PJI Treatment: Time to Reassess the Strategy?

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Disclosures

Consulting – Solventum (3M Company), Stryker

Research Support – Stryker, Zimmer Biomet, Solventum, Ferring Pharmaceuticals, Microgen Dx, Osteal Therapeutics, OREF

Patent - Magnetic Glycol Chitin-Based Hydrogel Nanocomposite for Combined Thermal and D-Amino Acid Assisted Biofilm Disruption






Objectives

- Identify some of the failure reasons of two-stage revisions and how to potentially mitigate them.
- Discuss alternatives including one-stage revision and the concept of 1.5 stage revision.
- Review some of the innovative treatments that are going through translational studies.

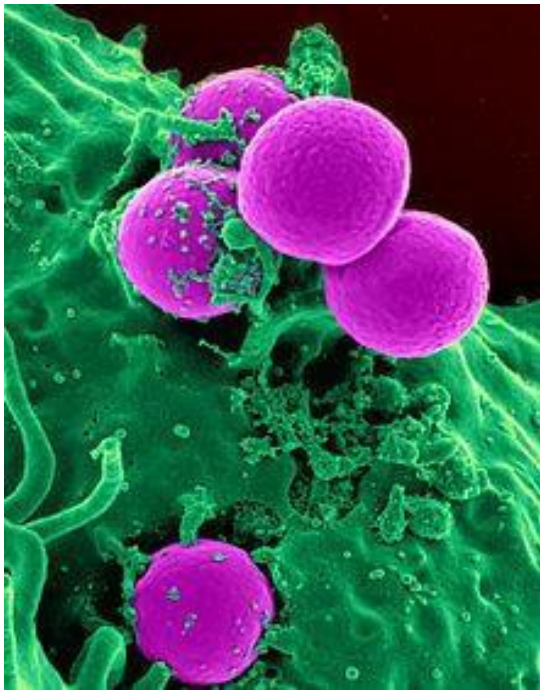
The Challenge

- Rates of reinfection after 1-stage: 24%[1]
- Rates of reinfection after 2-stage: 20%[1]
- **Five-year mortality after revision for PJI is 26%[2]**

1. Parvizi J, et al. *Act Ortho*. 2008;79(3):335-41
2. Zmistowski B, et al. JBJS. 2013:18;95(24):2177-84

Two–Stage Exchange Arthroplasty

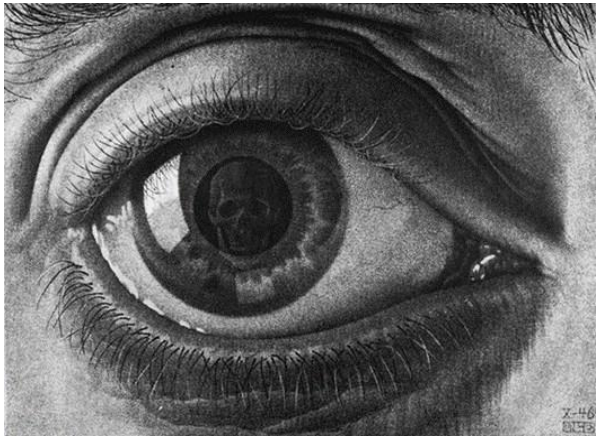
- MRSA infections 10 times (OR) more likely to fail[1]



1. Salgado C, et al. *CORR*. 2007;461:48-53
2. Image: en.Wikipedia.org

These Outcomes Are Worse When:

- Cultures are negative (>30%)
- 2nd stage revision misdiagnosis of persistent infections



Sequela…

Greater Prevalence of Mental Health Conditions in Septic Revision Total Knee Arthroplasty: A Call to Action

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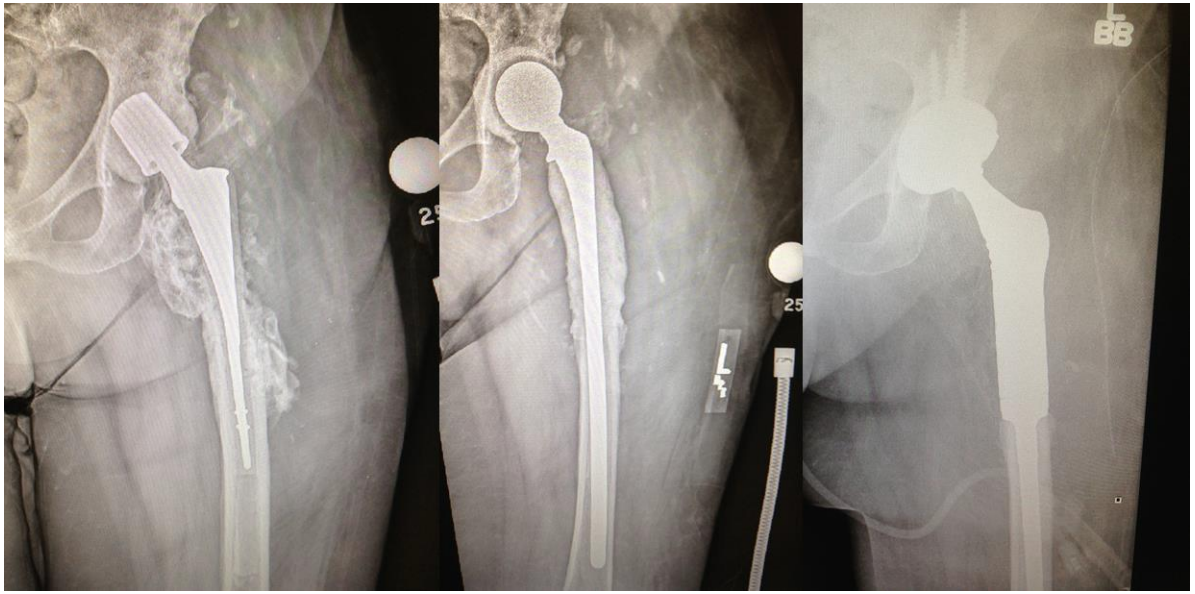
J Knee Surg 2022;35:190–197.

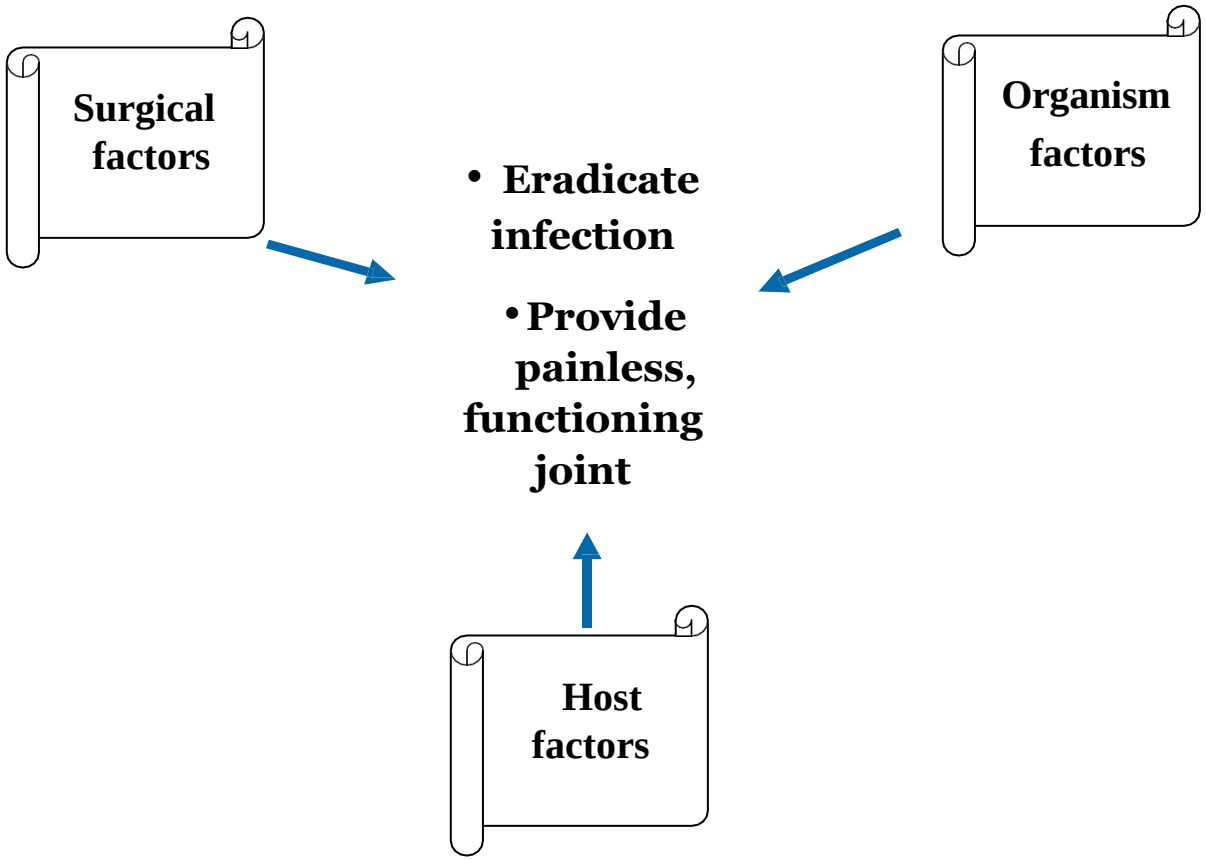
- Prevalence of mental conditions: 22.7%
- Depression
- Alcohol abuse
- Drug abuse

2X

Treatment Options



Goals of Treatment



MSIS PJI Classification

Category	Grading	Description
Infection type	I	Early postoperative infection (<4 weeks postoperative)
	II	Hematogenous infection (<4 duration)
	III	Late chronic infection (>4 weeks duration)
Systemic host grade (medical and immune status)	A	Uncompromised (no compromising factors)
	B	Compromised (1-2 compromising factors)
	C	Significant compromise (> 2 compromising factors) or one of the following:
		Absolute neutrophil count <1000
		CD4 T cell count < 100
		Intravenous drug abuse
		Chronic active infection other site
		Dysplasia or neoplasm of immune system
Local extremity grade	1	Uncompromised (no compromising factors)
	2	2 Compromised (1-2 compromising factors)
	3	Significant compromise (> 2 compromising factors)

Systemic Compromising Factors and Local Wound

Compromising Factors:

Systemic Host-Compromising factors (Medical and Immune)

- Age ≥ 80 years
- Alcoholism
- Chronic active dermatitis or cellulitis
- Chronic indwelling catheter
- Chronic malnutrition (albumin ≤ 3.0 g/dL)
- Current nicotine use (inhalational or oral)
- Diabetes (requiring oral agents and/or insulin)
- Hepatic insufficiency (cirrhosis)
- Immunosuppressive drugs (methotrexate, prednisone, cyclosporine)
- Malignancy (history of, or active)
- Pulmonary insufficiency (room air arterial blood gas O2 < 60%)
- Renal failure requiring dialysis
- Systemic inflammatory disease (rheumatoid arthritis, systemic lupus erythematous)
- Systemic immune compromise from infection or disease

Local Extremity (Wound) – Compromising factors

- Active infection present > 3-4 months
- Multiple incisions (creating skin bridges)
- Soft tissue loss from prior trauma
- Subcutaneous abscess >8 cm^2
- Synovial cutaneous fistula
- Prior periarticular fracture or trauma about joint (especially crush injury)
- Prior local irradiation to wound area
- Vascular insufficiency to extremity (absent extremity pulses, chronic venous stasis disease, significant calcific arterial disease)

Classic Treatment Options

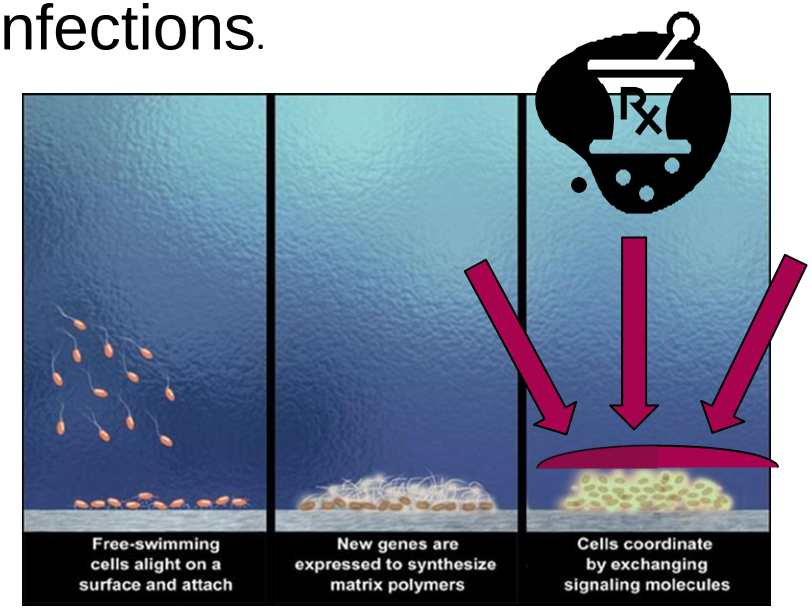
- Antibiotic suppression alone
- Irrigation and Debridement
- Debridement-Antibiotics-and-Implant-Retention (DAIR)
- Prosthesis Removal
  - One-stage exchange arthroplasty
  - Two-stage exchange arthroplasty
- Arthrodesis
- Amputation / Disarticulation

Treatment Options

Treatment	Relative Indications
Antibiotics Only	Patient C with well fixed implants
I&D / DAIR (doble)	Patient A or B with Extremity 1-2 (well fixed components, mega-prothesis, long stems)
1 stage revision	Patient A or B with Extremity 1 (**+ cultures with susceptibility to antibiotics**)
1.5 revision	Any patient with Extremity 1-2 (Acceptable Bone Stock)
2 stage revision	Only patients with extensive bone loss or needing soft tissue reconstruction
Arthrodesis	Patients A or B with Extremity 1-2
Amputation / Disarticulation	Any Patient with Extremity 3

Biofilm

- The formation of biofilm is what determines the difference in treatment and success between acute and chronic infections.



