HK99: Is there a role for two-week antibiotic holiday in patients undergoing two-stage exchange arthroplasty for prosthetic joint infection (PJI)?

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Response/Recommendation:
There is no conclusive evidence that two-week antibiotic holiday improves the outcome of two-stage exchange in patients with PJI. On the other hand, continuous therapy may result in better outcomes for some such as immunocompromised patients.

Strength of recommendation: Low

Delegate Vote:

Rationale:
An "antibiotic holiday" period can be observed before reimplantation in a two-stage exchange procedure for prosthetic joint infection (PJI) to identify patients with a latent infection prior to reimplantation. This approach was first described by Insall et al. in 1984 as a strategy to address the risk of infections that may be suppressed but not eradicated before reimplantation (1). Building on Insall's work and other early reports, the practice of a two-week antibiotic holiday emerged, theoretically allowing latent infections to become clinically evident before reimplantation (2, 3). However, the absence of reliable thresholds for serological markers to indicate infection control or persistence, as well as the low accuracy of microbiologic investigations in predicting infection recurrence remain unsolved challenges in this field (4). Additionally, withholding antibiotics for two weeks can extend the interval between surgical stages, potentially leading to worse treatment outcomes (5).
A meta-analysis was completed utilising the PRISMA protocol to review the effect of an antibiotic holiday versus continuous antimicrobial therapy on treatment failure. Following de-duplication, 1974 records were available for title and abstract screening, of which 185 proceeded to full-text screening. No randomized controlled study was available. Six retrospective cohort studies were identified to have directly compared treatment failure rates between patients who underwent antibiotic holiday and those who were subjected to continuous antibiotic therapy (6-11). Three of six included studies were at serious risk of bias, and the remaining three were at moderate risk of bias. (Table 1). Ascione et al. (6) found that absence of antibiotic holiday predicted favourable outcome in terms of treatment failure ($p=0.029$). Lee et al. (9) found that the lack of antibiotic holiday was a risk factor for treatment failure. Mont et al. (10) reported a benefit to the use of an antibiotic holiday. Chang et al. (8), Castellani et al. (7) and Van Dijk et al. (11) found no difference.
Random effects meta-analysis calculated a risk ratio of 0.77 (95% confidence interval 0.40-1.46) for the outcome of treatment failure with use of antibiotic holiday (Fig 1). This indicates that there is comparable risk of treatment failure between patients who underwent antibiotic holiday and those who underwent continuous antibiotic therapy between stages (12). The I^2 value was 63.1% (95% confidence interval 10.6-84.8%), and the prediction interval was 0.13-4.44, indicating substantial heterogeneity (13-16).
Ascione et al. (6) reported the largest comparative cohort study of the outcomes of continuous antimicrobial therapy versus an antimicrobial holiday, involving 196 patients with a minimum follow-up of 96 weeks. Those undergoing continuous therapy had a significantly better success rate of 91% (104/114) compared to those undergoing an antimicrobial holiday 79% (65/82) ($p = 0.029$). This study was the only one to find a statistically significant

