G85: How can we determine that a patient with an implant infection has received adequate duration of antimicrobial therapy?

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Recommendation:

In the absence of any relaible marker to determine the resloution of infection, the length of antimicrobial treatment needs to be decided based on the type of infection (4-6 weeks following resection arthroplasty vs 6-12 weeks after implant retainment), host status, antimicrobial efficacy, initial treatment response and patient compliance.

Strength of recommendation: Moderate

Delegate vote:

Rationale:

Clinical, biochemical and radiological cues for discontinuation of antimicrobial therapy and sufficient treatment durations in various orthopedic implant infections is insufficiently examined in high-quality studies. At the outset expert opinion dictated 3–6-month or longer courses for orthopedic implant infections, especially following debridement strategies (1, 2). Prolonged iv (often 6 weeks) lead-in was mainstay even in revision cohorts without apparent superiority to present-day results (3). Current recommendations (4, 5) are mostly based on observational studies or comparisons of predetermined treatment durations unsuited to identify determinants for customized discontinuation. Shortening courses with retained efficacy is imperative for reducing local and global antimicrobial resistance as well as toxicity and drug interactions. Conversely, treatment failure due to prematurely discontinued antibiotics increases patient suffering, healthcare strain and contributes to antimicrobial resistance from repeat courses.

For this narrative review, a MeSH search was undertaken in Medline, Embase and Cochrane on reports of antibiotic treatment duration, markers (CRP, ESR, synovial WBC) for discontinuation and outcome of prosthetic joint infection (PJI), fracture related infection (FRI) or peri-implant spinal infection (PSII), with a minimum 12-month follow up after discontinued antibiotics. When available, only data on relapses after antibiotic discontinuation were considered, since failure during treatment is irrelevant to the review question.

Certain antibiotic combinations such as rifampicin (RIF) and fluoroquinolones (FQ) have been put forward as superior over the last decades (6, 7), especially in staphylococcal (RIF + FQ) and gram-negative (FQ) infections (8), despite current evidence challenging this assertion (9-11). Suzuki and co-workers tried to assess effect and optimal duration of adjunctive RIF with partly conflicting results in a large (n=4628), but biased cohort of *Staphylococcus aureus*-PJIs subjected to DAIR (12). Gellert *at al.* reported 24-month infection free survivals of 48% and 67% (p = 0.038) (13) in surgically similar knee-PJI cohorts on “biofilm-active” and non-biofilm antibiotics respectively. Although treatment durations were not clearly specified, the “non-biofilm-active” cohort received 9-21 weeks of oral antibiotics compared to 10 weeks in the “biofilm-active” cohort. Scheper *et al.* concluded from a prospective cohort that clindamycin (mean 56 (range 40–62) days) or flucloxacillin (41 (33–50)) based treatment with 5 days of initial rifampicin was as effective

as a rifampicin combination 94 (85–103 days) in 200 patients (94% DAIR, 6 % 1-stage) (11). Other studies report outcomes after defined treatment durations for specific antibiotics. A RCT (n=75) comparing 6 weeks of daptomycin 6 and 8 mg/kg to a vancomycin/teicoplanin control at 2-stage reimplantation for *S. aureus* PJIs, demonstrated higher microbiological (50, 52 vs. 38 %) and clinical cure rates (58, 61 vs. 38%) for the comparator (14). No robust conclusions can be drawn from the very few publications that deal with two-dosed dalbavancin in hardware infections (15-17). Spitzmuller *et al*. found no apparent benefit from more than 31 days of treatment with regiments containing a FQ (OR 1.42 (0.34–5.85)) and/or rifampicin (OR1.41 (0.35–5.60)) in preventing relapse in an intent-to-cure case control study of infected internal fixations (18). Certain microbes such as RIF- or FQ- resistant strains, enterococci and *Candida* spp. is considered harder to treat, and guidelines commonly recommend staged revisions, but offer meagre guidance on treatment duration. *S. aureus* including MRSA (19-23) and hematogenous infection (24, 25) are frequently reported as independent risk factors for failure in DAIR, likely more influential than time on antibiotics (25). Two papers (26, 27) report 68 and 57 % resolution after a median 83 (range 38–133) and 88 (SD 127) days of antibiotics for streptococcal PJI (hematogenous in 95 and 52 %) treated according to DAIR in 55 % and 100 % respectively.