Three Distinct Reservoirs of Bacterial Biofilm Including:

1. Staphylococcal abscess communities in the local soft tissue and bone marrow
2. Glycocalyx formation on implant hardware and necrotic tissue
3. Osteocyte-lacuno canalicular network (OLCN) of cortical bone

REVIEW ARTICLE OPEN

Evolving concepts in bone infection: redefining "biofilm", "acute vs. chronic osteomyelitis", "the immune proteome" and "local antibiotic therapy"

Elysia A. Masters[1,2], Ryan P. Trombetta[1,2], Karen L. de Mesy Bentley[1,3,4], Brendan F Boyce[1,3], Ann Lindley Gill[5], Steven R. Gill[5], Kohei Nishitani[1,6], Masahiro Ishikawa[1,6], Yugo Morita[1,6], Hiromu Ito[6], Sheila N. Bello-Irizarry[1], Mark Ninomiya[1], James D. Brodell Jr.[1], Charles C. Lee[1], Stephanie P. Hao[1], Irvin Oh[1,4], Chao Xie[1,4], Hani A. Awad[1,2,4], John L. Daiss[1,4], John R. Owen[7], Stephen L. Kates[7], Edward M. Schwarz[1,2,3,4,5] and Gowrishankar Muthukrishnan[1,4]

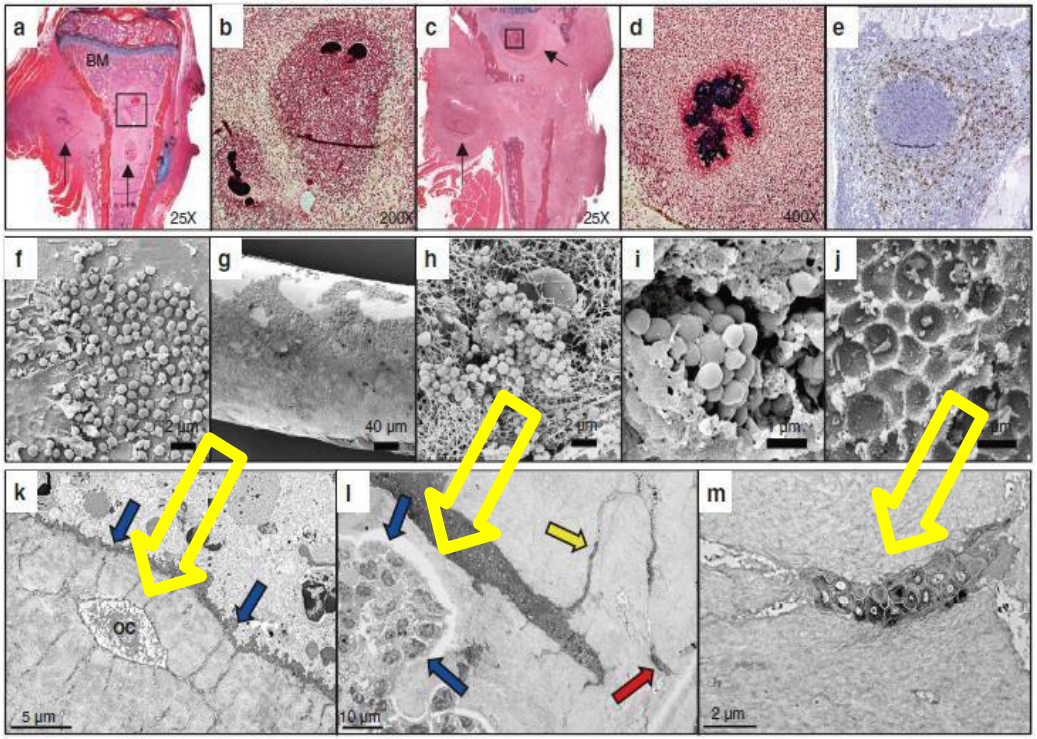
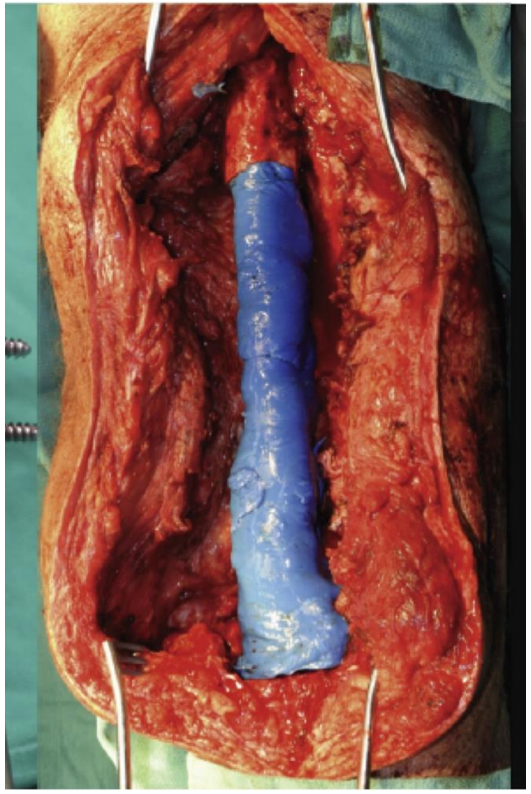


Fig. 2 Three distinct reservoirs of bacteria in chronic osteomyelitis. Chronic implant-associated osteomyelitis was established in mice with *S. aureus* as previously described,[84,93,117,267] and the bacterial burden: (1) in *Staphylococcus* abscess communities (SACs) assessed by histology (**a**–**e**), (2) on the implant assessed by SEM (**f**–**j**), and (3) in cortical bone assessed by TEM (**k**–**m**) is shown. Micrographs of orange G/alcian blue-stained histology of tibiae 7 days (**a**) and 14 days (**c**) post-infection are shown highlighting SACs (arrows) in the bone marrow and adjacent soft tissues. The boxed regions in (**a**), (**c**) are shown in Brown and Brenn-stained parallel section (**b**, **d**) to highlight the Gram+ bacteria (dark blue) surrounded by dead and dying neutrophils following NETosis (red cells), which are surrounded by a ring of macrophages (white layer). Chronic infection is clearly established by day 14, as evidenced by the complete replacement of hematopoietic bone marrow (BM) with inflammatory tissue, and the presence of M2 macrophages (brown cells) surrounding the SAC, as seen by immunostaining with antibody against arginase-1 (**e**). Biofilm formation on the implant commences with planktonic bacterial adhesion (**f**), as illustrated in this case of in vitro *S. aureus* attachment onto a stainless-steel wire incubated in a flow chamber system (×10 000). Following transtibial implantation, the planktonic bacteria rapidly transition to biofilm (**g**), seen as uniform glycocalyx coating the stainless-steel pin 14 days post-op (×200). High power images of the biofilm on the implant reveal cocci adhering to fibrin strands (**h**, ×2 500), and clusters of *S. aureus* forming bacterial pods (**i**, ×5 000). By day 14 post-infection, bacterial emigration from the pod is complete, as evidenced by the empty lacunae (**j**, ×30 000). *S. aureus* colonization of cortical bone commences with eradication of bone lining cells to expose canaliculi (blue arrows) leading to an embedded osteocyte (OC) (**k**, ×6 000). Subsequently, *S. aureus* invasion and propagation through osteocyte lacuno-canalicular network (OLCN) renders the biofilm bacteria (*) inaccessible to activated neutrophils outside the bone (blue arrows) (**l**, ×1 800). The uninhibited bacteria demineralize and consume the cortical bone to expands a canaliculus, and propagate into neighboring canaliculi (yellow arrow), to reach a distant osteocyte (red arrow). **m** High power TEM (×12 000) of the osteocyte in (**l**) killed by *S. aureus* bacterial occupation of its lacunar space

How Do We Control the Infection?

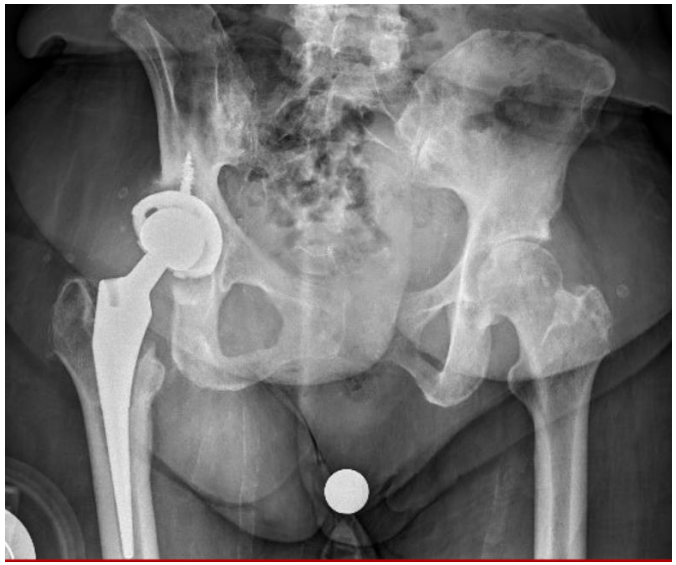
- Evacuation of purulence – solution dilutes pollution!
- Debridement of necrotic and non-viable tissue
- Disruption of biofilm (mechanical or chemical)
  - Change of modular parts vs explantation
- Local delivery of high-concentration antibiotics + systemic antibiotics

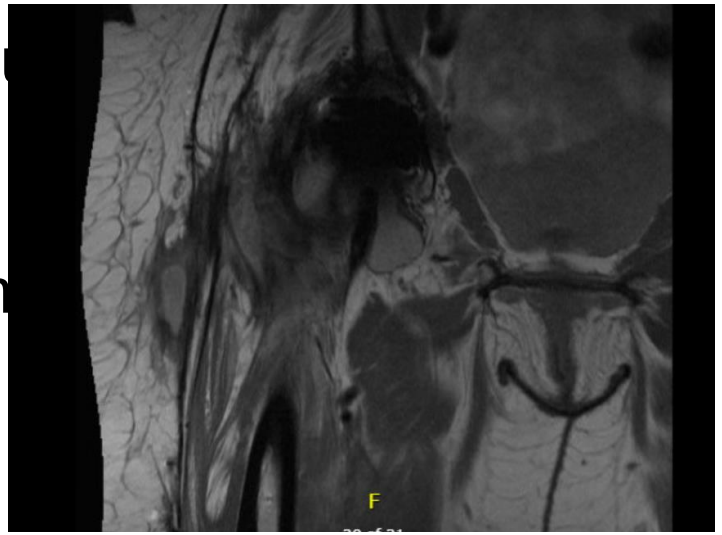
Extensive and radical – Tumor treatment



+ Mechanical & Chemical Disruption Biofilm
+ High Concentration of Local Antibiotics

Debridement – Issues?





- Time dependent – mature biofilm
- Lack of reproducibility
- Inability to identify the affected tissu implant
  - Need for staging? Cross-section imaging?
- Inability to disrupt biofilm – Bone?
- **–Inadequate debridement - FAILURE**

Contents lists available at ScienceDirect

The Journal of Arthroplasty

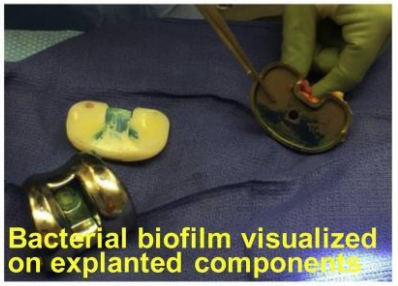
journal homepage: www.arthroplastyjournal.org

Complications - Infection

Methylene Blue—Guided Debridement as an Intraoperative Adjunct for the Surgical Treatment of Periprosthetic Joint Infection

Jeremy D. Shaw, MD, MS [a,*], Steve Miller, MD, PhD [b], Anna Plourde, MD [c], Daniel L. Shaw, BA [d], Rosanna Wustrack, MD [a], Erik N. Hansen, MD [a]

- 16 TKA patients with PJI undergoing first stage
- Dilute methylene blue (0.1%) in the joint
- Cationic biding with devitalized tissue and biofilm
- Results: More bacteria and neutrophils on stained tissues – 100% eradication 1Y



One Vs. Two-Stage Revision Arthroplasty

Clin Orthop Relat Res
DOI 10.1007/s11999-013-3294-y

Clinical Orthopaedics and Related Research®

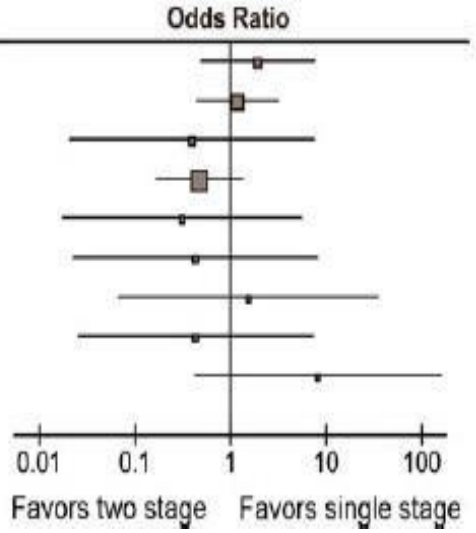
SURVEY

Single- or Two-stage Revision for Infected Total Hip Arthroplasty? A Systematic Review of the Literature

Hugh A. C. Leonard MA, BMBCh, Alexander D. Liddle BSc, MRCS, Órlaith Burke PhD, David W. Murray MD, FRCS(Orth), Hemant Pandit FRCS(Orth), DPhil

Received: 6 June 2013 / Accepted: 12 September 2013

Study or Subgroup	Single stage Events	Total	Two stage Events	Total	Odds Ratio
Carlsson et al. [4]	7	54	4	18	1.92 [0.49, 7.52]
Sanzen et al. [24]	17	72	8	30	1.18 [0.44, 3.12]
Hope et al. [11]	9	72	0	8	0.39 [0.02, 7.38]
Morscher et al. [21]	20	47	7	27	0.47 [0.17, 1.33]
Garvin et al. [8]	1	10	1	30	0.31 [0.02, 5.48]
Wilson & Dorr [28]	1	7	1	15	0.43 [0.02, 8.04]
Oussedik et al. [22]	0	11	2	39	1.53 [0.07, 34.29]
De Man et al. [4]	1	22	1	50	0.43 [0.03, 7.18]
Klouche et al. [12]	0	38	4	46	8.15 [0.42, 156.41]



No study showed a statistically significant difference in terms of reinfection rate

Surgical Treatment of Chronic Periprosthetic Joint Infection: One-Stage versus Two-stage

Thomas Fehring MD	OrthoCarolina	Principal Investigator
Javad Parvizi MD, FRCS	Rothman Institute at Thomas Jefferson University	Co-Principal Investigator
Antonia Chen MD, MBA	Rothman Institute at Thomas Jefferson University	Other Investigator
Michael Cross MD	The Hospital for Special Surgery	Other Investigator
Craig Della Valle MD	Rush University Medical Center	Other Investigator
Carlos Higuera MD	The Cleveland Clinic	Other Investigator
Bryan Springer MD	OrthoCarolina	Other Investigator

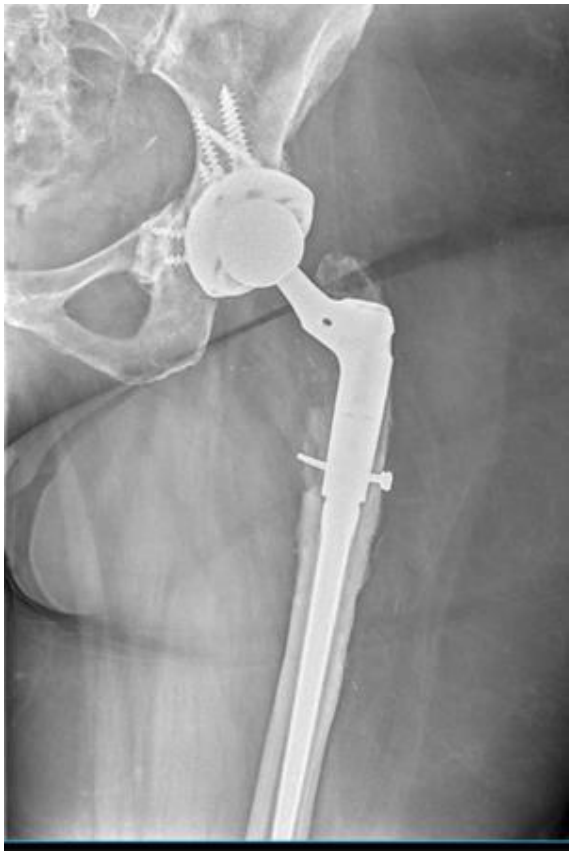
One-Stage vs. Two-Stage treatment for PJI: A Prospective, Randomized Trial
Fehring T, et al. – *AAHKS annual meeting 2023*

- Multicenter
- MSIS Criteria with known organisms. Fungal infections excluded
- Success @ 1 year defined as no additional surgeries
- N=321 (one stage N=164, two stage N=157)
- 16% (N=50) lost to follow up
- **One stage success was 98% vs. two stage 94% (p=.15). 61% reduced RR of failure with One stage**

One–Stage Exchange Arthroplasty

- Advantages
  - One surgical procedure
  - Shorter overall recovery
  - Decreased risk, patient burden and cost

- Disadvantages
  - Possible increased failure rate?
  - And then what???



