strongly advocate in favor of minimal (at least 4 days) "antibiotic-free window" before elective surgery, whenever clinical feasible. In former days, clinical experts used to reclaim a two-week's window prior to intervention, in order not to compromise the diagnostic yield. Today, many clinicians abandoned this practice, because enhanced microbiological techniques very frequently grow pathogens, especially when using technologies such as the PCR[44] or the sonication[63]. But the antibiotic-free window is not only important regarding the diagnostics. It also reduces the pressure for pathogen selection. The proper duration of antibiotic-free window is unknown and might largely depend of the previously antibiotic agents used (and their half-life periods). According to expert opinion two weeks are still recommended. According to our own retrospective analysis with more than 2700 orthopedic infections, an antibiotic-free-window of at least 4 days was not inferior to longer periods up to two weeks in terms of culture negative diagnostics or pathogen selection, especially when using beta-lactam antibiotics[14]. A shorter window of less than 4 days increased the likelihood of negative cultures and the likelihood of multi-resistant pathogens[14]. With the use of newer, week-long acting antimicrobial agents[18], or in the presence local (intraosseous) antibiotics, an antibiotic free window seems not to be feasible.

Finally, a high incidence of 5%-15% of secondary SSIs warrants an adaptation of the protocolled and standardized perioperative

prophylaxis at least for surgeries with a high-risk of selection. Standard prophylactic agents such as the second-generation cephalosporins or vancomycin[2,26] lack the necessary coverage in view of the random nature of new SSI pathogens[11]. An optimal coverage would hence theoretically consist of a combination of glycopeptides with aminoglycosides, or glycopeptides with carbapenems, piperacillin-tazobactam and similar spectra[11]. However, this concept must be investigated in randomized trials before being implemented.

In the literature, several author groups proposed different strategies to improve the perioperative prophylaxis: e.g. combining with local prophylaxis (e.g. local vancomycin in spine surgery[65]), double agent prophylaxes against Gram-negative[66] and Gram-positive[67] pathogens, or universal glycopeptide prophylaxis[26,68]. All of these studies generally failed to reveal a better preventative outcome for an unselected study population; but were not investigated specifically for the strata of high-risk patients only. The ongoing BAPTIST trial is a randomized-controlled trial to test the superiority of the broad-spectrum prophylaxis[64] among selected orthopedic interventions. In operations with a high risk for SSI (open fractures, surgery under therapeutic antibiotics, tumor surgery, spine surgery with ASA-Score (American Society of Anesthesiologist) ≥ 3 points, a standard prophylaxis with cefuroxime is tested versus a broad-spectrum prophylaxis of a single-shot of vancomycin 1 g & gentamicin 5 mg/kg parenterally. The primary outcomes are "clinical remission" at 6 weeks; or at 1 year for implant surgeries.

Our review has limitations. The most important, is the lack of specific literature on this topic and the large heterogeneity of available information "between the lines" of existing literature. Secondly, the literature almost always interprets the antibiotic susceptibility in a dichotomous way: resistant versus susceptible. In reality, the susceptibilities might be gradient basing on the minimal inhibitory concentrations (MIC). It could be that the MIC level itself might influence the selection process and the degree of antibiotic resistance of future pathogens, as it has been demonstrated for various vancomycin MIC levels in orthopedic surgery [69]. In our review, we failed to find articles linking the selection of pathogens to the MIC level of the microorganisms of the index infection.

Conclusion

Surgical site infection with selection of more antibiotic-resistant pathogens in orthopedic surgery is an increasing clinical challenge, occurring in approximately 10% of the corresponding surgeries. This selection has considerable clinical consequences which go against the principles of antibiotic stewardship and might expose the patients to a broader-spectrum regimen, a prolongation of its course and even to another intervention; all depending on the interpretation of these novel findings. First measures to diminish the selection risks are an adequate diagnostic approach (i.e., renouncing on microbiological samples only for control reasons), to maintain an "antibiotic-free window" of some days prior to elective surgeries, to make every effort to obtain a primary wound closure already at the first intervention and by limiting antibiotic treatments to evidence-based indications according to established guidance. Finally, a prospective

trial randomizing a standard versus broad-spectrum perioperative antibiotic prophylaxis is under way in patients with a high risk of pathogen selection (orthopedic surgery under therapeutic antibiotics and with open wounds).

Conflict of Interest Statement:

All authors declare no potential conflict of interest.

