Intra-Articular Antibiotic Delivery Systems for PJI

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Disasters in Arthroplasty
September 20, 2018
Miami, Fl

Disclosures

Potential conflict

Joint Purification Systems
Founder, Board member, Stock

Acelity/KCI
Consultant

No conflict

Link Orthopedics
Consultant, Speaker, Royalties

MicroPort Orthopedics
Consultant, Royalties

Current treatment for PJI

Cochran et al. (JOA 2016)
16,622 Medicare patients 2005-2011

Reinfection rates at one year

- Incision and Drainage (I&D) 28.2%
- I&D with Polyethylene Exchange 25.7%

- One-stage Exchange Arthroplasty 24.6%
- Two-stage Exchange Arthroplasty 19.0%

How are we *really* doing? Well… it depends on definition of success

Gomez et al. (2015 JBJS)

504 cases
- 82.7% achieved reimplantation
- 11.9% required additional spacers
- 36 patients died prior to stage 2


The Fate of Spacers in the Treatment of Periprosthetic Joint Infection

" Conclusions: The commonly held belief that two-stage exchange arthroplasty carries a high success rate for the eradication of periprosthetic joint infection may need to be reexamined."

Defining success

% reimplanted x % infection free = success rate

Table 2: **Proportion of all PJI Patients Who Achieve Re-Implantation and Clinical Success**

Study	No. of Studies	Stage 2 Reimplantation Rate	Stage 2 Reported Success Rate	Composite Success Rate
Gomez et al. [13]	1	417/504 (82.7%)	268/329 (81.4%)	67.3%
Berend et al. [14]	21	1407/1537 (91.5%)	1250/1407 (88.8%)	81.3%

Failure to complete treatment

Cancienne et al. (2017, 2018 JOA)

Medicare
Intent-to-treat as two-stage arthroplasty

PJI cases	% completing Stage 2 within one year
18,533 knee	61.6%
7,146 hip	60.2%

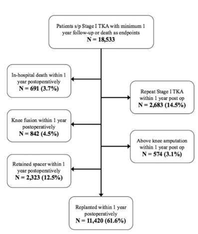
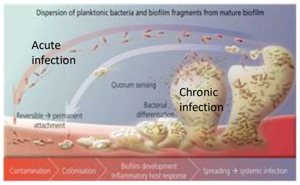


Fig. 1. Flow chart depicting the fate of patients who underwent knee arthroplasty prosthesis removal and cement spacer placement for infection. TKA, total knee arthroplasty.

The problem? B I O F I L M eradication

- *Planktonic* state
  MIC (Minimal Inhibitory Concentration)
- *Biofilm based* state
  MBEC (Minimal Biofilm Eradication Concentration)



MBEC may be 100 to 1,000 times the MIC !!!

Minimal Biofilm Eradication Concentration

Table 1. Therapeutic Ranges and MBEC Values for Various Antibiotics

Antibiotic	Therapeutic Peak (mg/L; ug/mL)	MBEC (mg/L; ug/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

SOC: two-stage utilizing a spacer

- PMMA spacers have limited antibiotic elution abilities
- Combined w/ systemic antibiotics (limited by toxicity)
- Local antibiotic levels above MIC, but below MBEC
- Total abx released < 200 mg
- Duration 6-12 weeks

Table 2. Peak Local Antibiotic Concentrations via Cement Elution

Study	Cement Protocol	Peak Joint Concentrations
Masri et al [8]	ALCS: 1.2 to 4.8g of tobramycin and 1 to 2g of vancomycin per 40g pack	1.25 to 16.97 mg/L
Hsieh et al [7]	ALCS: 4 g vancomycin powder and 4g aztreonam per 40g pack	Vancomycin: 1538 mg/L; Aztreonam: 1003.5 mg/L
Anagnostakos et al [9]	ALCS + beads: 1g gentamicin and 4g vancomycin per 40g 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

The solution? Intraarticular antibiotic delivery (IAA)

Treatment of acutely infected arthroplasty with local antibiotics. Davenport K, Perry CR: J Arthroplasty June, 1991

Clinical results of infected total knee arthroplasty treated with intraarticular antibiotics. Melaragno P, Whiteside L: 67th AAOS 2000

Direct exchange treatment of septic total joint arthroplasty with intraarticular infusion of antibiotics: technique and early results. Nayfeh T, Whiteside L: Orthopedics Sept 2004.

- 34 cases; 94% success rate
- Intraarticular levels reported 100-500x higher than spacer + systemic

2005: IAA *combined* with NPWT for a 7 day two-stage exchange

Why NPWT?

