

HK101:Should patients undergoing reimplantation surgery in whom intraoperative cultures isolate organism(s) be treated with antimicrobials?

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Response/Recommendation:

Yes. Patients undergoing reimplantation surgery in whom positive cultures are detected should be treated with antimicrobials if two or more cultures detect the same organism, a single positive culture is identified that is the same as first stage findings, or if there is clinical concern for infection. The optimal duration for antimicrobial therapy is unknown and 4-6 weeks may be appropriate in many cases.

Level of evidence: Moderate

Delegate vote: Agree %, Disagree%, Abstain%

Rationale:

The diagnosis of persistent infection and need for extended antibiotics in patients undergoing two-stage exchange arthroplasty for PJI is challenging especially when a positive culture at reimplantation is detected. How to best differentiate isolates representing contamination from pathogens is unclear especially when a new organism is identified that differs from first stage microbiology. This review examines the role of intraoperative cultures at the time of reimplantation in the management of implant related infection.

Eleven identified studies and one meta-analysis performed in 2019¹ examined the association of positive reimplantation cultures with treatment outcomes.(Table 1) Seven reviewed studies were included in the meta-analysis of 11 studies by Xu et al.¹⁻⁷ Of identified studies, one evaluated hips alone,¹ one evaluated knees alone,⁸ six evaluated both hips and knees,^{2-5,7,9} two evaluated hips, knees and shoulders,^{6,10} and one evaluated hips, knees and elbow.¹¹ Eight studies confirmed that an antibiotic free period occurred between resection and completion of antimicrobial therapy, and reimplantation.^{1,3-5,7,8,10,11} Five studies considered positive cultures as significant infection if two or more cultures identified the same organism, or if a single culture found the same organism as that detected at first stage resection.^{2,3,6,7,9} Two studies considered two or more positive cultures with the same organism as significant,^{5,10} one study considered growth >20 CFU as significant,⁴ and three studies considered any positive culture as significant.^{1,8,11} Included studies reported a wide range of positive cultures at reimplantation (5.2%-60%), and those that were considered significant (24%-100%). Three studies examined the role of spacer sonication cultures in detection of subclinical infection with two reporting improved sensitivity with this technique compared to tissue culture alone.^{3,4,6} The majority of positive cultures differed from first stage cultures suggesting that superinfection is more common than persistence of initial infection. Failure was defined by clinical parameters in 11 studies,¹⁻¹¹ by the need for extended oral antibiotic suppression in two,^{2,4} and by reimplantation cultures in one study.³

Six studies found that positive cultures at reimplantation significantly increased the chance of subsequent failure.^{1,2,4,6,7,9} Xu et al. performed both a retrospective study of 117 patients with hip

PJI correlating a positive culture at reimplantation with failure¹, and a meta-analysis of 11 studies that included 141 cases with positive cultures at reimplantation and 784 cases with negative cultures finding that positive cultures were significantly associated with failure as compared to negative cultures (26.1% vs 6.4%, $p<0.001$).¹ Several studies reported an increased risk of failure with a single positive culture.^{2,7,9} Conversely, three studies found no correlation between positive cultures at reimplantation and subsequent failure.^{5,8,11} Two studies provided descriptive results only with one finding a greater number of infections in positive culture cases, and the other finding the opposite.^{3,10}

Eight studies reported the duration of administered antimicrobial therapy in cases with significant positive cultures with most treatment courses ranging from 4-12 weeks,^{1-3,5,7,9,10} but one extending to over a year.¹¹ As the majority of patients with positive reimplantation cultures considered significant received antimicrobial therapy, the benefit and optimal treatment duration is not well examined. The meta-analysis by Xu et al. reported as a subgroup analysis that pooled data from five studies found that treatment with at least 6 weeks of antibiotics in cases with positive cultures decreased the risk of subsequent failure.¹

The interpretation of positive cultures at the time of reimplantation remains difficult. Direct comparisons between reviewed studies are limited by variation in study design, identification of culture significance, definition of failure, and length of follow up. Nevertheless, while three studies did not significantly correlate positive cultures with failure, six did find a significant association, underscoring the potential relevance of positive findings and role for antimicrobial therapy. Most studies distinguished relevant culture results from contaminants by the finding of the same organism in multiple samples. This is common in clinical practice and likely to continue as a means to identify higher risk patients. Other considerations factoring into management include: persistent detection of the organism identified during first stage surgery, the identification of a virulent organism such as *Staphylococcus aureus* in a single culture, and clinical concern for infection.