One–Stage Exchange Arthroplasty

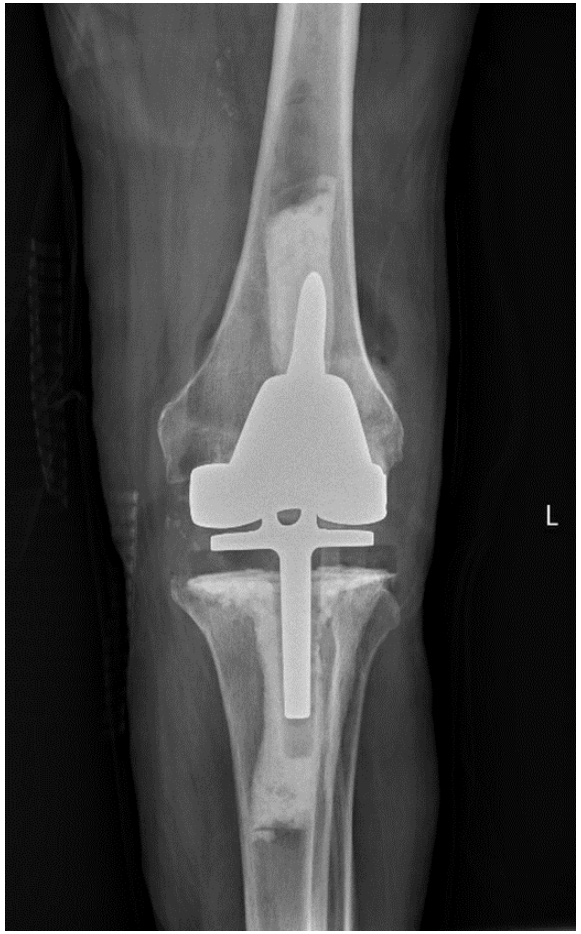
- Indications
  - Elderly patient?
  - Absence of sinus formation
    - Good soft tissue coverage

  - Unable to tolerate multiple procedures
  - Favorable identified organism
  - Favorable antibiotic profile
    - Able to suppress with oral antibiotics

1. Parvizi J, et al. Proceedings of the International Consensus Meeting on PJI. 2013, DataTrace.

1.5 stage revision

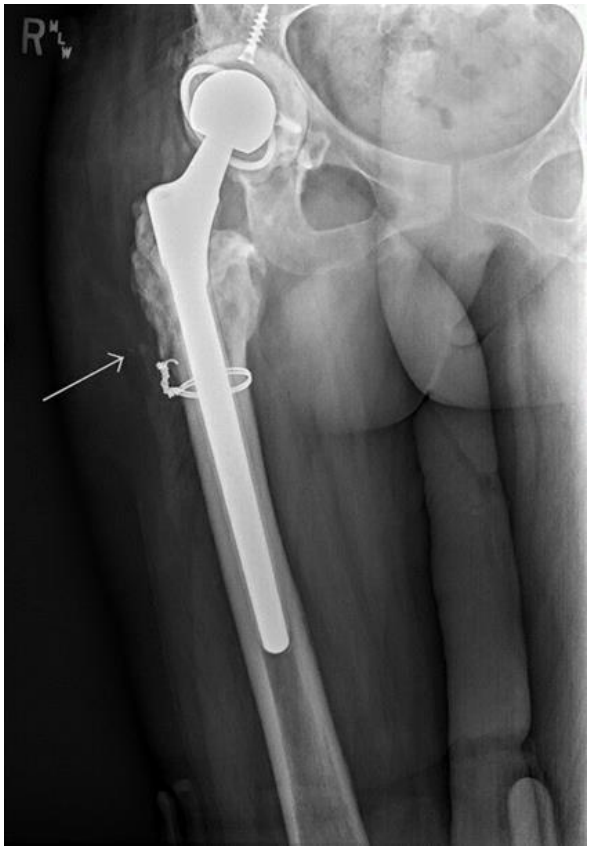
- Indications
  - Any patient, even high risk
  - Unable to tolerate multiple procedures
  - No identified organism
  - Soft tissues +/-
  - Acceptable bone stock



1.5 stage revision

- Advantages
  - 1 surgery
  - Shorter recovery
  - Decreased risk, cost and burden to the patient
  - If there is a failure, it is relatively easy to treat (remove)

- Disadvantages
  - Possible increased failure rate?
  - Need for 2nd surgery in the near future



Keys to Success with 1 and 1.5-Stage Exchange Arthroplasty

- Appropriate optimization
- Removal of all components and cement (oncologic approach)
  - Can be guided by methylene blue
- Mechanical and chemical disruption of the biofilm
  - Thorough and aggressive debridement – reaming of medullar canals
  - Use of antimicrobial solution (H_2O_2, Daiken's, Povidone Iodine, Chlorhexidine) + **IO Vancomycin**
- Partial closure and new draping of surgical site
- Replant with new instrument set
- Tailored antibiotic cement and hybrid fixation as needed (if + cultures)
- Meticulous closure (+/- Drain)
  - Use of incisional VAC dressings
- Chronic suppression for 3 months

One–Stage Exchange Arthroplasty

- Outcomes
  - 95% success rate in THA excluding MRSA[1]
  - 18% success rate if includes MRSA[2]
  - 100% success rate in 1 recent series[3]

- Key factor is the use of cemented components
  - THA hybrid fixation or use of high dose abx delivery (cement)
- Tailored antibiotics cement (2 abx have synergistic effect, hand mixed after initial mix – better elution)
- Tantalum and/or silver coated components ?

1. Singer J, et al. *CORR*. 2012;470:1461-71
2. Bradbury T, et al. *JOA*. 2009;24:101-4
3. George DA, et al. *JOA*. 2015

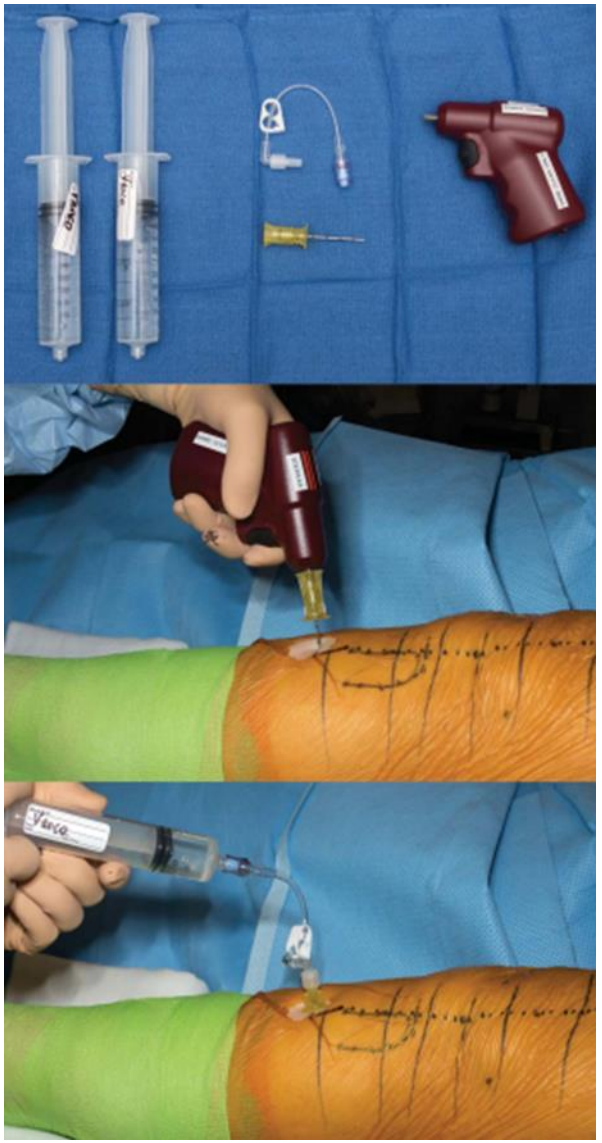
PJI eradication when ABX added to the cement, or there is local delivery of high concentration of ABX

– Steinbrik et al.	88%
– Wrobleski et al.	91%
– Rudelli et al.	93.7%
– Ji B et al.	87% (5 years all comers)
– Ji B, Zhang X et al.	67% (5 years in fungal PJI!)

BETTER!!!

Intraosseous Antibiotics

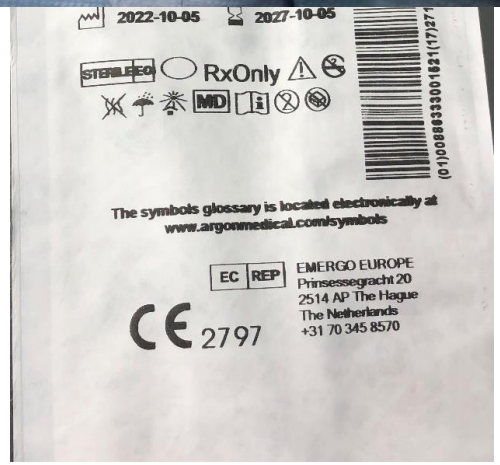
- Fehring et al. BJJ 2021
  - –35 TKA PJI DAIR with IO vancomycin
  - –26 acute hematogenous and 9 chronic
  - –1 year f/u
  - –92.3% success rate



Fehring, et al. BJJ 2021; 103-B(6 Supple A):185–190.

We use our own system

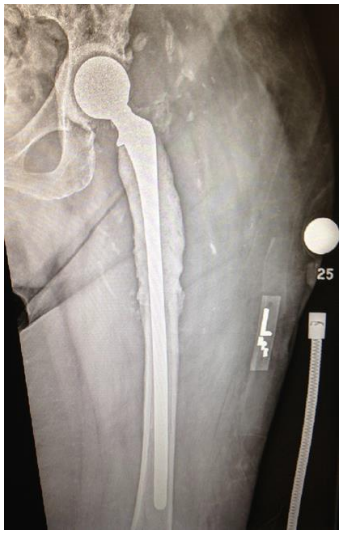
- Vancomycin IO (500mg in 150mL SSN) using canula (bone marrow bx needle)
- Proximal tibia using a drill (1.7mm) close to the pes anserinus bursa (65mL)
- 75mL in proximal femoral condyles (18Ga needle)
- 10mL in the patella
- Keep tourniquet for 1 hour

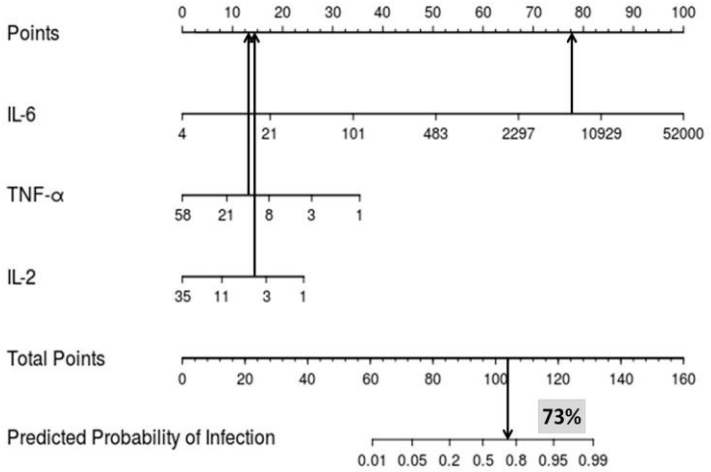


WHEN TO REIMPLANT?

BIG PROBLEM!!!

- No reliable test (neither serum nor synovial fluid) – MSIS criteria is not a good predictor for infection control
- D-Dimer has low specificity (different threshold)
- Combined biomarkers - nomogram (IL-6, IL-8, IL-1)
- <u>α-defensin is not a good biomarker to predict infection control</u>
- Lymph nodes biopsy?





D-DIMER

Clin Orthop Relat Res (2021) 479:1458-1468
DOI 10.1097/CORR.0000000000001738

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Selected Proceedings from the 2020 Musculoskeletal Infection Society Meeting
Guest Editor: Charalampos G. Zalavras MD, PhD

Plasma D-dimer Does Not Anticipate the Fate of Reimplantation in Two-stage Exchange Arthroplasty for Periprosthetic Joint Infection: A Preliminary Investigation

Tejbir S. Pannu MD, MS[1], Jesus M. Villa MD[1], Charles Engh III MS[2], Arpan Patel MS[2], Brett R. Levine MD[2], Nicolas S. Piuzzi MD[3], Carlos A. Higuera MD[1], Aldo M. Riesgo MD[1]

Predicting the fate of reimplantation

44 cases (17 THAs/27 TKAs) with min. 1-year FU

Plasma D-Dimer threshold= 3,070 ng/mL

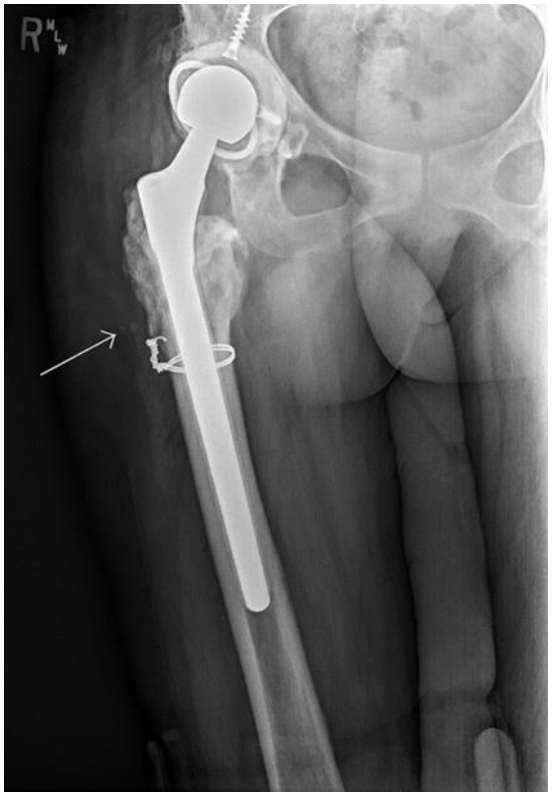
High sensitivity (90%) but low specificity (47%)

ROC-curve: AUC=0.62 (poor predictive accuracy)

<u>No ability to predict the fate of reimplantation</u>

THA Implants – 1.5 Spacer

- Cemented acetabular component
  - Harrington technique as needed
  - Semi-constrained liner
  - Tobramycin 2.4 g + Vancomycin 2 g / pack (variable) – synergy (sometimes antifungal)
  - High viscosity cement has better elution properties
  - Add antibiotic powder 30 seconds after the cement has been mixed
- Uncemented stem covered with cement in between splines
  - Monoblock, Conical, with splines stem type (i.e, Wagner)
  - Wires vs. cables if needed

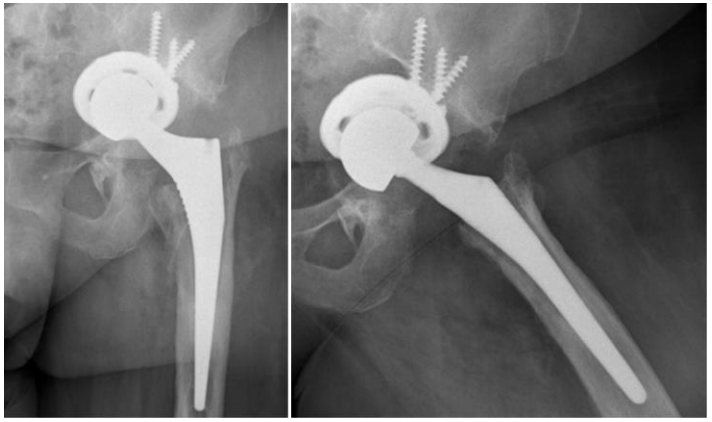


Surgical technique

Antibiotic cement spacer for isolated medial wall acetabular deficiency in the setting of infected hip arthroplasty

Kevin S. Weiss, DO [a], Kyle V. McGivern, DO [b], Juan C. Suarez, MD [c, *], Jesus M. Villa, MD [d], Preetesh D. Patel, MD [d]

