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QUESTION 6: Is there a role for direct intra-articular antibiotic infusion following irrigation and debridement (I&D) for periprosthetic joint infection (PJI)?

RECOMMENDATION: The concept of achieving a minimum biofilm eradication concentration (MBEC) of antibiotics at the site of the infection is compelling. Despite the presence of retrospective studies reporting favorable outcome, because of heterogeneity in terms of adjunctive antibiotics, absence of a control group and small cohort size, the routine administration of intra-articular antibiotics in treatment of PJI is not justified. Prospective, randomized controlled trials (RCTs) are needed to support the routine use of intra-articular antibiotics as a stand-alone or adjunct treatment of PJI.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 6%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Current published evidence for intra-articular antibiotic infusion following irrigation and debridement for PJI is limited to small case series and retrospective cohort studies. The authors of all studies aimed to achieve higher concentrations of antibiotics at the site of the infection than is possible with systemic therapy. PJI is associated with the presence of biofilms and sessile bacteria that are encapsulated within a biofilm matrix are more difficult to eradicate than planktonic bacteria [1–7]. Biofilm is the single most important factor causing resistance of bacteria to antibiotics in the treatment of PJI. While modest antibiotic concentration can prevent biofilm formation, eliminating established biofilm is a different matter. Bacteria protected by biofilm requires concentrations that are orders of magnitude greater than the minimal inhibitory concentration for the planktonic forms of the same bacterium to eliminate resistant organisms that are protected by the glycocalyx.

A systematic review of the literature revealed that biofilm encapsulated bacteria requires MBEC of antibiotics that are several orders of magnitude (100-1000+) above the minimum inhibitory concentrations (MIC) sufficient to eradicate planktonic bacteria (Table 1). Currently, MBECs at the site of the joint infection are not achievable with traditional intravenous (IV) antibiotic therapy without systemic toxicity (Table 1). IV antibiotics generally do not achieve these levels of concentration in synovial fluid, but instead achieve levels around two to three times the MIC.

Even though extensive work has been done to develop adjuvant agents such as antibacterial peptides and chelating agents to reduce the resistance of biofilm bacteria to antibiotics, the only clinically viable method available now is to apply antibiotics directly to the affected joint where the implant resides to achieve concentrations high enough to approach MBEC. The use of antibiotic-impregnated polymethyl methacrylate spacers is the most common method used to deliver antibiotics directly into the joint as part of treatment of PJI. While intra-articular concentration of antibiotics is significantly higher when antibiotic-loaded spacers are used, the level is still an order of magnitude (perhaps thousands of times) lower than what is needed to eradicate the biofilm. Local delivery of antibiotics with antibiotic-laden bone cement does not apply a consistent dose for enough time, with most the elution occurring in the first 48-72 hours and by day 5, the concentrations are often sub-therapeutic [8]. Time is an important factor in management of biofilm and exposure to high concentrations for long periods enhances the ability to achieve MBEC.

Direct antibiotic infusion through an infusion pump can achieve extremely high local levels of antibiotics for a prolonged period.In addition, when the antibiotic is delivered through an external portal, it can be discontinued if toxicity or sensitivity occurs. Perry et al. were the first group to describe intra-articular instillation of antibiotics in 1992 [9]. They used an implantable pump with a catheter from the wound surface, to deliver 200-350 mg of amikacin in a 50mg/ml dilution for 8-15 weeks, to 72 patients with acute infections. Of these patients, 49 underwent debridement and retained their prostheses and 23 had their prostheses removed after the initial debridement. They only reported in detail on a subset of 12 patients (10 knees and 2 hips, median age of 59) with no prior history of infection and with a 37-month follow-up. Local levels of antibiotics were assessed by assaying wound drainage or synovial fluid and ranged from 150 ug/ml to 1688 ug/ml. Serum levels were 10ug/ml, except for one patient whose serum concentration rose to 13ug/ml. Two patients developed recurrent infection, one with the same organism *Staphylococcus aureus (S. aureus)* and the other patient was infected with *Staphylococcus epidermis,* after originally infected with *S. aureus.* In the series of 49 patients who retained their prostheses, 38 patients were infection free, however, follow-up times ranged from 1-58 months.