Acknowledgement Statement:

We are indebted to all colleagues of the Balgrist and Limmattal Hospitals for providing ideas in the redaction of this review.

Financial Funding Statement:

None

Ethical and regulatory aspects:

Not applicable.

Authors contributions:

All four authors contributed to the literature review and the writing of this review.

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Appendix:

Table 1: Pre-operative prophylaxis, or prior antibiotic treatment, and effects on culture results

Pre-operative prophylaxis or prior antibiotic treatment and effects on culture results						
Study Details	Study Design	Antibiotic, Dosage	Duration, timing antibiotics	Most relevant pathogens	Target Group	Summary
Al-Mayahi, 2015 Switzerland [14]	Case control study	**A: N** 154 different regimens N = 718 (26%) parenteral treatment N = 706 (26%) b-lactam antibiotic N = 131 (5%) quinolone N = 222 (8%) long acting iv. agent (e.g., ceftriaxone, vancomycin, daptomycin, teicoplanin or ertapenem) N = 93 (3%) Single -Shot Prophylaxis **B:**no therapy	14 days prior to surgery (median = 4 days)	**A:** Staphylococcus aureus N = 343 (36%); Skin commensals N = 121 (13%); non-fermenting gram-negative rods N = 159 (17%); Polymicrobial N = 268 (28%) **B**: Staphylococcus aureus N = 709 (48%); Skin commensals N = 170 (12%); non-fermenting gram-negative rods N = 99 (7%); Polymicrobial N = 304 (21%)	N = 2740 **A**: (prior antibiotics) N = 1167 **B**: (no prior antibiotics) N = 1573)	-A: N = 220 (19%) culture negative vs. N = 96 (6%) in **B**. **A**: more non-fermenting rods and skin commensals (odds ratio 2.8 and 3.0) in multivariate analyses Preoperative Prophylaxis associated with culture negative results (19/93 vs. 297/2350) and skin commensals (17/74 vs. 274/2350) 38% (N = 28) of culture positive pathogen were resistant to the prophylaxis
Burnet, 2010 USA [12]	Prospective cohort	Single dose: cephalosporin (cefazolin) / vancomycin i.v	First dose Cephalosporin: and Vancomycin: immediately after the aspiration of TKA infection site	Pathogen after prophylaxis N = 9 Staphylococcus aureus (cloxacillin-sensitive) N = 4 Coagulase-negative Staphylococcus species N =2 Gram-negative species	N = 26 infected TKA and a known infecting organism from previous aspiration no control group	N 26 organism(s) cultured on the preoperative aspiration and from the operating room cultures before antibiotic infusion, were the same organism
Pérez-Prieto, 2016 Spain [30]	RCT	A: Prophylaxis with cefazolin, glycopeptide i.v B: no prophylaxis	30 min prior surgery	*A: Staphylococcus aureus N = 1 (11%)* Coagulase-negative staphylococci N = 3 (33%) B: *Staphylococcus aureus,* Coagulase-negative staphylococci, *Streptococcus* spp	N = 28 A: N = 14 B: N = 14	Antibiotic prophylaxis did not affect intraoperative cultures

				Corynebacterium spp, Gram negatives N = 1 (11%) *Enterococcus* spp N = 1 (20%) *Propionibacterium* spp N = 1 (20%)		
Uçkay,2012 Switzerland [17]	Single-center cohort	Cefuroxime/vancomycin (if MRSA body carriage) as prophylaxis N=1167 (43%) received antibiotics prior surgery		Intraoperative samples of 100 different infections (3.6%) (Enterococcus faecalis N=95; Enterococcus faecium N=2; and other enterococci N=3) 15/100 (15%) monomicrobial N=19/2740 nosocomial (N=15 with cephalosporin prophylaxis)	N=2740 orthopedic infection N=665 (24%) with implants	Nosocomial enterococcal infections associated with prophylaxis diabetic foot infection and polymicrobial infection: main predictors of enterococcal infection
Jamei, 2017 Switzerland [16]	Case control study	single intravenous dose of 1.5g cefuroxime or 1g vancomycin		N= 430 (24%) gram-negative N=194/430 (11%) non fermenting (NFR) N=143 (8%) *P. aeruginosa* N=6 (0.01%) ESBL-producing gram-negative rods. Proportion of NFR among Gram-negative pathogens was 45%	N=1840 Osteoarticular infection and implant-related infection	Polymicrobial infections and prior antibiotic treatment only significant predictors for gram-negative infection
Ghanem, 2007, USA [31]	Retrospective cohort	**A:** vancomycin (49%), first-generation cephalosporin (29%), ciprofloxacin (9%). **B:** no preoperative antibiotics with positive culture results	No data	A: N = 63 (87.5%) positive culture B: N = 91 (92%) positive culture 97% identical organisms isolated pre- and intraoperatively initial organisms isolated from the aspiration culture: E. coli S. aureus (MRSA) Enterococcus species, S. epidermidis. N = 4 out of Group B	N = 171 undergoing resection arthroplasty or irrigation and debridement for an infected TKA **A**: N = 72 **B**: N = 99	No difference in the incidence of false-negative cultures between **A and B** 97% identical organism isolated pre- and intraoperatively