Arthroplasty Today 4 (2018) 454–456

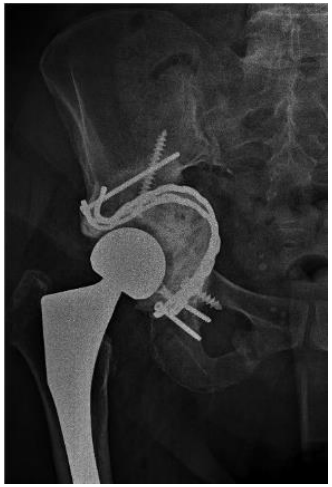


THE INTERNATIONAL HIP SOCIETY

Hip Reconstruction In Situ with Screws and Cement (HiRISC) construct to treat large acetabular bone defects

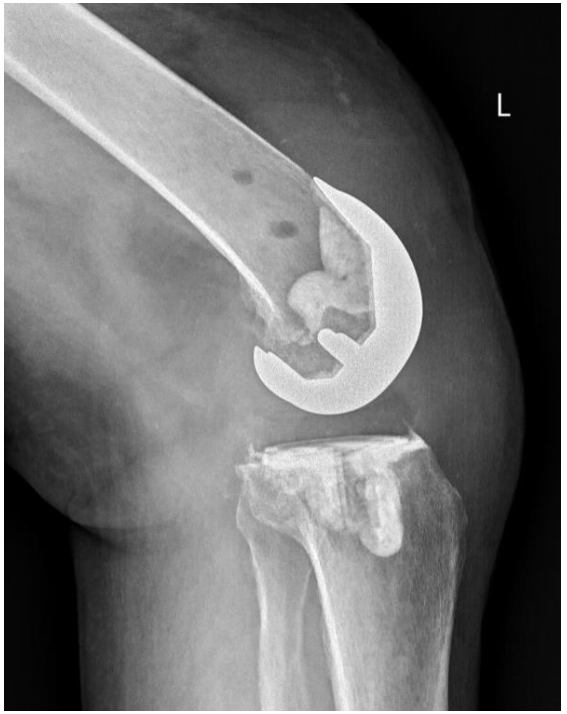
A CASE SERIES

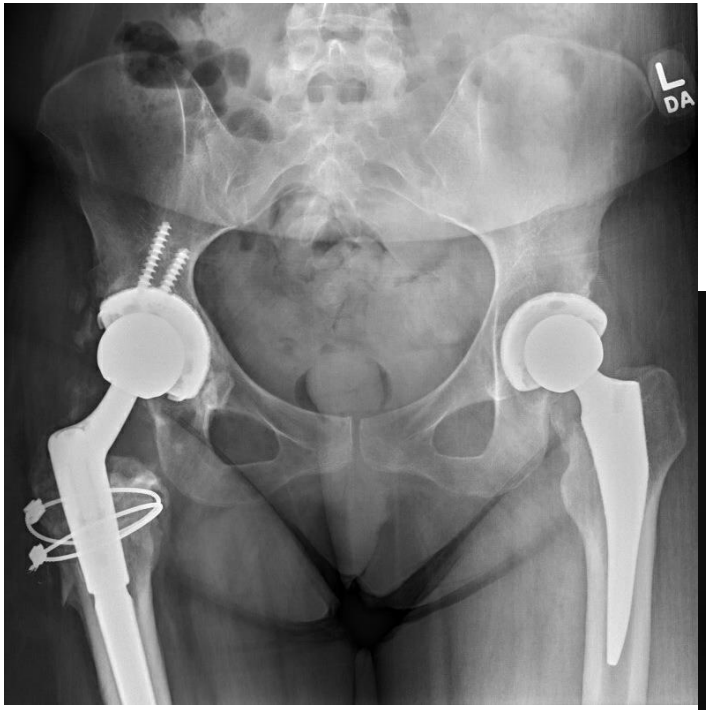
Cite this article: *Bone Joint J* 2024;106-B(5 Supple B):82–88.



TKA Implants – 1.5 Spacer

- Cemented components
  - Femur PS+
  - Polyethylene tibial component
  - Femur 1st the tibia.
  - Cement patella when bone available
  - Tobramycin 2.4 g + Vancomycin 2 g / pack (variable) – synergy (sometimes antifungal)
  - High viscosity cement has better elution properties
  - Add antibiotic powder 30 seconds after the cement has been mixed

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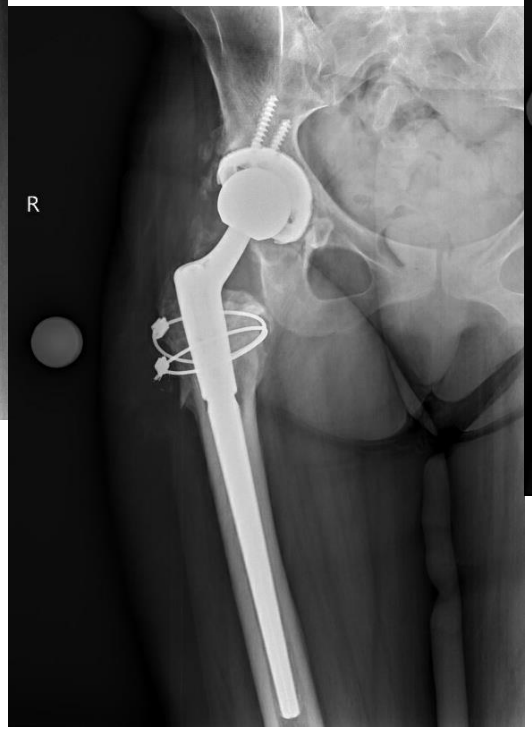
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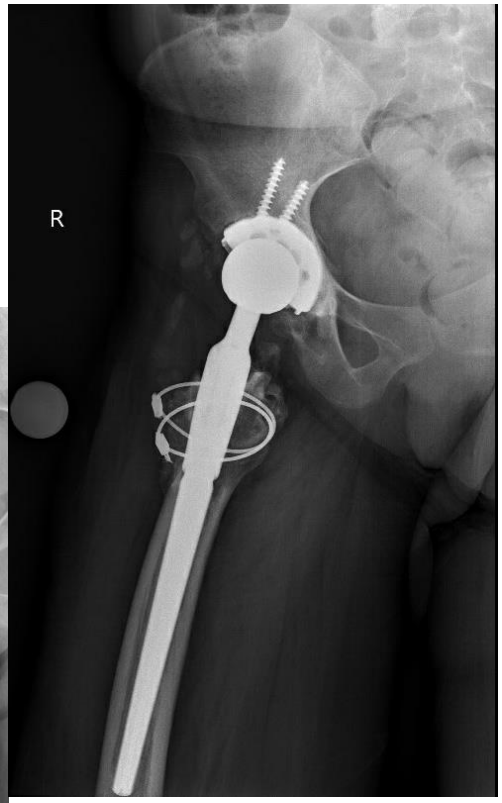
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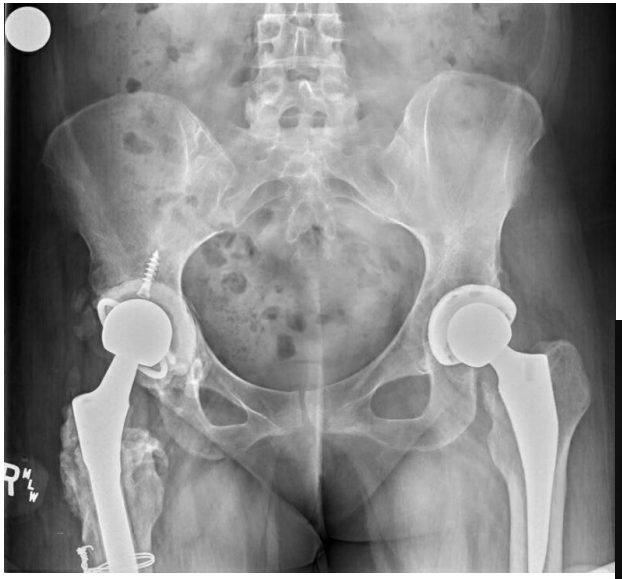

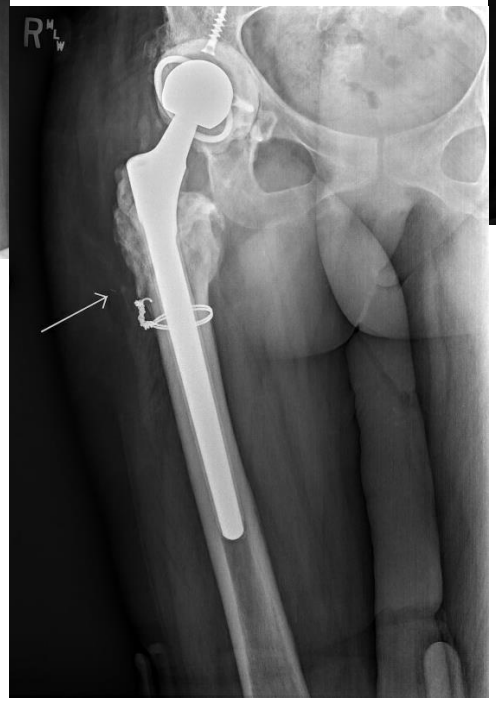

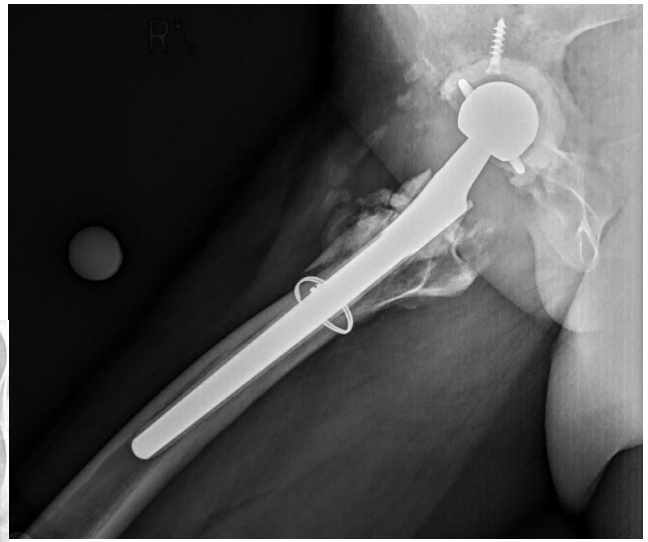

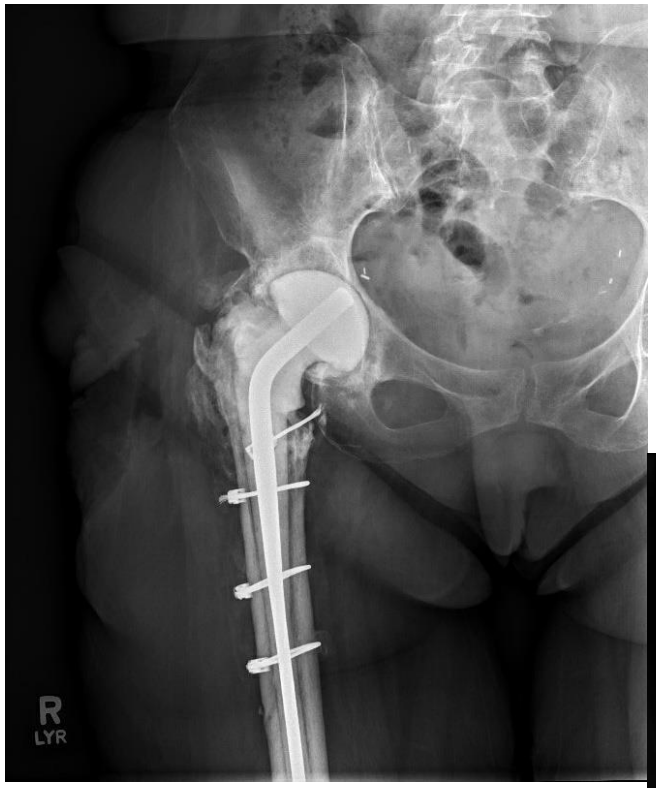
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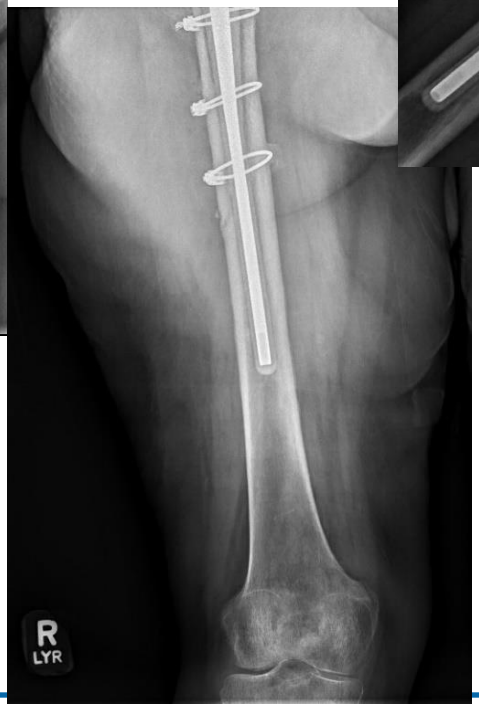
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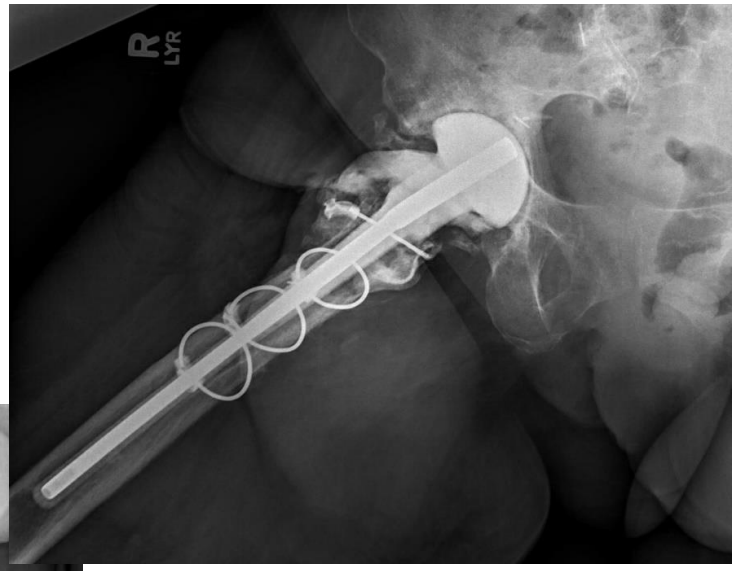
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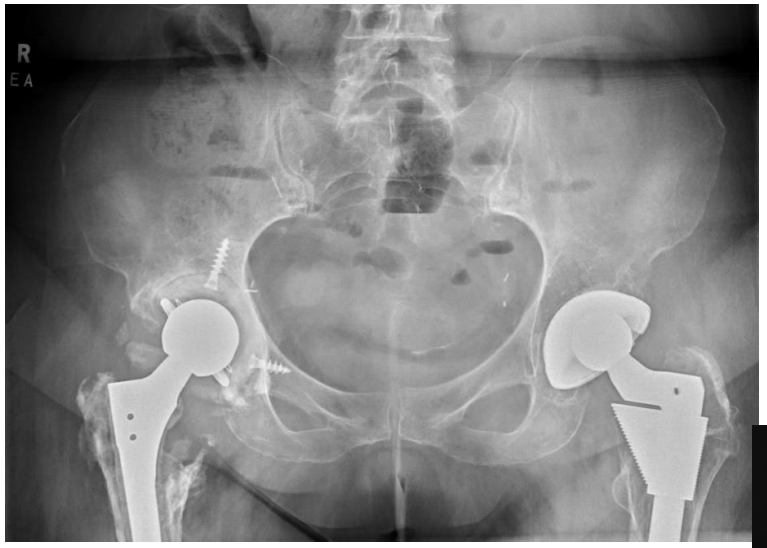
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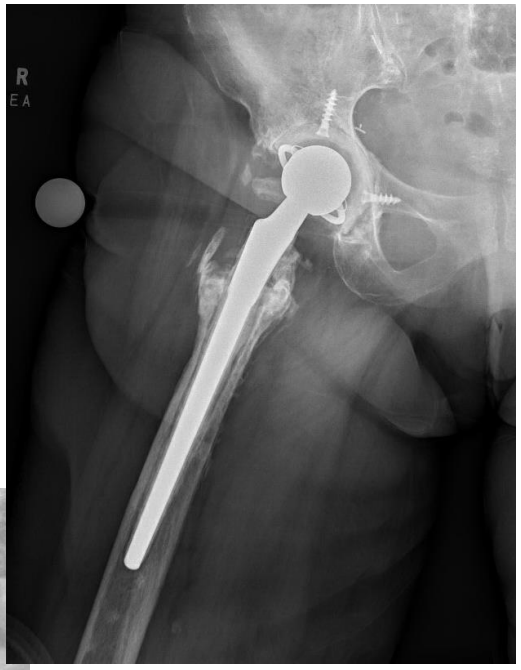
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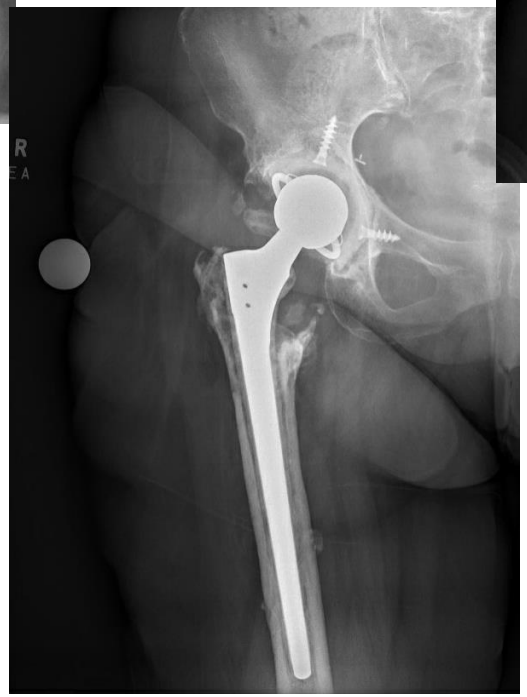
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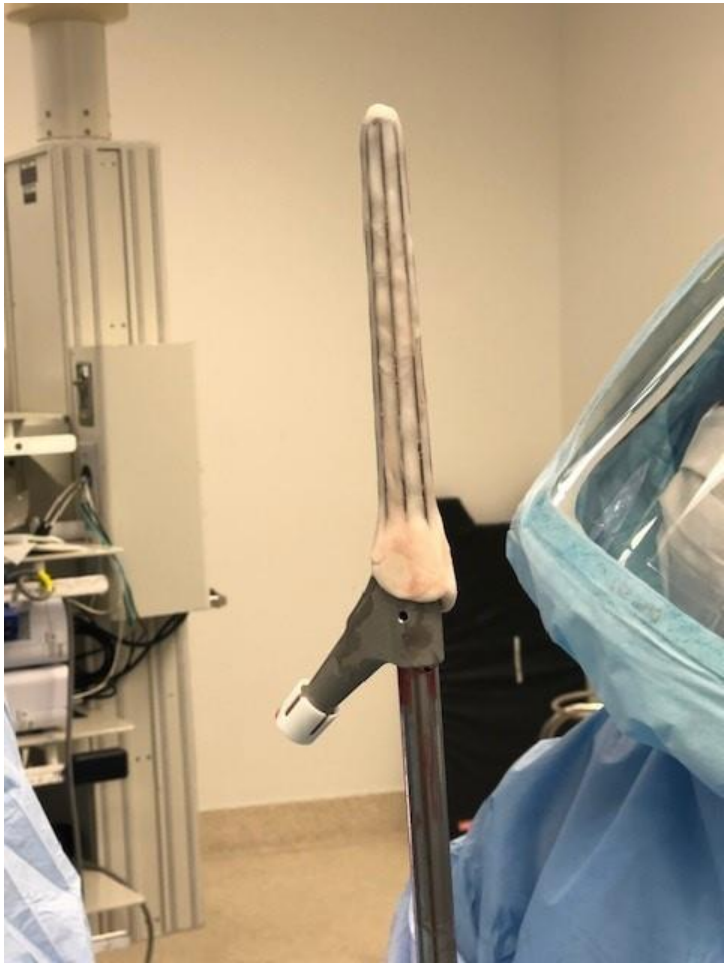