Fukagawa et al. reported on their experience with 15 patients (16 knees) treated for PJI with stable prostheses [10]. A causative microorganism was identified in eight patients. Patients were treated with open synovectomy, debridement, exchange of polyethylene insert and retained their implant. In the five patients with tumor megaprostheses, the anchors were retained. A Hickman catheter was inserted percutaneously and organism specific antibiotics (if an organism was cultured) were infused into the joint space twice per day until clinical signs of infection resolved, and white blood cell (WBC) count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) normalized, at which point the catheters were pulled. The mean infusion duration was 20.8 days +/- 11.7 days. Intra-articular antibiotics used were: amikacin (400 mg/day), gentamicin (80mg/day) and arbekacin (200 mg/day). No serum antibiotic levels were reported. All patients also received IV or oral antibiotic therapy for 1-3 months. All patients were considered infection free and clinically healed during the first follow-up period of 46.7 months (±25.7 months). However, four of the five knees treated with tumor megaprostheses developed recurrent infection after a mean of 28.3 (±26.1 months). These patients were treated with intra-articular antibiotics again for 13-22 days and the infection was clear at last follow-up. No local toxicity or infection at the catheter site was reported.

Tsumura et al. [11] reported on the treatment of early knee PJI in ten patients with continuous, concentrated, antibiotic irrigation for 7-29 days. Antibiotics were administered through a Salem double lumen catheter after debridement with implant retention. Eight of the 10 patients were infection free and able to retain the original prostheses. The two failures were the only patients with methicillin-resistant *Staphylococcus aureus* (MRSA). Antibiotics administered were: clindamycin, amikacin, cefotiam, imipenem, arbekacin, piperacillin, cefazolin, ampicillin and vancomycin. No serum or synovial antibiotic levels were reported.

In two recent publications, Whiteside et al. reported on a retrospective cohort of 18 total knee arthroplasty (TKA) patients with recurrent knee PJIs treated with single-stage (10 patients) or two-stage revision arthroplasty (8 patients), including 3 patients that required limb lengthening and soft tissue expansion [12,13]. Intra-articular antibiotic infusion using a Hickman catheter was performed as an adjunct to meticulous debridement. The authors administered 100 mg of vancomycin or 20 mg of gentamicin in 3 mL of saline into the joint space and increased the dosage to 500 mg of vancomycin or 80 mg of gentamicin in 8 ml of saline, every 12 or 24 hours as tolerated, once the wound was stable and dry. Patients were also treated postoperatively with 1 gm of IV vancomycin and 80 mg of IV gentamicin for 48 hours. The intra-articular antibiotics were continued for six weeks, with intra-articular vancomycin levels ranging from 10,233- 20,167 mg/L. Mean serum vancomycin peak and trough levels were 4.1+/- 1.2 µg/mL and 3.3 +/- µg/mL respectively. Three patients had to have a reduction in the antibiotic dose due to excessive rise in the level of antibiotics. Follow-up ranged from 2.3-12 years, with a mean of 6.1 years. One patient had a recurrent, postoperative infection at 13 months. No other patients had clinical or serological signs of infection and no patient was placed on chronic suppressive antibiotics. Similarly, Roy et al. compared synovial concentrations of antibiotics with IV vs. intra-articular administration in a subset of patients in the Whiteside study cohort, and found an average, peak intra-articular vancomycin concentration of 9,242 ± 7,608 mg/L following intra-articular antibiotic infusion compared to an average intra-articular concentration of 6.8 µg/mL following IV administration [14]. These data suggest with reasonable certainty that direct intra-articular infusion of antibiotics offers a significant benefit in treating resistant organisms, but certainly do not rise to the same level of evidence as would a RCT performed at the same center.

Revision after reinfected, two-stage revision total joint arthroplasty is an especially challenging clinical problem and is even more difficult when multiple failures have occurred. The complication rate of using antibiotic spacers is substantial including dislocation, fracture and migration of the spacer with bone loss that must be considered when contemplating a second two-stage exchange procedure. A revision with intra-articular antibiotic infusion may play a role in this scenario to reduce morbidity. Antony et al. described intra-articular antibiotic infusion as an adjunct to single-stage revision for previously failed single- or two-stage revision for knee, hip or shoulder PJI, in 57 patients with a mean age of 65 years [15]. Hickman catheters were used for intra-articular infusion of organism specific antibiotics for approximately 4-6 weeks, once or twice per day without concomitant systemic antibiotics. The intra-articular antibiotic dose administered was determined to be 50% of the serum dose given the enclosed space. Infection eradication was defined as negative culture, and normal ESR and CRP and 89.5% of patients were successfully treated at 11 months follow-up. Synovial levels of antibiotics were not collected.