Conclusion:

Persistent infection as a complication of two-stage exchange arthroplasty for the management of PJI is a serious event, and future work should better define infection at the time of reimplantation. The optimal duration of antimicrobial therapy in cases with positive cultures that are considered significant remains unknown and the role for treatment beyond 4-6 weeks (with the potential for adverse antibiotic effects) is not well examined.

Table 1 Prognostic value of positive cultures at reimplantation

Study, Year	Design	Level of Evidence	Number of Joints, (n)	(+) cultures (n,%)	(+) cultures considered pathogens (n,%)	ATB*	(+) cultures, failure (n,%)	(-) cultures, failure (n,%)	(+) cultures, predictor of failure
Murillo 2007	Prosp.	III	25 (10 hips, 14 knees, 1 shoulder)	15/25 (60%)	7/15 (47%)	6-8	0/7 (0%)	2/18 (11%)	NA
Bejon 2009	Retrospect.	III	152 (71 hips, 77 knees, 4 elbow)	21/152 (14%)	19/21 (91%)	6- >52	NA**	NA	p=0.6

Cabo 2011	Prosp.	III	41 (18 hips, 23 knees)	18/41 (44%)	4/18 (22%)	4-6	4/18 (22%)	1/23 (4%)	NA
Mortazavi 2011	Retrosp.	III	117 knees	19/117 (16%)	NA	NA	6/19 (32%)	27/98 (28%)	p=0.33
Sorli 2012	Prosp.	III	55 (17 hips, 37 knees, 1 shoulder)	14/55 (25%)	11/14 (79%)	NA	7/11 (64%)	11/44 (25%)	p=0.021
Puhto 2013	Retrosp.	IV	107 (61 hips, 46 knees)	5/97 (5.2%)	5/5 (100%)	8-12	1/5 (10%)	4/92 (4%)	p=0.24
Nelson 2014	Prosp.	III	36 (7 hips, 29 knees)	18	9/18 (50%)	N/A	9/18 (50%)	2/18 (11%)	p=0.0189
Tan 2016	Retrosp.	III	267 (81 hips, 186 knees)	33/267 (12%)	25/33 (76%)	6-12	15/33 (45%)	49/234 (21%)	p=0.02
Akgun 2017	Retrosp.	III	163 (84 hips, 79 knees)	27/163 (17%)	15/27 (56%)	12	8/27 (30%)	20/136 (15%)	p=0.049
Xu 2019	Retrosp.	III	117 hips	23/117 (20%)	23/23 (100%)	6-10	6/23 (26%)	6/94 (6%)	p=0.022
Xu 2019	Meta-analysis	III	925 joints	141/925 (15%)	NA	2-12	58/141 (41%)	116/784 (15%)	p<0.001
Theil 2020	Retrosp.	III	204 (93 hips, 111 knees)	51/204 (25%)	12/51 (24%)	2-6	17/51 (33%)	25/152 (16%)	P=0.014

Prosp.=prospective; Retrosp.=retrospective; NA=not available; ATB*=Antibiotic duration after reimplantation (weeks);

**Reported Cox univariate analysis: Hazard Ratio 1.3 (95% CI 0.4-3.7)

References:

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Search methods/results:

Two databases were searched for relevant terms: PubMed and Scopus. Sixty-five studies were identified: 32 from PubMed, 22 from Scopus and 11 by citation searching of identified studies. Eight duplicate studies were removed. Of 57 studies screened, 24 were irrelevant, 33 underwent full text review with 22 excluded (11 wrong setting, 9 wrong patient population, 1 wrong outcome, 1 wrong indication), leaving 11 included studies.