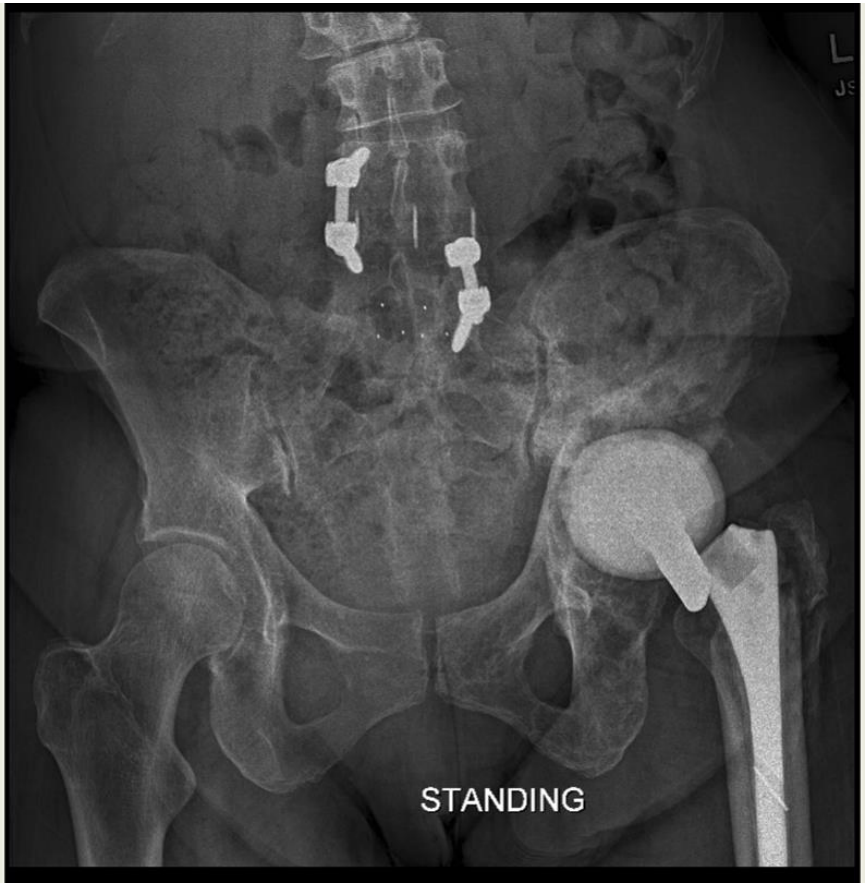
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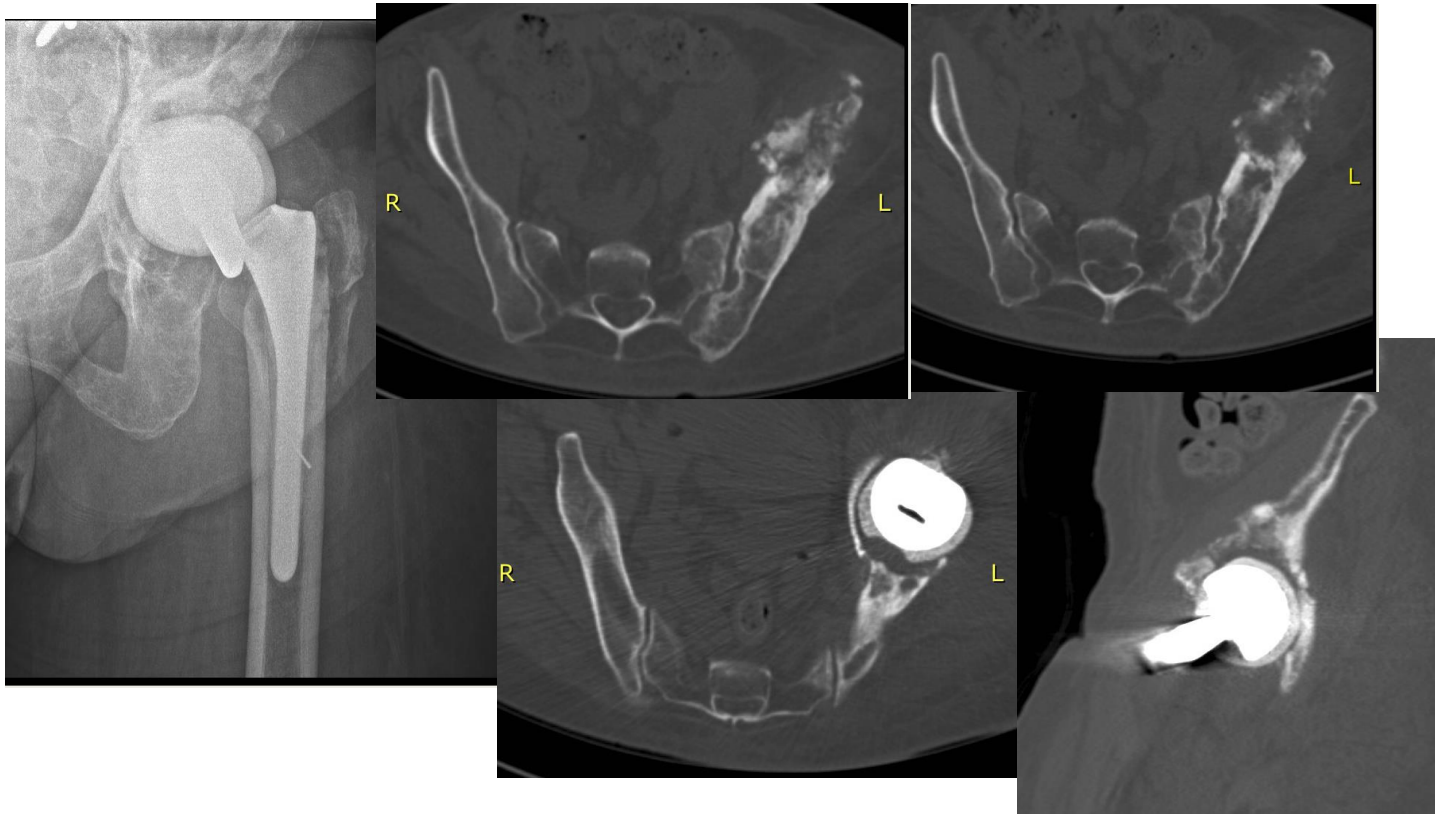
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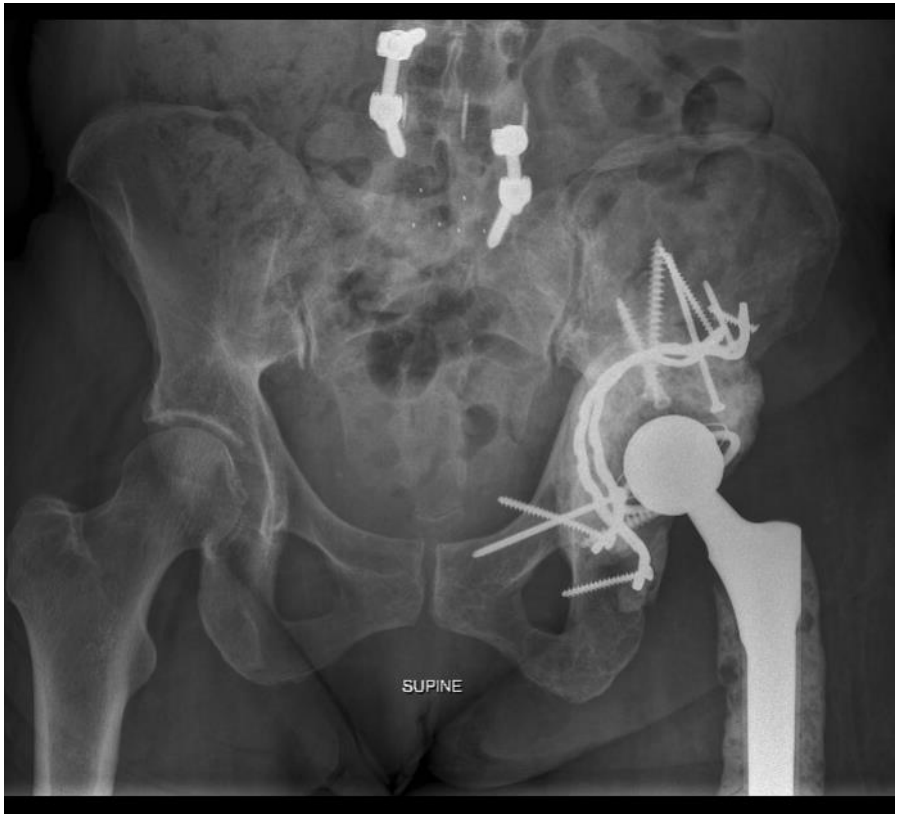
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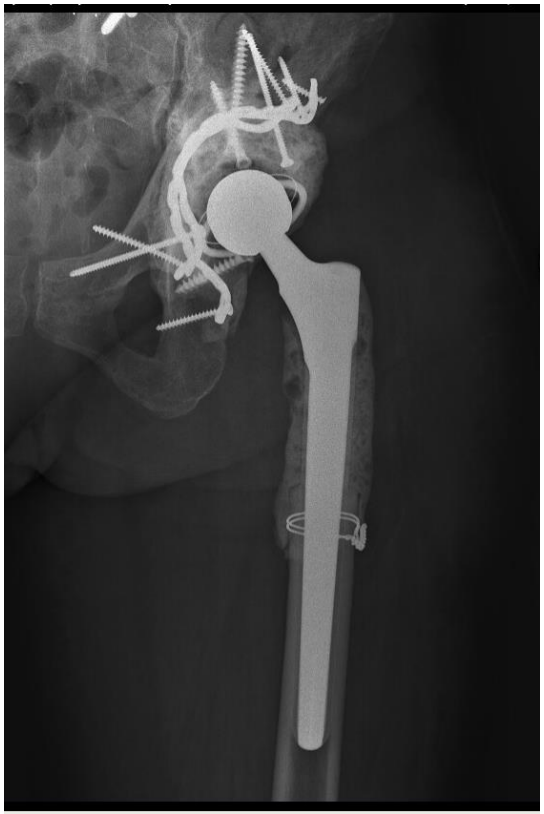