Berbari, 2007, USA [32]	Retrospective cohort	Prior antibiotic use: N=32(53%) (b-lactams N=13 (41%), quinolones N=5 (16%) and others) Antibiotic therapy was discontinued immediately/1 week/2/13 weeks after culture negative prosthetic joint infection	median 28 days (range, 1–1440 days)	N=60 (7%) culture negative PJI Patients had received prior course of antimicrobial therapy in 53%	N=897 PJI	Only 20 (62%) of 32 antimicrobials had a concordant spectrum of activity between the antimicrobials used prior to and those used after the diagnosis of CN PJI
Malekzadeh, 2010, USA [33]	Retrospective case-control	**A**: N=85(64%) Culture Negative PJI (CN PJI) **B**: N=34 (25%) Culture Positive PJI most used: **A**: N=22(16%) cefazolin N=20 (15%) ciprofloxacin N=16(12%) cephradine	Median 34.5 days (1-2600 days)	B: N= 59 (44%) coagulase-negative Staphylococcus, N=25 (19%), Streptococcus sp. N=14 (10%) N=37 (27%) polymicrobial infection (anaerobes, aerobic Gram-negative bacilli, Enterococcus sp., Candida albicans, Gram-positive bacilli).	**A**: N=135 CN PJI **B**: N=135 CP JI	**A**: CN PJI more postoperative wound drainage and prior antibiotic therapy compared to **B** (CP PJI)
Shahi, 2015 USA, [34]	Retrospective data analysis	**A:** prior antibiotics **B:** no antibiotic treatment	-	Negative culture results A: N=14 (26.4%) B: N=14(12.9%)	N= 161 Late PJI after TKA **A**: N=53 (33%) **B**: N=108(66%)	**A**: prior antibiotic treatment more often negative culture results PJI
Stephan, 2021 Germany [13]	Retrospective, comparative study	**A:** single shot prophylaxis **B**: preoperative treatment **C:** no treatment	**B** more than 24h before surgery	Removed implant for sonication N=114 identified pathogens 77 (68%) detected by SFC a 82 (72%) by tissue culture. most common: staphylococci followed by streptococci and enterococci in FRI N=7 (6%) negative with SFC and N=17(15%) with tissue N=6 (B) and N=3 (A) only detected by SFC	N=90 (74.4% PJI and 25.6% FRI) **A**: N=27 **B**: N=33 **C:** N=30 of	In **A** and **B** cultures not affected by antibiotic treatment

