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QUESTION 4: Can short term (two weeks or less) antibiotic treatment be considered following resection arthroplasty for chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. Following an aggressive debridement and insertion of an antibiotic-loaded cement spacer (ALCS) or beads, a short-term course of less than two weeks of systemic antibiotic therapy can be considered. Several studies show promising results with infection eradication rates comparable to when a much longer course of antibiotic treatment is used.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 64%, Disagree: 32% Abstain: 4% (Super Majority, Weak Consensus)

RATIONALE

Successful management of PJIs requires appropriate surgical intervention with additional antibiotic therapy. PJIs can be treated by several surgical strategies that range in invasiveness, including debridement and irrigation of the infected prosthesis, one- to two-stage exchange with or without the placement of a spacer or an extension device, resection arthroplasty and amputation. However, the ideal duration of antibiotic therapy, intravenous (IV) alone or combined IV and oral antibiotics, is not known. With increasing concerns about the emergence of antibiotic resistance and the spiraling costs of healthcare worldwide, shorter courses of antibiotic therapy, if equally efficacious to the more traditional 6- to 12-week course, would be a very attractive proposition.

The rationale of using a shortened duration of systemic antibiotics is based on the high local levels of antibiotic that can be achieved following elution from antibiotic-loaded bone cement, whether this is in the form of spacers or cement beads. Local tissue levels of antibiotic are above the minimum inhibitory concentration (MIC) for commonly infecting organisms [1–3] (Tables 1 and 2), and the levels are greater than that which can be achieved with IV administration alone.

Although some groups have reported good clinical outcomes with meticulous debridement and combinations of local and short-term systemic antibiotic therapies, most of the studies examining short-term inter-stage antibiotic treatments were retrospective cohort studies on a small number of patients. There were very few studies in which antibiotic therapy was less than two weeks duration. In addition, there was significant inter-study heterogeneity in the definition of infection, in the treatment approach with regard to the debridement method, in differing combinations of systemic and ALCSs and in the antibiotic therapy after reimplantation. Although the results appear promising, the inter-study heterogeneity makes it difficult to utilize the studies as collective evidence to support short-term inter-stage antibiotic treatment.

In a small randomized controlled trial that did not meet Consort guidelines, Nelson et al. compared inter-stage treatment with antibiotic-laden cement beads, combined with no more than five days of inter-stage systemic antibiotic therapy, to traditional inter-stage systemic antibiotic therapy alone in 26 patients treated for PJIs with two-stage resection arthroplasties. All patients were reimplanted at 6 weeks following stage-I surgery. After a mean follow-up period of 32 months, infection eradication was 100% in the group treated with antibiotic-laden cement beads and 93% in the group treated with systemic antibiotics alone [4].

In a retrospective cohort study, McKenna et al. assessed the effectiveness of a five-day inter-stage course of systemic vancomycin combined with an ALCS containing vancomycin, gentamicin, and tobramycin, following resection arthroplasty for failed total knee arthroplasty (TKA) due to PJIs in 30 consecutive patients. At the gentamicin of reimplantation (mean = 16 days) no infection recurrence was reported. A second five-day course of systemic antibiotics was administered following second-stage reimplantation. At a mean follow-up of 35 months, infection eradication remained at 100% [2].

In a retrospective cohort study, Whittaker et al. assessed a two-week inter-stage course of systemic vancomycin combined with a vancomycin and gentamicin loaded spacer, for hip PJIs. Three patients required a repeat debridement prior to reimplantation due to recurrent infection (7%). Of those patients receiving second-stage reimplantation, 92.7% were infection-free at a mean follow-up of 49 months [5].

Hoad-Reddick et al. reported on a retrospective cohort study that included 38 patients who underwent staged exchange with a combination of ALCS, antibiotic-laden cement (ALC) beads (loaded with vancomycin, gentamicin or both) and broad-spectrum prophylactic systemic antibiotics administered at 8 and 16 hours with no further systemic antibiotics given. Infection eradication after second-stage reimplantation at a mean follow-up of 56.4 months was 89% [6].

In a retrospective cohort study that included 107 patients with hip PJIs (36 of which had recurrent PJIs), Hseih et al. compared outcomes of 56 patients treated with one week of inter-stage IV antibiotic therapy to outcomes of 51 patients treated with 4-6 weeks of IV therapy, followed by two additional weeks of oral antibiotic therapy after reimplantation. Both groups also had antibiotic-impregnated spacers. Infection eradication was achieved in 92.4% (1 week) and 91.3% (4-6 weeks) of patients, respectively at a mean follow-up time of 43 months (range = 24-60 months) [7]. The number of patients in these studies who were infection-free after completing the two-stage procedure ranged from 86.7-100%, comparable to the rates achievable with a standard 4- to 6-week antibiotic regimen.

Appropriate usage of antibiotics is of paramount importance, more so today than ever, in view of emerging antibiotic-resistant organisms. Short-term therapies (i.e., less than two weeks) can be considered when managing patients with PJIs. However, prospective randomized controlled trials are needed to further explore this issue.

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TABLE 1. Therapeutic ranges and minimum biofilm eliminating concentration (MBEC) values for various antibiotics

Antibiotic	Therapeutic Peak (mg/L; µg/mL)	MBEC (mg/L; µg/mL)				
		S. aureus	*MRSA*	*P. aeruginosa*	*S. epidermidis*	*E. coli*
Azithromycin	0.3 - 0.6		5120	2560		
Ceftazidime	< 150			2560 - 5120		
Ciprofloxacin	2.5 - 4		256 - 1280	80 - 1280		
Clindamycin	< 0.5		64 - > 1024			
Colistin	1 - 4			160 - 2560		
Daptomycin	6 - 10	600	1014			
Doxycycline	< 10		64 - 128			
Erythromycin	0.5 - 3	6400	64 - > 1024	2560		
Gentamicin	5 - 10	6400	1 - > 256	512xMIC		
Linezolid	0.5 - 4	6400	4 - > 1024			
Piperacillin	5 - 20			> 5120		
Tobramycin	5 - 10	160 - 4000	≥ 8000	250 - 2000	≥ 8000	62.5 - 125
Vancomycin	25 - 50	2000 - 8000	2000 - 8000		1000 - 8000	

MBEC, minimum biofilm eliminating concentration; MRSA, methicillin-resistant *Staphylococcus aureus*

TABLE 2. Peak local antibiotic concentrations via cement elution

Study	Cement Protocol	Peak Joint Concentrations
Masri et al. [8]	ALCS: 1.2 - 4.8 gm of tobramycin and 1 - 2 gm of vancomycin per 40 gm pack	1.25 - 16.97 mg/L
Hsieh et al. [7]	ALCS: 4 gm vancomycin powder and 4 gm aztreonam per 40 gm pack	vancomycin: 1538 mg/L; aztreonam: 1003.5 mg/L
Anagnostakos et al. [9]	ALCS + beads: 1 gm gentamicin and 4 gm vancomycin per 40 gm pack	gentamicin: 115.70 mg/L; vancomycin: 80.40 mg/L
Fink et al. [10]	ALCS: 'Pre-prepared' mix	gentamicin: 50.93 mg/L; vancomycin: 177.24 mg/L; clindamycin: 322.29 mg/L

ALCS, *antibiotic-laden* cement spacer

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