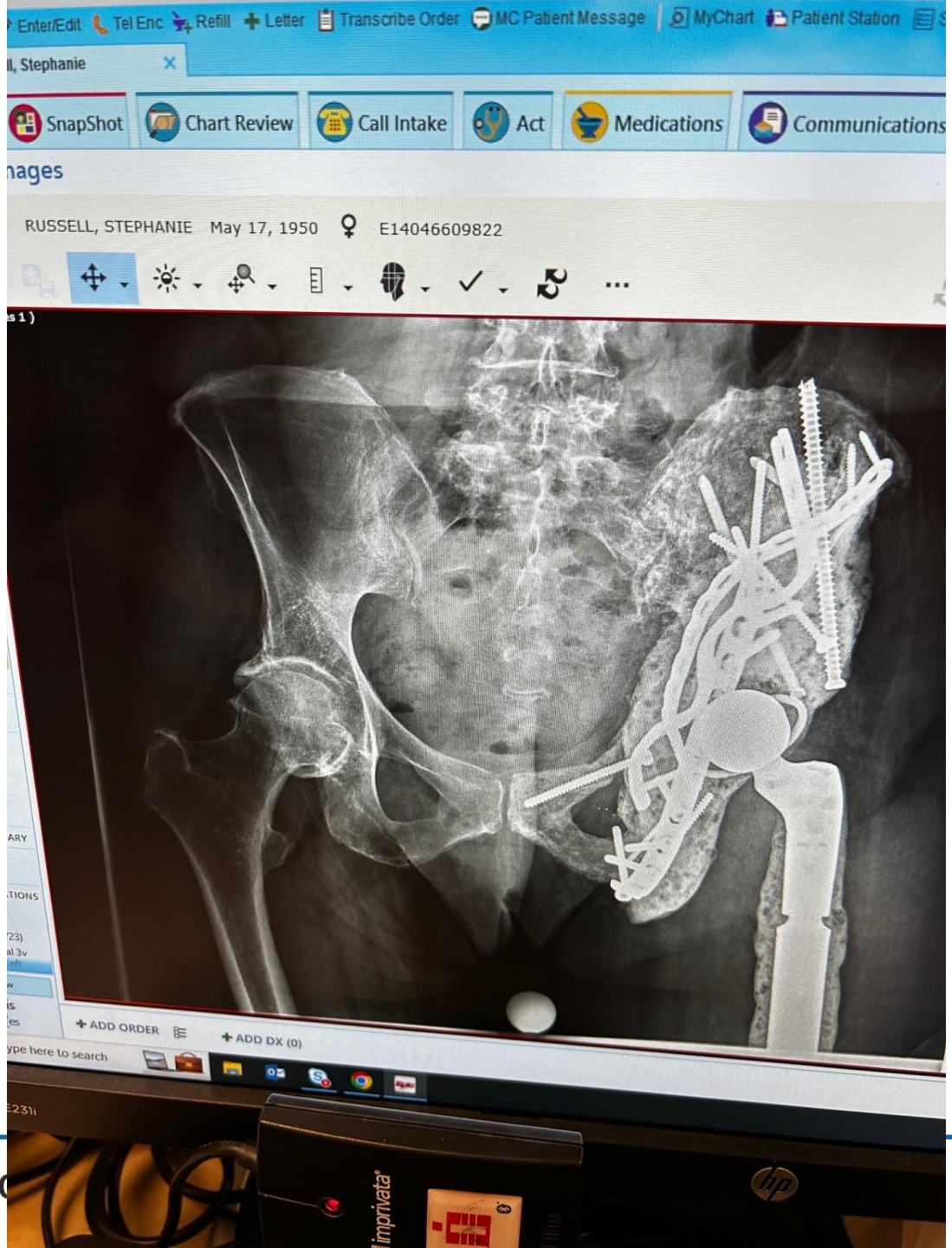
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Letter
Transcribe Order
MC Patient Message
MyChart
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Medications
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RUSSELL, STEPHANIE May 17, 1950
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ADD ORDER
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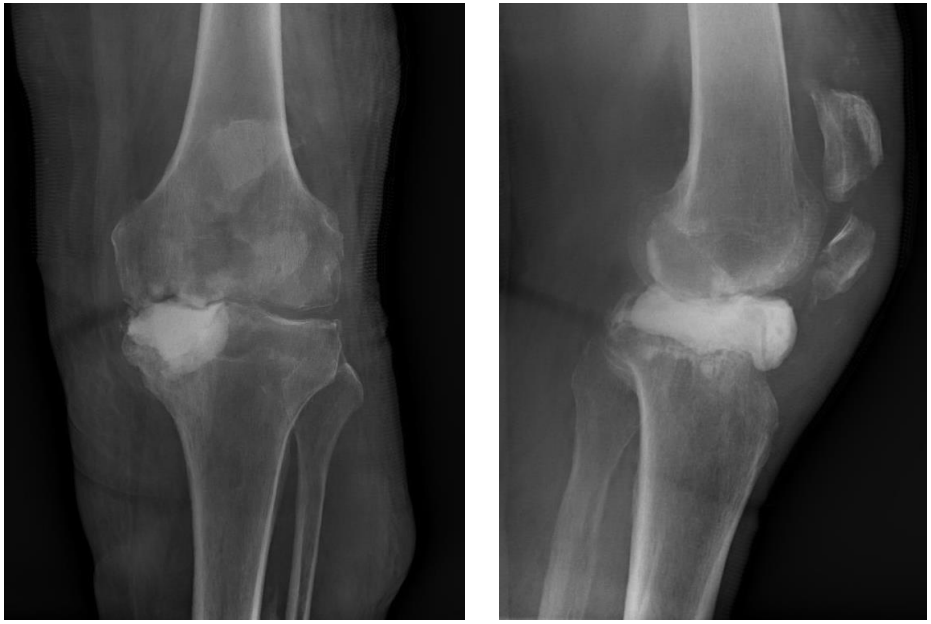

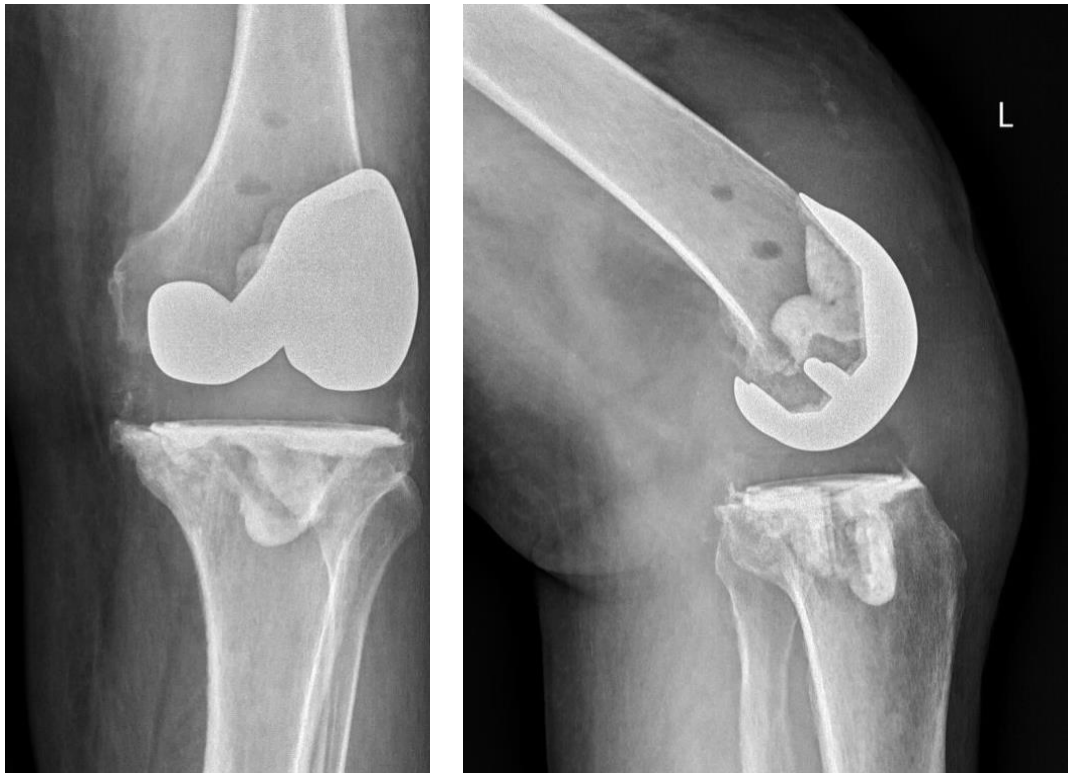
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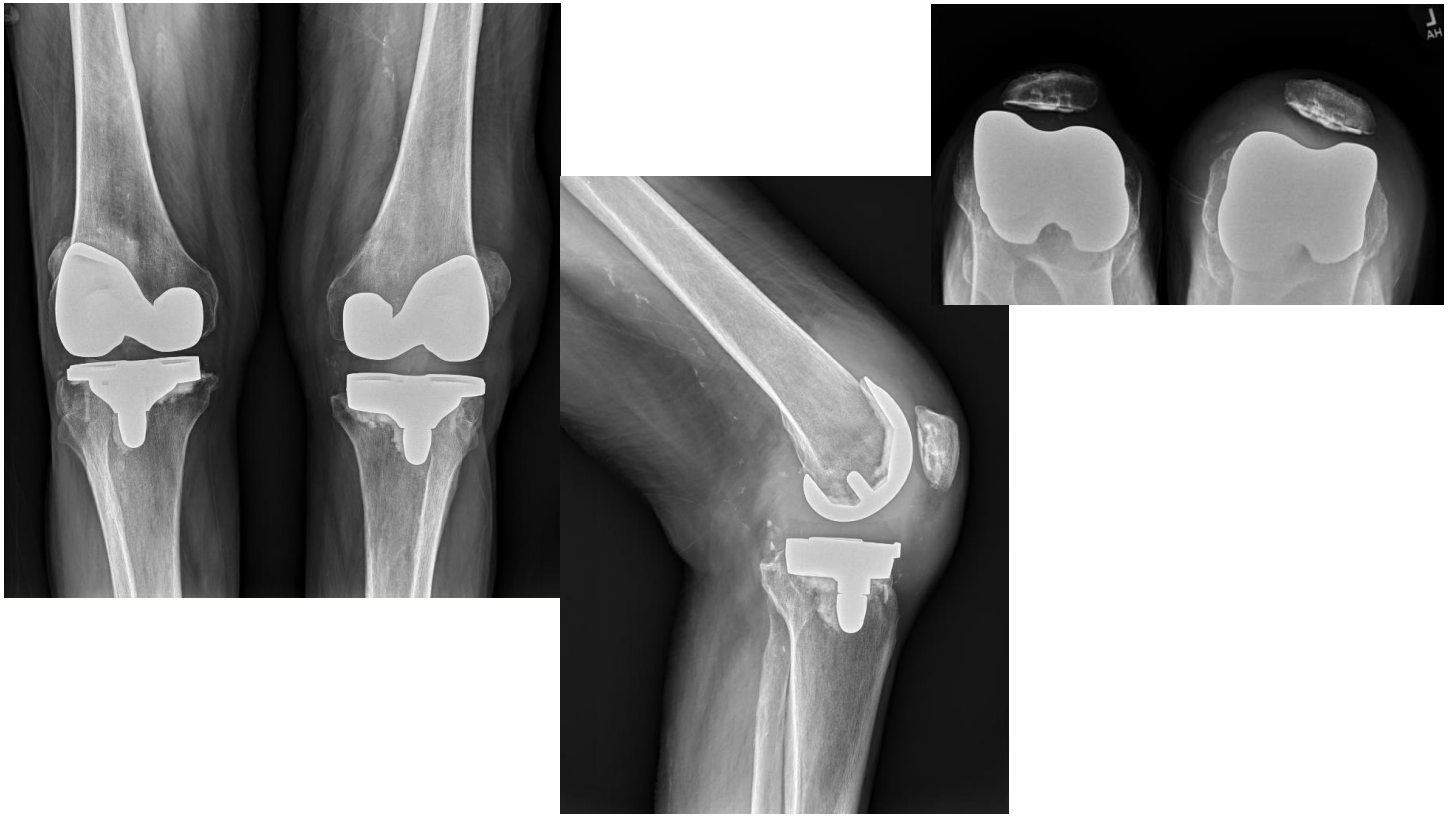

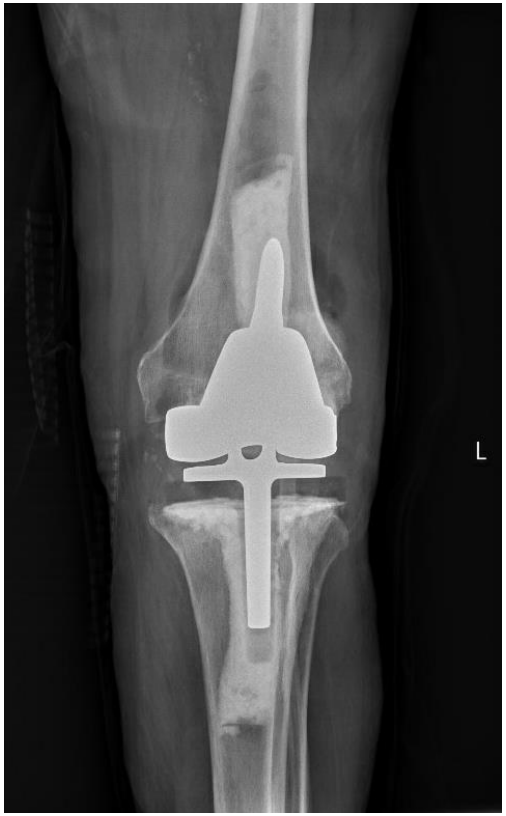
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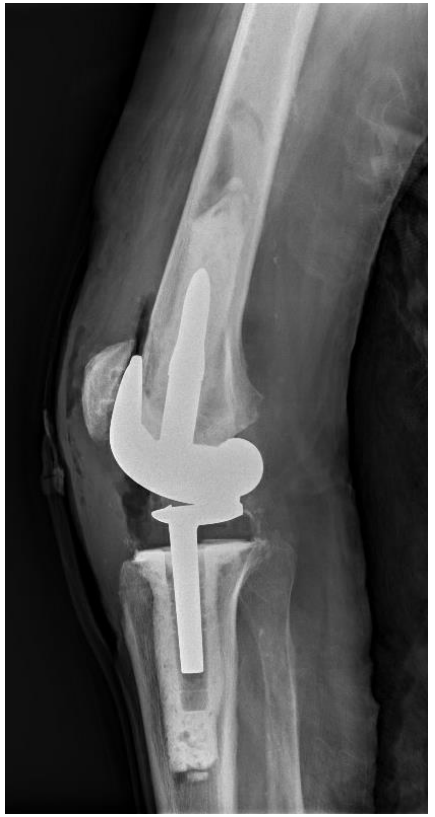