Table 2: Studies with focus on prosthesis-related infections

Prosthesis related joint infections (PJI)						
Study Details	Study Design	Antibiotic, Dosage	Duration of Antibiotics	Most relevant pathogens	Target Group	Summary
Siegert, 2022 Germany [35]	Retrospective cohort	Cement spacer first stage (1 g gentamicin, 1 g clindamycin per batch) - Additionally, antibiotic therapy adapted to microbiological results	Minimum 6 weeks before second stage mean time between first- and second-stage revision 21 weeks	N = 168 (58.7%) culture positive 28% changed spectrum between the two stages 30.2% polymicrobiological spectrum	N = 25 (two-stage revision shoulder PJI) N = 286 microbiological samples	High rate of changes in microbiological spectrum, resistance patterns between culture first and second stage, subsequent revision
Benito, 2019 Spain [36]	Cohort study	Cefazolin/cefuroxime Vancomycin/teicoplanin in penicillin-allergic patients.	unknown	**A**: N = 78 (15.7%) culture-negative PJI **B**: N = 101 (6.6%) culture-negative PJI Staphylococci (65.2%). In early postoperative most virulent and multi-drug resistant spectrum	2524 episodes of PJIs N = 2288 with microbiological diagnosis **A**: N = 497 **B:** N = 1530	Statistically significant rising linear trend for the proportion of infections caused by Gram-negative bacilli, Percentage of multidrug-resistant bacteria PJIs increased from 9.3% to 15.8% in 2011/2012 (p 0.008); significant increase in the percentage of fungi as causative pathogens
Young, 2023 UK [37]	Cohort study	**A**: Local antibiotics 74/125 (59.2%) gentamicin:53/125 (42.4%), tobramycin:18/125 (14.4%), vancomycin: 19/125 (15.2%) Combined (gentamicin, Vancomycin) 16/125 (12.8%)	Local antibiotics at time of operation acc. to surgeon' systemic iv. antibiotics acc. to culture results	re-operation: 48/125 (38.4%) same bacterial species as at initial infection 49/125 (39.2%) only new species were isolated 28/125 (22.4%) cultures negative. persistent species: Staphylococcus aureus (46.3%), coagulase-negative Staphylococci (50.0%), and Pseudomonas aeruginosa (50%)	N= 125 (Recurrent infection) **A**: With Local Antimicrobial Treatment N= 74 **B:** Without Local Treatment N = 51	Gentamicin non-susceptibility at re-operation not associated with previous local aminoglycoside treatment (21/71 (29.8%) vs. 19/54 (35.2%); p = 0.6) Emergence of new aminoglycoside resistance at recurrence was uncommon and did not differ significantly between those with and without local aminoglycoside treatment (3/71

						(4.2%) vs. 4/54 (7.4%); p = 0.7).
Olsen, 2018 USA [38]	Retrospective cohort	Spacer: Gentamicin/Vancomicin/tobramicin Additionally, i.v determined by culture suppression 3 months determined by cultures	6-week postimplant I.v antibiotic-free period of 12 ± 8.3 weeks.	Methicillin-sensitive Staphylococcus aureus (17%), coagulase-negative staphylococci (17%), β-hemolytic streptococci (12%) Positive sonication culture N = 2 (4.9%, yielded coagulase-negative staphylococci	N = 41 (25 TKA, 15 THA)	Positive sonication fluid culture of PMMA spacers during reimplantation surgery was not associated with persistent or recurrent infection at minimum follow-up of 1 year
Phillips, 2006 UK [39]	Prospective survey	Prophylaxis before index surgery in all cases, mostly cefuroxime	unknown	N = 23 (31%) >1 organism N = 52 (69%) 1 organism N = 27 (36%) CNS N = 19 (25%) Staphylococcus aureus N = 7 (9%) enterococci N = 3 (4%) each of methicillin-resistant Staphylococcus aureus (MRSA), Escherichia coli and Pseudomonas aeruginosa.	N = 10735 N = 34 (0.57%) Infection hip replacement N = 41 (0.86%) Infection knee replacement	No significant change in the infection rate or type of infecting micro-organism over the course N = 31 (41%) superficial wound infection treated with antibiotics before the deep infection developed When deep infection was preceded by a superficial infection, in 30% of cases positive wound culture with the same organism.
Lee, 2020 Korea [40]	Retrospective cohort study	Recent antibiotics Total: N=48 (26.5%) Native joint: N=31 (23.0%) Prosthetic joint: N=17 (37.0%) 0.067	-	Staphylococcus aureus (51.1%), Streptococci sp. (21.1%), Enterobacteriaceae (8.4 %) Gram-negative bacteria (13.7%) fungi (3.2%)	N=181 N=135 N=46	Risk factors: health care associated factors and previous antibiotics usage
Moojen, 2014 Netherlands [41]	Retrospective cohort	**A** and **B** received systemic antibiotics broad-spectrum intravenous antibiotics immediately after the intraoperative culture samples adjusted to the bacteria cultured and their resistance patterns. **A:** gentamycin fleece **B:** gentamycin beads	**A**: 13-12 weeks **B**: 23-26 weeks	**B:** emergence of resistant bacteria though initial cultures showed growth of sensitive bacteria, repeat cultures during the second or third debridement identified e.g. methicillin-resistant Staphylococcus epidermidis or Corynebacterium species	N = 68 patients with acute THA infection **A**: N=33 single surgical debridement **B**: N=35 always multiple surgical debridement	No change in outcome between the two groups. Single surgical debridement with only repeat surgery on indication proved to be at least as effective in controlling the infection and

						retaining the hip implant as routinely performing multiple debridement

Table 3: Selection in mostly fracture-related infections; including for open fractures