- *Edema reduction* lowers pressure compressing capillaries allowing increased O_2 delivery
- Tension applied to cells stimulates replication and *neovascularization*, thereby promoting granulation tissue
- Allows high volume *fluid exchange*

Stage 1 technique

Debridement complete

NPWT sponge placement

Local intraarticular antibiotic delivery system

Infusion line

Evacuation line

Protocol: IAA/ NPWT for 7 day interstage

- Tobramycin 80 mg/50 ml NS infused once *daily*.
  Soak time 2 hrs
- Vancomycin 3000 mg/1200 ml NS; infused 50 ml aliquots *hourly*.
  Soak time 30 min, VAC time 30 min. Total time 22 hrs.
- Total antibiotic load delivered over 7 days:
  tobramycin 560 mg
  vancomycin 21,000 mg
- Concentration:
  tobramycin 1600 ug/ml
  vancomycin 2500 ug/ml

In vitro studies supporting dose and duration

Minimum biofilm eradication concentration decreases during multi-day anti microbial exposure in vitro. Overstreet D, McLaren A, et al: MSIS 2015 (Cleveland, OH)

- Staph epi, S. aureus, MRSA, E. coli, P. aeruginosa
- Staphylococcal strains had MBEC **8,000** ug/ml or higher after one day vancomycin exposure. After **five days exposure, MBEC 2,000** ug/mg or less
- Similar findings for gram (-) organisms exposed to tobramycin

Does the MBEC decrease with in vitro exposure to anti microbial longer than 5 days?

MBEC decreases with long-term exposure to antimicrobials. Castaneda P, McLaren A, et al: 2016 MSIS (Charlotte,NC)

- S. Aureus and MRSA biofilms were exposed to vancomycin, tobramycin, and combo for 2,4,6 and 8 weeks in vitro
- Conclusion: Even when exposure time is 8 weeks, MBECs do not fall within *systemically achievable* levels

Biofilms can persist after "traditional " local (spacer) + systemic antibiotics

My initial experience (2005-2009) with the 7 day two-stage

Seven day abbreviated two-stage exchange arthroplasty for treatment of peri-prosthetic joint infection: 2-6 year results. de Beaubien B, Ekpo T, Parvizi J: 2012 EBJIS, (Montreux, Switzerland)

- Retrospective, one surgeon
- 73 consecutive patients with chronic PJI
- 10 patients excluded
- Reimplantation in 96%

Results 2005-2009

- Failure defined as recurrence of infection requiring revision
- Follow up 2-6 yrs (mean 4y)
- Success rate **89.1%** (57/64)
- 7 failures
- 6 patients underwent further surgery; all considered infection free

My latest data (March 2014 to Dec 2016)

- 66 consecutive patients treated with IAA /NPWT
- Updated antibiotic dosage, timing and automated pump
- At least 1 yr follow up
- Chronic PJI (sx lasting at least 4 weeks) per Tsukayama et al
- Diagnosis per MSIS 2018
- Primary outcome measured as relative risk of a **composite** outcome: the proportion of hip or knee PJI patients who had a revision prosthesis implanted by 12 weeks post Stage 1 surgery ***and*** showed no signs of infection, per the Delphi criteria, between implantation and one year.

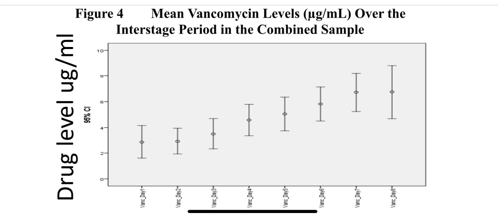
Demographics

Age (years)	64.95, range 45-88
Knee, n	43 (65.2%)
Hip, n	23 (34.9%)
Male, n	42 (63.6%)
Diabetes, n	27/65 (41.5%)
BMI, mean	35.40, range 22.24 to 54.82
Charlson Comorbidity Index, mean	3.48, range 0 to 9

Results

- Treatment success (Primary Composite Endpoint) in 57/66 patients (86.4%).
- Median interstage duration 7.0 days. 65/66 patients reimplanted within 9 days. One pt had repeat washout, but reimplanted day 13. 100% reimplanted.
- Mortality rate 3.0% (2 patients).
- Elevated sCr >50% or >0.3 mg/dl in 48 hrs occurred in 13 patients, all resolved without clinical intervention or medication of therapy.

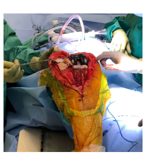
Interstage vancomycin serum levels

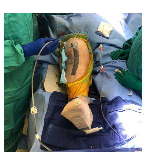
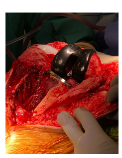


Conclusions

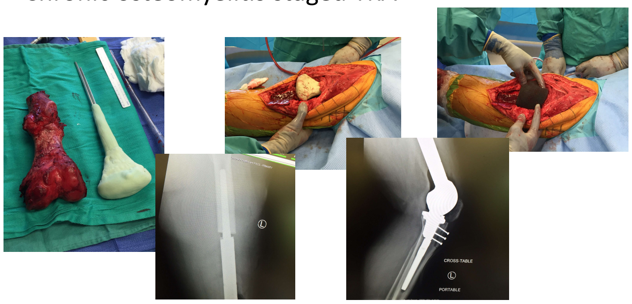
- Biofilm eradication is key to eliminating chronic PJI
- MBEC levels required for 5 days duration
- Local delivery is necessary, systemic therapy is not capable
- NPWT is helpful as adjunct therapy

DAIR combined with IAA



Chronic osteomyelitis staged TKA



Thank you!

- Delphi criteria: (1) infection eradication, characterized by a healed wound without fistula, drainage, or pain, and no infection recurrence caused by the same organism strain; (2) no subsequent surgical intervention for infection after reimplantation surgery; and (3) no occurrence of PJI-related mortality.