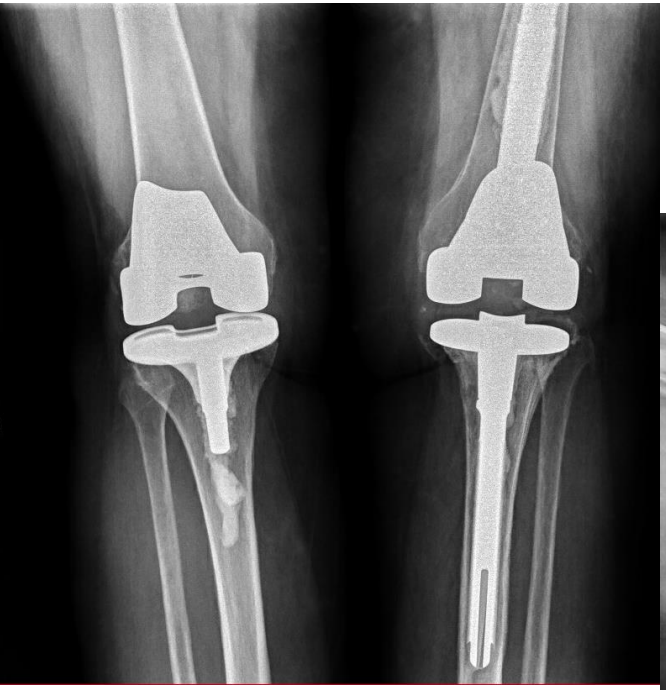

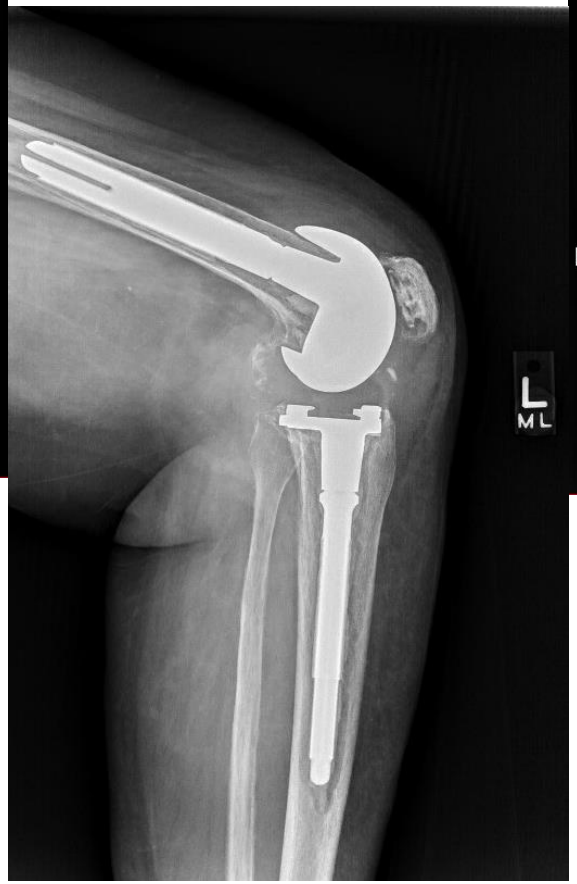
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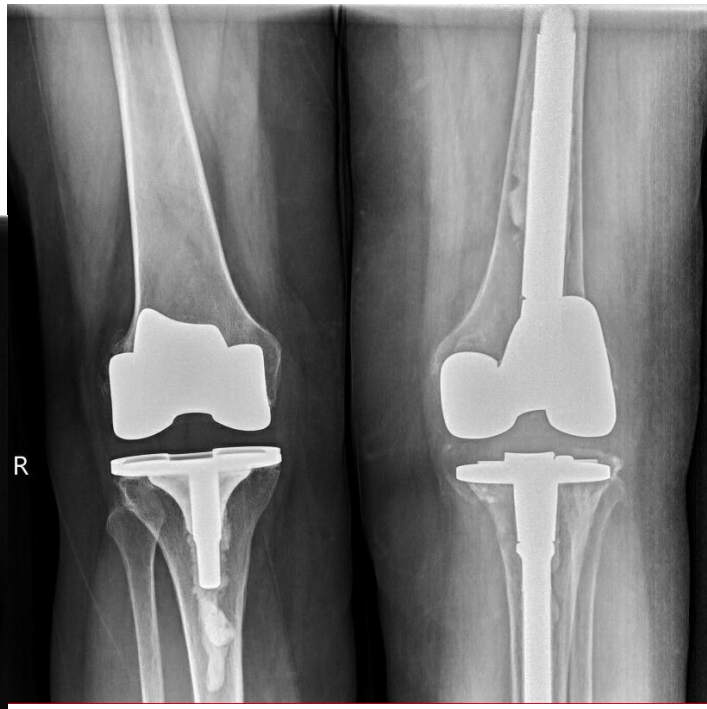
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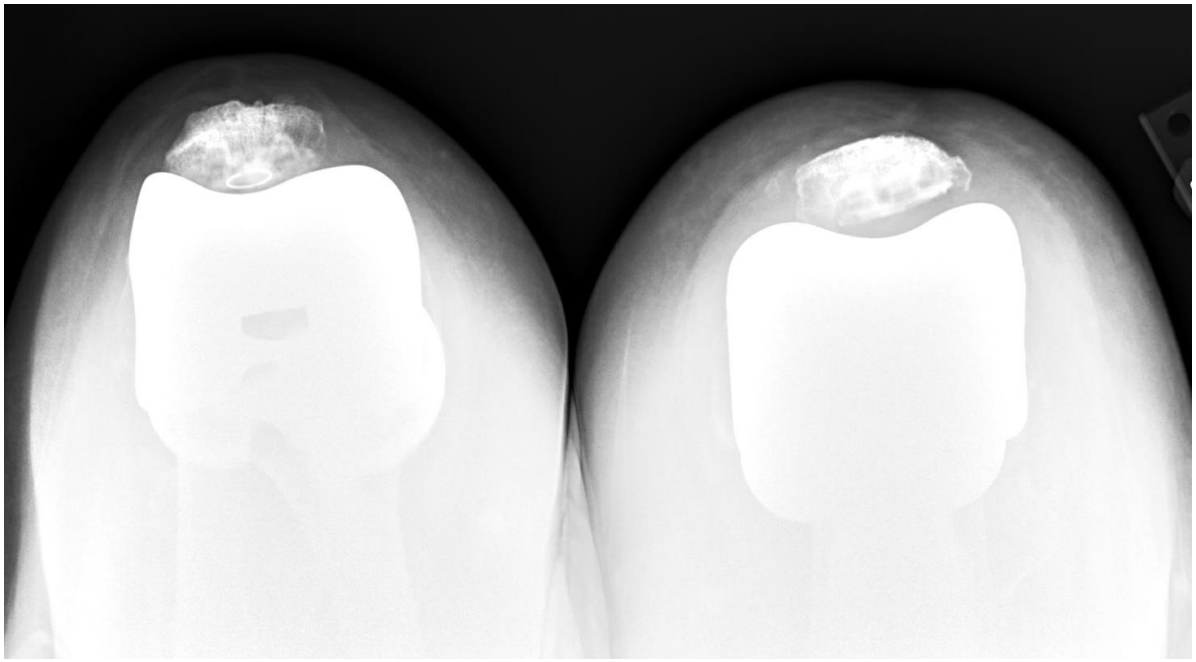

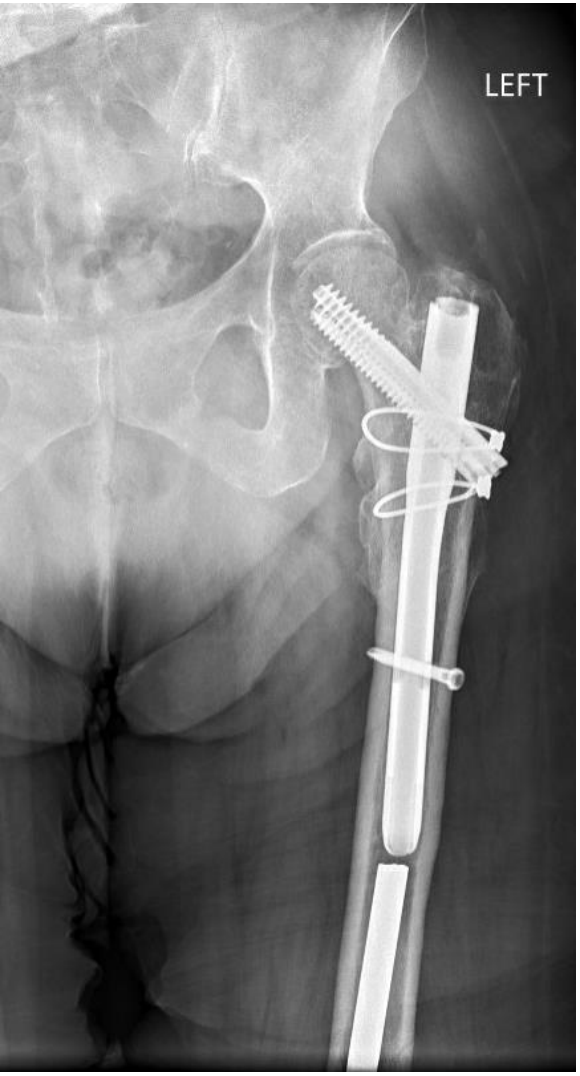
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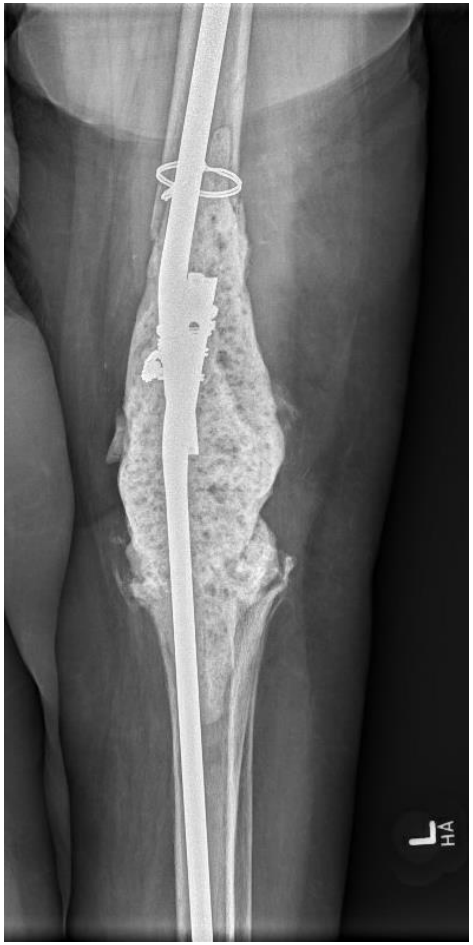
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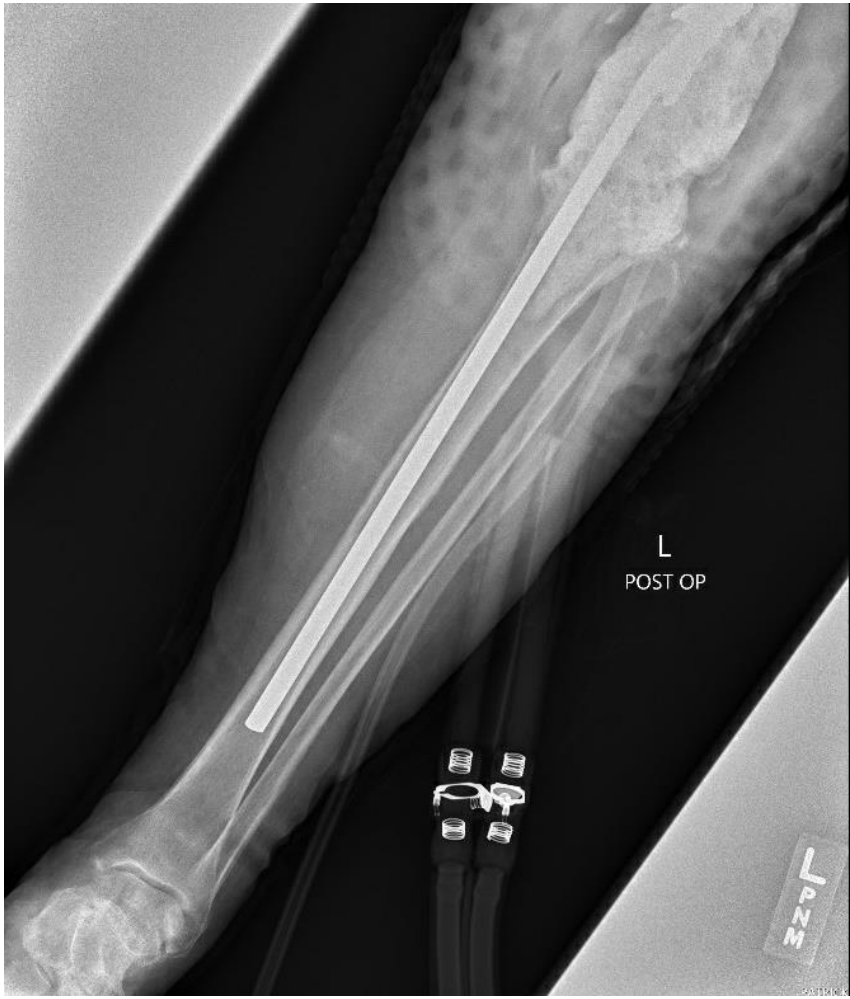
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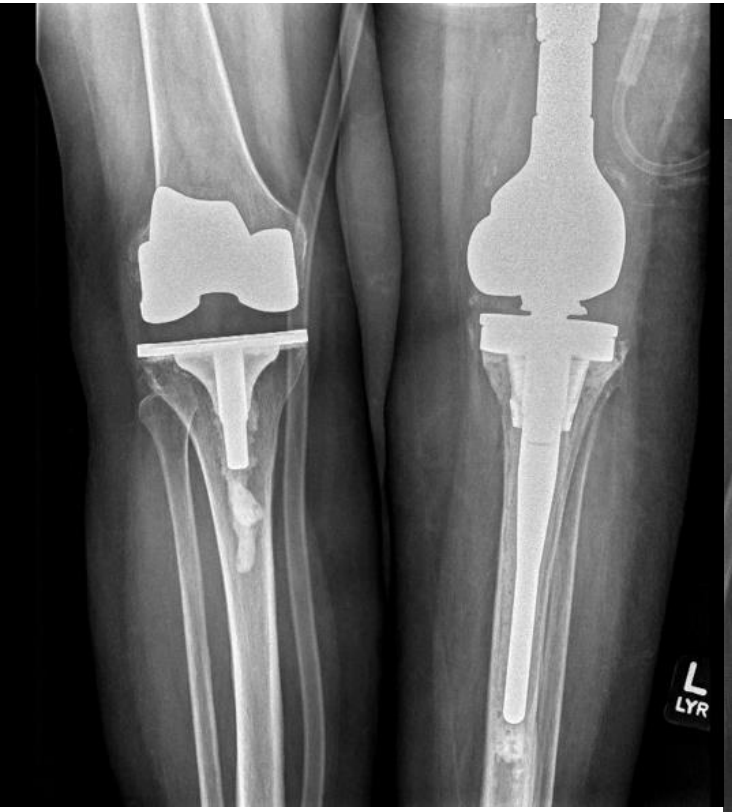
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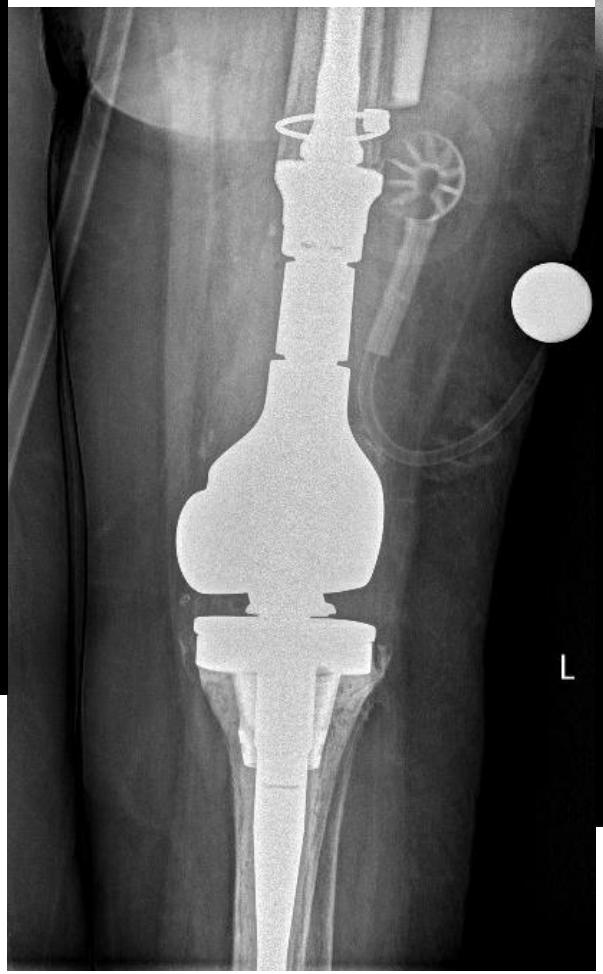
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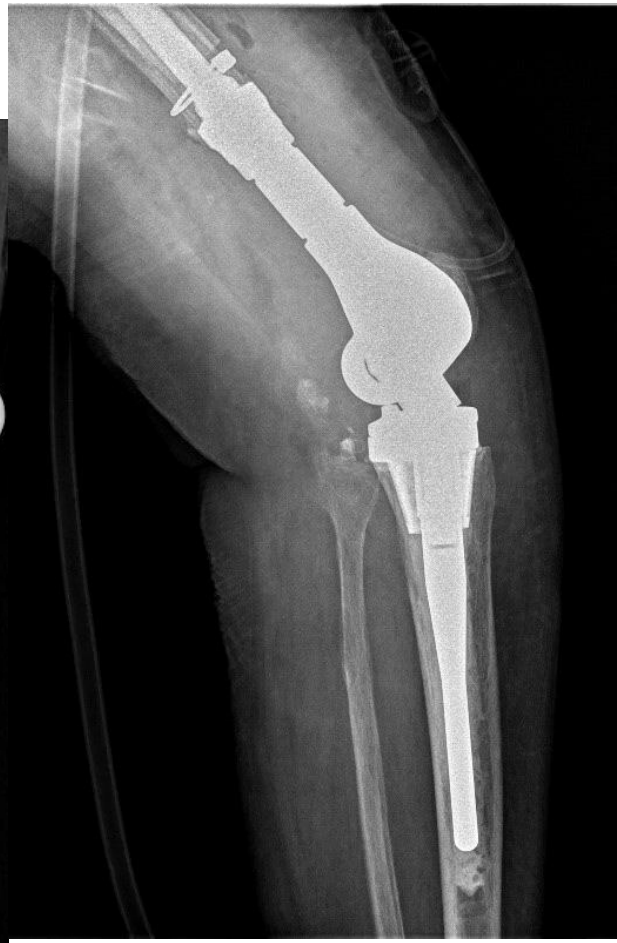


Outcomes 1.5 Stage THA

J Arthroplasty. 2024 May 10:S0883-5403(24)00447-9. doi: 10.1016/j.arth.2024.05.014. Online ahead of print.