Furthermore, the overall likelihood of a favorable outcome is greatly influenced by host physiology and causative microbes (28, 29). Albeit varying discriminatory performance, predictive scores for PJI (30, 31) may be used to predict outcomes but does not directly inform on treatment duration. Interestingly, neither initial treatment response nor antimicrobial compounds are predictors in any of these models. Joulie *et al.* examined factors influencing resolution of *S. aureus* infections in hip and knee arthroplasties and found no significant difference in mean durations of empirical intravenous, or total antibiotic treatment (7 ± 5.2 vs. 7.8 ± 7.4 days and 124 ± 62 vs 117.9 ± 69 days) in resolution and failure respectively (32). Unfortunately, it is unclear how most of above factors translate into optimal duration of antibiotic treatment. Most guidelines recommend longer courses in debridement and retention of implant compared to staged revisions, why current evidence in support of shortened antibiotics in DAIR procedures is the most desired. Antibiotic suppression may merely postpone relapses (1) and moreover bias results in studies where predetermined suppression (mainly DAIR) is categorized as failure. Another concern is the general compliance with prolonged per oral treatments in PJI and FRI which is not investigated but will influence ultimate outcomes and bias studies. In the controlled setting of the OVIVA trial including 31.5 % retained orthopedic implants and a median 71 (IQR 43-94) days of po antibiotics, an early iv to po switch did not impact one-year failures of 18.5 % and 14.2 % in peroral and intravenous administration respectively, but the study doesn´t report on outcome differences in short versus long treatments (33). In another study, early po switch (less than 5 days of iv, mean total 80 (SD 31.5) days) in implant infections only (62 % FRI, 41 % retention), was not associated to failure (aHR 0.8 95%CI 0.4–3.5, p = 0.66). (34). Moreover, intravenous antibiotics prolonged beyond 7 days doesn´t improve outcomes in early PJI subjected to DAIR. Meijer *et al.* report 41.5%, 44.4%, 42.1% overall failures (n=969) in <14, 14–27 and >27 days respectively (p=0.798), possibly with the exemption of highly inflammatory infection (CRP >115 mg/L) and replacement of modular components isn´t carried out (35).

It is well established that early surgery and complete implant removal increases the likelihood of success. Likely this is also true for modular component exchange in DAIR, but the jury is still out regarding to what degree (36). Controlled trials on antibiotic duration regarding implant retention in FRI are missing, and recommendations are largely extrapolated

from the existing data on PJIs. However, in a RCT (n=123) Benkabouche *et al.* demonstrated no difference in resolution rates after 4 and 6 weeks of antibiotics following mixed implant removals (37) including FRIs.

PJIs were defined according to EBJIS, MSIS or comparable criteria and most relevant studies stated that antibiotic suppression was considered failure. There are only 2 RCTs primarily addressing antibiotic treatment duration (38, 39) and no reports that systematically analyzed strategies for determining the optimal time to discontinue treatment. There is a fair amount of knowledge regarding the role of biomarkers such as serum-CRP and ESR in orthopedic implant infections. For example, CRP is inadequate in ruling out low grade PJIs (40) but levels above 150 mg/L at diagnosis of late acute PJI independently correlate to early failure in DAIR (20). Conversely, there were only a couple studies analyzing biomarkers for deciding when to stop antibiotics. Bejon *et al.* performed ROC and time adjusted ratios of 2326 serum-CRP measurements in 109 DAIR and 151 2-stage revisions respectively. The authors concluded that serial CRP measurements do not reliably detect failure within 180 days after DAIR with peroral suppression, nor predict outcomes in staged revisions and 6 weeks of parenteral antibiotics, (reimplantation ratio=0.84, 95% CI 0.65 –1.09, p=0.24), Ghanem *et al.* assessed the prognostic value of ESR and CRP prior to second stage after 6 weeks of parenteral antibiotics in 86 successful and 23 failed knee re-implantations and found poor AUROCs of 0.50 and 0.55 respectively. There are numerous studies on synovial WBC measurements prior to second stage revision collectively found unreliable in predicting persisting infection (41), but synovial WBC has not been assessed as a marker for stopping antibiotics. Two studies, however, evaluate synovial WBCs during the end of planned antibiotics. Ascione *et al.* found significantly higher WBC counts (median 1344 IQR 934-2776 vs. 471 IQR 290-804) and neutrophil percentages (61 IQR 52-78 vs. 36 IQR 28-51) in failures in an 82-patient primary 2-stage-revison cohort receiving 8 weeks of antibiotics (42).

Cohort studies (39, 43, 44) comparing 6-8 with 10-12 weeks of antibiotics in implant preserving PJI treatment indicated no additional benefit from longer courses at 12-24-month follow-up, but the DATIPO RCT (per protocol n=325) by Bernard *et al.* raised concerns by failing to demonstrate non-inferiority of 6 weeks compared to 12 weeks, particularly in DAIR where the risk difference for failure were 16.2 %-pts. (CI 2.9 to 29.5) (38). In a smaller (per protocol n=44) RCT on hematogenous or early post-surgical hip and knee PJIs, Lora-Tamayo *et al.* offer moderate strength evidence of non-inferiority in 8 vs 12 weeks of RIF+FQ (levofloxacin) therapy (39). Neither RCT was powered to significantly discriminate between hip and knee joints. Another French DAIR-cohort (n=60) appear to support that less than 3 months of antibiotics is independently associated (OR 20.0 CI 2.2-200) with failure, but the numbers were small and 40 % of failures occurred during antibiotic therapy (23). An RCT by Karlsen *et al.* challenged the need for rifampicin in DAIR for early staphylococcal PJIs and allocated both groups (n=48) to 6 weeks of antibiotics with 2-year cure rates of 73 %, without significant group differences (10). Indeed, examining per protocol outcomes after removal of failures occurring during treatment, success rates increase in both long and short courses, supporting reducing durations in cases of uneventful initial treatment (11, 38, 39, 45). Moreover, in the large (n=653) PIANO PJI-cohort, duration of neither iv nor po antibiotics was associated to success in DAIR (OR 0.99 CI 0.97–1.00 and OR 1.004 CI 0.993–1015) or 2-stage (OR 1.009 CI 0.97–1.00 and OR 0.985 CI 0.970–1.001) respectively (22). An observational study of shortened treatments in 1-stage revision by Chieffo *et al.* reported a 12-month remission rate of 90% in 50 PJIs treated by 1-stage and 6 weeks of various antibiotics (46). This is reinforced by the DATIPO 1-stage subgroup (risk difference 1.2 %-pts. CI −4.8 to 7.1) (38). Following second stage most authors suggest discontinuation