Fracture-related-infection (FRI)						
Study Details	Study Design	Antibiotic, Dosage	Duration of Antibiotics	Most relevant pathogens	Target Group	Summary
Yusuf, 2015 Switzerland [46]	Retrospective chart view	All Patient received Prophylaxis: N = 18 (60%) Amoxcicillin/clavulanic N = 19 (63%) agent was changed N = 11 (36%) stopped	Average 8.5 days (range 1-53 days)	Initial surgery: Cultures: N = 19 (63%) Positive N = 10 (53%) Isolates (N) /Resistance to amoxicillin/clavulanic (%) S. aureus: N =1 /Gram negatives: N =8 / 88%, Anaerobes: N = 1 / 0% Revision surgery (median: 7 days): Cultures: N=25 (83%) Positive N = 22 (88%) (Monomicrobial N = 5, Polymicrobial N = 17) Isolates: Coagulase-negative staphylococci: N =6 / 67%; Gram negative: N =32 / 30% : Anaerobes: N =2 / 0%	N = 30 Gustilo type III open fracture admitted to university hospital 2007-2011	Outcome: Median number of operations 8 N = 24 (80%) favorable outcomes despite prophylaxis did not cover the whole spectrum At initial 47% and at revision surgery 88% of the pathogens were amoxicillin/clavulanic acid resistant.
Velmahos 2002 USA [47]	Prospective non-randomized study	Number of antibiotics 1 (N=65), 2 (N=41), >2(N=11) A: combination piperacillin/ tazobactam, second/ third-generation cephalosporin, combination of ampicillin, gentamicin sulfate, and metronidazole B: 1 broad-spectrum antibiotic (e.g. cefoxitin sodium or ampicillin sodium/sulbactam sodium)	**A**: > 24 h (3-5 days) **B**: 24 h	No data for pathogens Resistant infections N =20 (69%) orthopedic injuries (N=77, 31% of all patients) vs. N=4 (33%) with non-orthopedic injuries (P = .045)	N = 250 **A**: 117 (LONG group) **B:** N = 133 (SHORT N = 77 (31%) orthopedic operation of all patients	Antibiotic LONG treatment group was an independent risk factor for the development of resistant infections prophylactic administration of > 1 antibiotic for > 24 h following severe trauma did not offer additional protection against sepsis, organ failure, and death, but increased the probability of resistance

Gonzalez 2014 Switzerland [28]	Retrospective case–control	Prophylaxis for all patients cefuroxime (1.5 g iv), amoxicillin-clavulanate (1.2 g i.v)	Median 3 days	A: mostly Enterobacter cloacae (n = 8), Pseudomonas spp (n = 8), Bacillus spp (n = 6). B: Pseudomonas aeruginosa (n = 4), Enterococcus faecalis (n = 4), Enterobacter cloacae (n = 4), and others.	N = 310 Gustilo-III open fractures N = 36 (12%) infection occurred **A**: N = 26 (72 %) pathogens susceptible to the prophylactic antibiotic **B**: N=10 (28%) resistant	**A**: only Gustilo-grade-IIIc fractures (vascular lesions) showed tendency to be infected with resistant pathogens (odds ratio 10; 95 % confidence interval 1.0–10; p = 0.058). No significant differences between **A/B** in patient's sex, presence of immune suppression, duration and choice of antibiotic prophylaxis, choice of surgical technique or materials, time delay until surgery,
Dunkel, 2013, Switzerland [26]	Retrospective case-control	Cefuroxime: N= 1067 (72%), Amoxicillin/Clavulanate: N=63 (4%) 40 different regimens	3 days (range 1-3 days)	Pathogens resistant to the empirical antibiotic regimen N = 35 (71%) (Enterococci, Enterobacter spp, Pseudomonas spp) (71%). Enterobacter N=15 (31%) Pseudomonas spp N=15 (31%) Enterococcus spp N = 13(Staph aureus N=8 N=13 (other gram positives N=30(60%) gram-negative non-fermenting rods N=28 (57%) polymicrobial	N = 1492 open fractures Median number of interventions 2 (Range 1-9) N =54 infection N=49/54 pathogen identified	N= 35 (71%) antibiotic regimens did not cover the infecting pathogen Grade III fractures N=29/90 (32%) samples of first intervention bacteria not responsible for later infection In multivariable regression analyses, grade III fractures and vascular injury or compartment syndrome significantly associated with infection. Duration of antibiotics did not show significant differences in infection risk
Ukai, 2020 Japan [48]	Retrospective observational study	Prophylaxis: N = 96 fractures with first generation cephalosporin N = 18 combination cephalosporin and aminoglycoside < 80kg 1g i.v twice a day > 80 kg 2g i.v twice a day Dosage aminoglycoside accompanied by drug monitoring	Mean duration: 11.9 days (range 2–34 days) **A**: median duration 14.1 days **B**: 11.2 days	Pathogens from cultures during debridement for deep infection (N=18): Staphylococcus aureus (MRSA) (N=9), methicillin-resistant staphylococci (MRS) (N=1), other bacteria (N=8)	N = 114 Lower limb open fractures of G–A type III **A**: N=18 fractures with deep infection B: N=96 no infection	Duration of antibiotic prophylaxis significantly longer in patients with drug-resistant bacterial infections (19.8 versus 11.2 days, P < 0.01)
Suzuki, 2023 Japan [49]	Retrospective cohort study and review	Prophylaxes: **A**: cefazolin N = 482 (89.6%) Ampicillin/sulbactam n=30 (5.6%).	Prophylaxis always i.v before initial debridement	**A** : N = 43 (8%) deep SSI infection **B** : n=49 (9.8%) deep SSI infection No difference after matching (42/425 9.9%	= 1041 Type III open fractures evaluated within	Deep SSI rates did not differ between **A/B** Importantly, the risk of deep SSI was not reduced in **B** (broad spectrum)