TABLE 1. Therapeutic range, toxicity, minimum biofilm eradication concentration (MBEC), and minimum inhibitory concentration (MIC) of antibiotics used to treat biofilm-encapsulated bacteria

Antibiotic	Therapeutic Range	Toxic Plasma Concentration	*S. aureus*		*MRSA*		*P. aeruginosa*		*S. epidermidis*		*E. coli*	
			MIC	MBEC	MIC	MBEC	MIC	MBEC	MIC	MBEC	MIC	MBEC
Azithromycin	0.04-1	-			512	5120		2560				
Ceftazidime	<150	-					1-4	2560-5120				
Ciprofloxacin	2.5-4	11.5			0.06->32	256 - 1280	0.25-2	80-1280				
Clindamycin	<0.5	-			0.015 - 0.06	64 - >1024						
Colistin	1-4	-										
Daptomycin	6-10	-	0.25	600	0.125	1014						
Doxycycline	<10	30			0.064 - 0.125	64 - 128						
Erythromycin	0.5-6	12-15	1	6400	0.12 - >256	64 - >1024		2560				
Gentamicin	5-10	12	1	6400	0.06 - 64	1 - >256		512xMIC				
Linezolid	0.5-4	-	1	6400	1 - 2	4 - >1024						
Piperacillin	5-20	-					4-128	>5120				
Rifampicin	0.1-10	204	0.16	40								
Tobramycin	5-10	12-15	1	160-4000	1	≥8000	0.2-16	250-2560	32	≥8000	2	62.5-125
Vancomycin	<5-10	30	2	2000-8000	0.25 - 2	2000-8000			2	1000-8000		

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QUESTION 7: Can debridement, antibiotics and implant retention (DAIR) be utilized in patients with an acute chronic infection of a unicompartmental knee arthroplasty (UKA)?

RECOMMENDATION: In the event of acute infection following UKA, early DAIR can be considered. However, if initial treatment effort results in failure or chronic infection is present, the implanted prosthesis should be removed and a one-stage or two-stage conversion to total knee arthroplasty (TKA) should be performed in combination with antibiotic therapy.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 2%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

The main reasons for revision of UKA are loosening, progression of osteoarthritis to another compartment and infection [1]. The incidence of infection after UKA at 0.2 to 1% is lower than that reported after total knee arthroplasty (TKA) [1,2]. A distinctive feature of UKA infection is that both the prostheses and the native cartilage are involved [1]. This is in part attributed to the use of minimally invasive exposures, with less damage to the adjacent soft tissue and sparing of bone and ligamentous structures [3].

In the event of immediate or acute infection following UKA, early irrigation and debridement followed by antibiotic administration can be a proper treatment solution. However, if the initial treatment effort ends up in failure or chronic infection is present, the implanted prosthesis should be removed and a one- or two-stage revision surgery should be carried out [3]. Labruyere et al. reported on failures for nine infected UKA cases managed with one-stage irrigation, debridement and conversion to TKA in combination with three months of antibiotic therapy [1]. Of note, five of these cases first failed DAIR. Kim et al. reported management of five infected UKA cases with two-stage conversion to TKA [3]. Bohm et al. reported two infected UKAs, one of which was managed with one-stage conversion

TABLE 1.Summary of infected UKA cases in the literature

Author/Year	N (infected UKA cases)	Failed DAIR	Treatment	Failures	Follow-up
Labruyere 2015[1]	9	5	one-stage conversion to TKA (9)	0	Median 60 months
Bohm 2000[4]	2 (0.7% infection rate)	?	one-stage (1) two-stage (1)	1 (AKA)	Mean 4 years
Saragaglia 2013[5]	8 (2% of failed UKAs)	?	?	?	?
Kim 2016[3]	5 (0.3% infection rate)	?	two-stage (5)	?	?