of antibiotics in clinically uninfected and culture negative cases. This was tested by Chen and collaborators in an RCT comparing 2 and 12 weeks, yielding identical outcomes at three-year follow-up (47). An similarly designed RCT (per protocol n=133, mean follow up >3 years) comparing 12 and 0 weeks, conversely reported 8 (13%) vs. 20 29 %) failures, where 55 % in the control group failed within 2.5 months (48) , i.e., antibiotics provided short-term improvement in infection-free survival. There were only a few papers regarding FRI. Al Mayahi and co-workers concluded that more than 42 days (OR 0.1 42-63 days (0.1–2.5)) of total antibiotics didn't affect outcome in a multivariate analysis of 139 patients with mixed material FRIs where DAIR was performed in 14 % (49). Regarding PSII, the evidence level is even weaker, but despite method shortcomings there is indications that shorter treatments may be opted for. Bosch-Nicolau *et al.* reported in a retrospective DAIR cohort study that 8 weeks of treatment didn't perform worse than 12 weeks in acute PSII (54% staphylococci)(50). Oral antibiotic choices were similar in the groups, but no beta-lactams were used. In a mixed case cohort study, more than 42 days of total antibiotic treatment did not lead to increased healing (51). A 1-year observational study (n=85, 74 implants) of DAIR and 6 weeks of oral antibiotics in early PSII treated, only 7 patients required reoperation due to infection (52) and Pull ter Gunne *et al.* found no relapses within one year in a PSII cohort of 132 patients after a mean 40.8 (SD 17.0) days of mainly parenteral antibiotics. The median time to diagnosis was 15 days and surgery was implant preserving in 73% and one-stage revision in 15% (53). In previous observational studies treating physicians may have opted for early discontinuation in uncomplicated cases partly explaining why apparent short course efficacy could not be replicated.

Conclusion

Optimal antibiotic treatment duration in different orthopaedic implant infections is largely undefined and due to the sparcity of bespoke high quality studies, poor evaluability of unstandaridzed discontinuation practices and evolving surgical methods. Overall, in orthopedic implant infections, the limited reports available on CRP, ESR and synovial WBCs does not support their use in guiding discontinuation of antibiotics. In pre-treatment likelihood of success, even in implant preserving procedures, it´s plausible that shorter treatments than current mainstay are equally efficacious. Thus, being knowledgeable of host and microbe specific factors associated with failure in addition to the significance of prompt initial treatment response, may inform shortened treatments with retained levels of success. Evidently, there is urgent need for well-designed site and condition-specific studies, especially regarding implant preservation, particularly for FRI and PSII.

Studies comparing treatment durations in various orthopedic implant infections.

Author/year	Design	N	Type	Joint/ bone	Procedure	(No. weeks) Success %	(No. weeks) Success %
Benkabouche *et al.* 2019	RCT	123	PJI/ FRI	Mix	2-stage	(4) 94	(6) 95
Bernard *et al.* 2010	Prosp. cohort	135	PJI	Hip/knee	DAIR, 1- & 2-stage	(6) 89	(12) 66

Chaussade *et al.* 2017	Retro. cohort	87	PJI	Hip/knee	DAIR	(6) 70.5	(12) 67.4
Chen *et al.* 2024	RCT	60	PJI	Hip/knee	2-stage, second stage	(2) 96.7	(12) 96.7
Yang *et al.* *et al.* 2020	RCT	107	PJI	Hip/knee	2-stage, second stage	(0) 83.7	(12) 96.6
Lora-Tamayo *et al.* 2016	RCT	63	PJI	Hip/knee	DAIR	(8) 91.7	(12/24) 95.0
Bernard *et al.* 2021	RCT	410	PJI	Hip/knee	DAIR, 1- & 2-stage	(6) 83.4	(12) 93.1
Puhto *et al.* 2011	Retro. cohort	86	PJI	Hip/knee	DAIR	(12) 87.5	(24.5) 89.5

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