difference between the groups and found that immunocompromised patients had the highest advantage with continuous therapy.
Van Dijk et al. (11) reported on a cohort of 105 patients undergoing a two-stage exchange. Infection control rates were comparable between patients with an antibiotic-free period (87%) and those with continuous antibiotics (82%), with no statistically significant difference ($p = 0.6$). Similarly, Castellani et al. (7) reported on the outcomes of 75 patients that underwent a two-stage exchange and found no difference in treatment success between continuous therapy versus the use of an antimicrobial holiday (9/47 vs 3/16 failures; $p = 1$). This finding is limited by small numbers of patients undergoing continuous therapy. Chang et al. (8) reported on 58 patients with 31 receiving an antimicrobial holiday and 27 continuous therapy. Whilst the two-year survival rate was higher in the antimicrobial holiday group (89.3% vs 78.8%), this failed to reach statistical significance ($p = 0.263$). Furthermore, patients undergoing an antibiotic holiday period before reimplantation had an overall lower CRP at the end of antibiotic treatment period, suggesting better infection control in this group. Of note additionally is the fact that this study employed long intervals of 4.5 – 6.5 months between the first and second stages, limiting it's generalisability.
Several studies have reported negative findings with respect to treatment success when continuous therapy is employed. Mont et al. (10) reported on 69 patients who underwent a two-stage exchange, 35 receiving continuous therapy and 34 receiving an antibiotic holiday period. They found a higher rate of treatment failure in continuous therapy group compared to the antibiotic holiday (14% (5/35) vs 3% (1/34); ($p < 0.05$)). There were however methodological discrepancy between groups. Routine joint aspiration occured before the second stage reimplantation in the antibiotic holiday group, while the continuous therapy group did not undergo aspiration. Negative cultures led to reimplantation, while positive cultures prompted additional debridement which may have led to lowered reinfection rates in the antibiotic holiday group. Lee et al. (9) reported that the lack of an antimicrobial holiday was a risk factor for treatment failure in their series of 101 patients undergoing a two-stage exchange. Only 13 patients in this series received continuous therapy with a reported failure rate of 46.4%. The treatment methodology in this series stated that antibiotic regimes were individualised and dependant on response to treatment. If the clinical condition improved and CRP levels declined, the patient was switched to oral antibiotics or antibiotic treatment discontinued. If recurrence of PJI was suspected, the patient would receive further debridement and spacer exchange. This may explain the finding in this series of a higher failure rate for those receiving continuous therapy.

The wide prediction interval calculated in this meta-analysis represents the range within which the true effects of 95% of future studies, conducted under similar conditions as those included in this meta-analysis, are expected to fall (16). This suggests that there may be settings in which antibiotic holiday may be beneficial in terms of treatment failure, and settings in which it may be harmful, however based on published literature it is not known which factors nor their magnitude. As such, this meta-analysis should be interpreted cautiously in the context of substantial multifactorial heterogeneity which renders interpretation of the independent effect of antibiotic holiday on treatment failure rate difficult and complex. Given the heterogeneity of the data, further research is needed to clarify the optimal approach.

Figure 1.

Forest plot: Values to the right side of the line of no effect (risk ratio = 1) indicate increased risk of failure with antibiotic holiday.

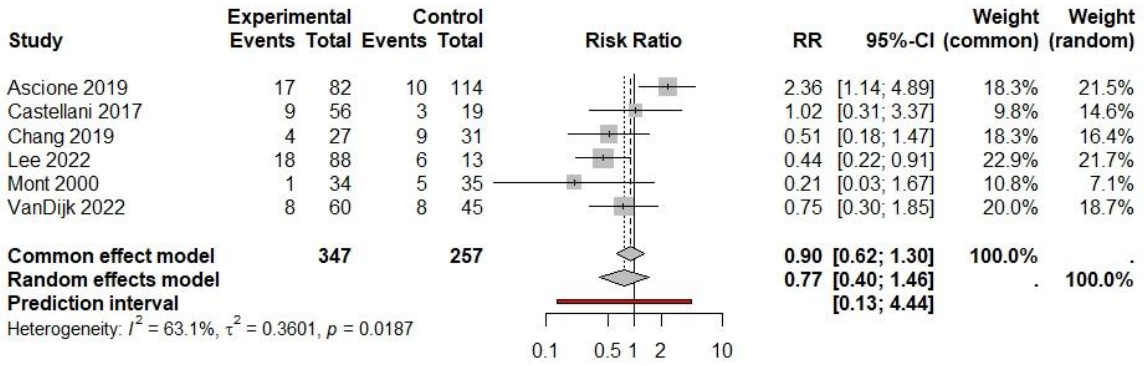

Table 1: Critical appraisal

Study ID	Bias due to confounding	Bias due to participant selection	Bias due to intervention classification	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias due to selection of reported result	Overall risk of bias
Ascione 2019 (6)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Castellani 2017 (7)	Serious	Serious	Low	Moderate	Moderate	Low	Low	Serious
Chang 2019 (8)	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Lee 2022 (9)	Serious	Serious	Low	Moderate	Moderate	Low	Low	Serious
Mont 2000 (10)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Van Dijk 2022 (11)	Serious	Serious	Low	Moderate	Moderate	Low	Low	Serious

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