		B: aminoglycosides, third- and fourth-generation cephalosporins, penicillin with activity against P. aeruginosa, fluoroquinolones, monobactams, carbapenems Aminoglycosides		narrow vs. 40/425 9.4% broad) **A:** polymicrobal N=12 Staphylococcus species N=18 (41.9%) Gram-negative rod N=20 (46.5%) **B:** polymicrobal N=18 (36.7%) Staphylococcus species N=41 (83.7%) ($p < 0.001$). Gram-negative rods: N=15 (30.6%) ($p = 0.117$).	3 months after trauma Unmatched: **A**: N=538 narrow-spectrum antibiotics **B**: N=503 broad-spectrum antibiotics N=425 pairs matched pairs were analyzed	
Lebowitz2017 Switzerland [50]	Retrospective cohort-study	Cefuroxime prophylaxis Vancomycin if MRSA carriage Antibiotic therapy 14 days prior surgery and sampling: N=1167 (43%) in total **A**: N=28 (43%) (prior therapy) **B**: N=1139 (43%) (no therapy)	Perioperative prophylaxis	Most common anaerobes: Propionibacterium acnes: N=35 (53%), Fusobacterium spp N=7 (10%) and Bacteroides spp N=5(4%). C. acnes N=23 (85%) device infections as fracture fixation plates, spondylodesis	N=2740 Orthopedic surgery because of clinical infection Positive culture=2424 **A**: N= 65(2.4%) anaerobes **B**: N=2675 other pathogens (97.6%)	No difference between groups **A/B** for prior antibiotic therapy The occurrence of anaerobic orthopedic infections among patients with prior antibiotic administration did not differ significantly from that of non-anaerobic infections
Uçkay, 2011 Switzerland [22]	Retrospective cohort			SSI risk with coagulase-negative staphylococci in 0.14% Implant-related infection 0.28% N=45(75%) methicillin resistant coagulase-negative staphylococci	N=44,237 orthopedic procedures and 21,299 (48%) implants	The majority (up to 70%) of surgical site infections due to coagulase-negative staphylococci was resistant to prior antibiotic prophylaxis
Benkaboucche, 2019 Switzerland, [51]	Prospective randomized-controlled trial	Intravenous therapy: vancomycin (*n* = 23), amoxicillin/clavulanic acid (30) and cefuroxime (17) Oral therapy: fluoroquinolones (*n* = 32), clindamycin (24), doxycycline (21), amoxicillin/clavulanic acid (30) and co-trimoxazole (13)	**A**: six weeks treatment **B**: four weeks treatment	Selected pathogen resistant to prior treatment in three cases S. aureus -> to community-acquired MRSA Enterococcus faecalis/to Enterobacter spp. P. aeruginosa to Staphylococcus epidermidis	N= 123 implant related infection **A**: N=62 (4-week arm) **B**: N=61 (6-week arm) Median of 2 surgeries	No significant difference in microbiological recurrence (N=2 in **A**; N=1 in **B**) No difference for type of infection or pathogen (Gram-negatives, staphylococci, streptococci, and skin commensals)