Use of 1.5-stage Functional Articulating Hip Spacers for Two-stage Treatment of Hip Infection

Boyong Wang [1], Mingzhang Li [1], Jin Wang [1], Pei Han [1], Qiaojie Wang [1], Hao Shen [2]

Affiliations + expand

PMID: 38735548 DOI: 10.1016/j.arth.2024.05.014

- N=50 (23=2-stage and 27=Functional articulating spacer) with minimum 2 years f/u.
- Similar reinfection rate (0 vs 4%). More fractures in 2-stage.
- Beter function.
- Reimplantation rate (42 vs 82%).

Proceedings of The Hip Society 2022

1.5-Stage Versus 2-Stage Exchange Total Hip Arthroplasty for Chronic Periprosthetic Joint Infections: A Comparison of Survivorships, Reinfections, and Patient-Reported Outcomes

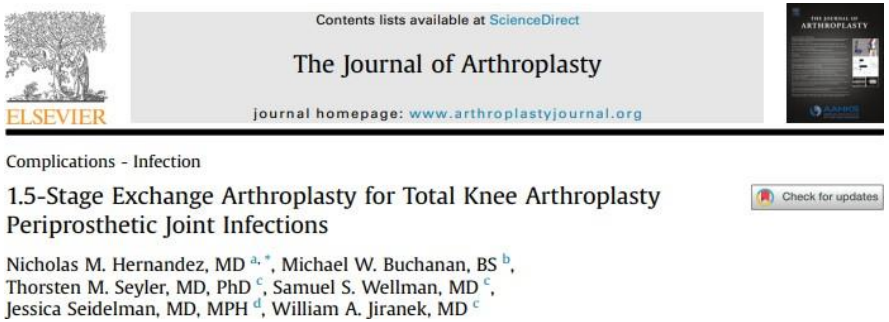
James Nace, DO, MPT *, Zhongming Chen, MD, Sandeep S. Bains, MD, DC, MBA, Michael E. Kahan, DO, Gregory A. Gilson, DO, Michael A. Mont, MD, Ronald E. Delanois, MD

LifeBridge Health, Sinai Hospital of Baltimore, Rubin Institute for Advanced Orthopedics, Baltimore, Maryland

The Journal of Arthroplasty 38 (2023) S235–S241

- N=123 (1.5=54, 2-stage=69), minimum f/u 2.5 years.
- 1.5-stage had 11% greater infection free survivorship (94 vs 83%, p=.048).
- 16% radiolucencies 1.5-stage.

Outcomes 1.5 Stage TKA



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The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

ELSEVIER

Complications - Infection

1.5-Stage Exchange Arthroplasty for Total Knee Arthroplasty Periprosthetic Joint Infections

Nicholas M. Hernandez, MD [a,*], Michael W. Buchanan, BS [b], Thorsten M. Seyler, MD, PhD [c], Samuel S. Wellman, MD [c], Jessica Seidelman, MD, MPH [d], William A. Jiranek, MD [c]

Check for updates

25 out of 28 TKA retained the prosthesis at 2.7 years

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

ELSEVIER

Complications - Infection

Primary Total Knee Arthroplasty Implants as Functional Prosthetic Spacers for Definitive Management of Periprosthetic Joint Infection: A Multicenter Study

Ahmed Siddiqi, DO [a,*], James Nace, DO, FAOAO, MPT [b], Nicole E. George, DO [b], Eric J. Buxbaum, DO [c], Alvin C. Ong, MD [c], Fabio R. Orozco, MD [c], Danielle Y. Ponzio, MD [c], Zachary D. Post, MD [c]

Check for updates

57 1.5 stage vs. 137 2-stage had similar success rate at 2-year f/u (79 vs 71%)

A Comparative Analysis of 1.5-Stage and 2-Stage Exchange Revision for Periprosthetic Joint Infection after Total Hip Arthroplasty: Is 1.5-Stage Really Equivalent?

A total of 77 rTHAs (1.5-stage: n=38; 2-stage: n=39)
Mean follow-up of 56.4 ±15.9 months

More MRSA (5.3 vs 0%), fungal (7.9 vs 5.2%) and polymicrobial in the 1.5- stage group (23.7 vs 5.1%). Likewise, more (-) cultures (34.2 vs 23.1%).

All but one re-revisions on the 1.5-stage group were due to recurrent PJI (29%), whereas smaller % (10%) was the case in 2-stage group.

The 1.5-stage revision was an independent predictor of more re-revisions in the regression model (OR 3.5 95% CI 1.02 – 12.43 P<0.046).

Table 2. Reimplantation outcomes [N=77].

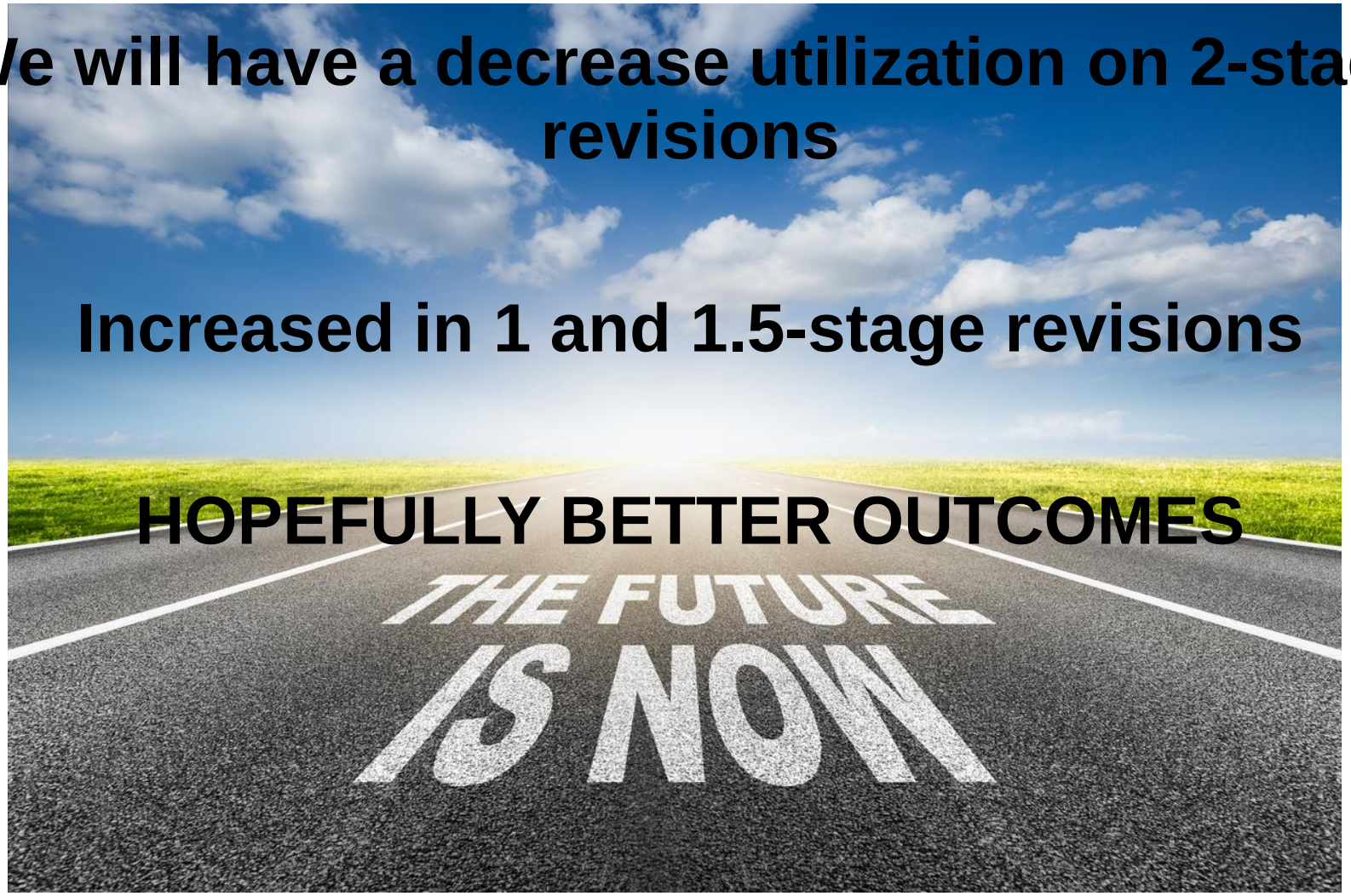
Outcome	1.5-stage [N=38]	2-stage [N=39]	P value
Re-revision (%)	11 (28.9)	4 (10.3)	0.038*
Re-operation (%)	3 (7.9)	4 (10.3)	0.999

* P < 0.05

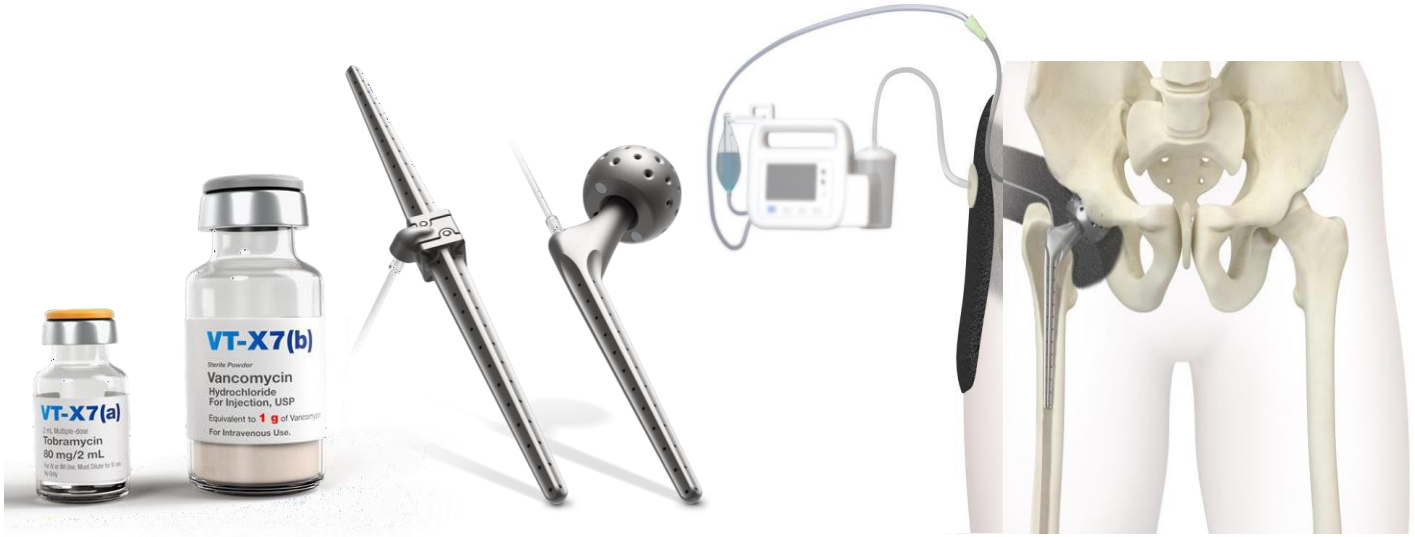
We will have a decrease utilization on 2-stage revisions

Increased in 1 and 1.5-stage revisions

HOPEFULLY BETTER OUTCOMES

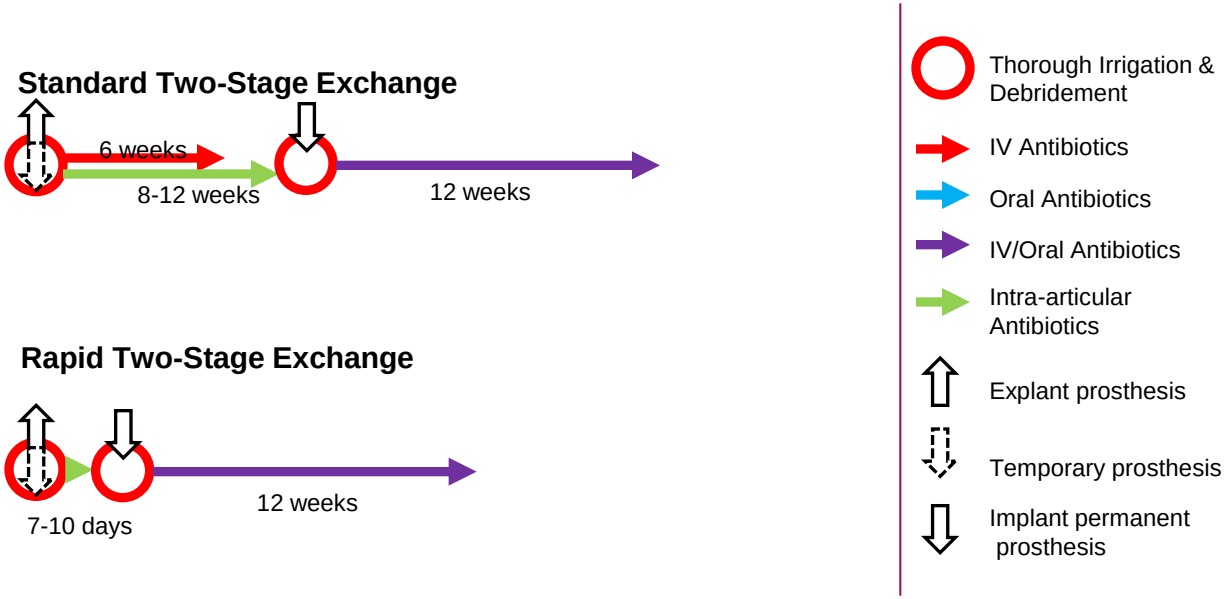


VT-X7: Local Irrigation of Vancomycin and Tobramycin via Patented, Anatomic Specific Delivery Devices



VT-X7 delivers 150 cycles of local antibiotic therapy in 7 days using a commercially available negative pressure wound therapy (NPWT) system

Rapid vs SOC Two-Stage Exchange



Adapted from Gina Sug, MD, MSIS 2023

Safety Profile of Seven-Day Antibiotic Irrigation for the Treatment of Chronic Periprosthetic Joint Infection: A Prospective Randomized Phase II Comparative Study

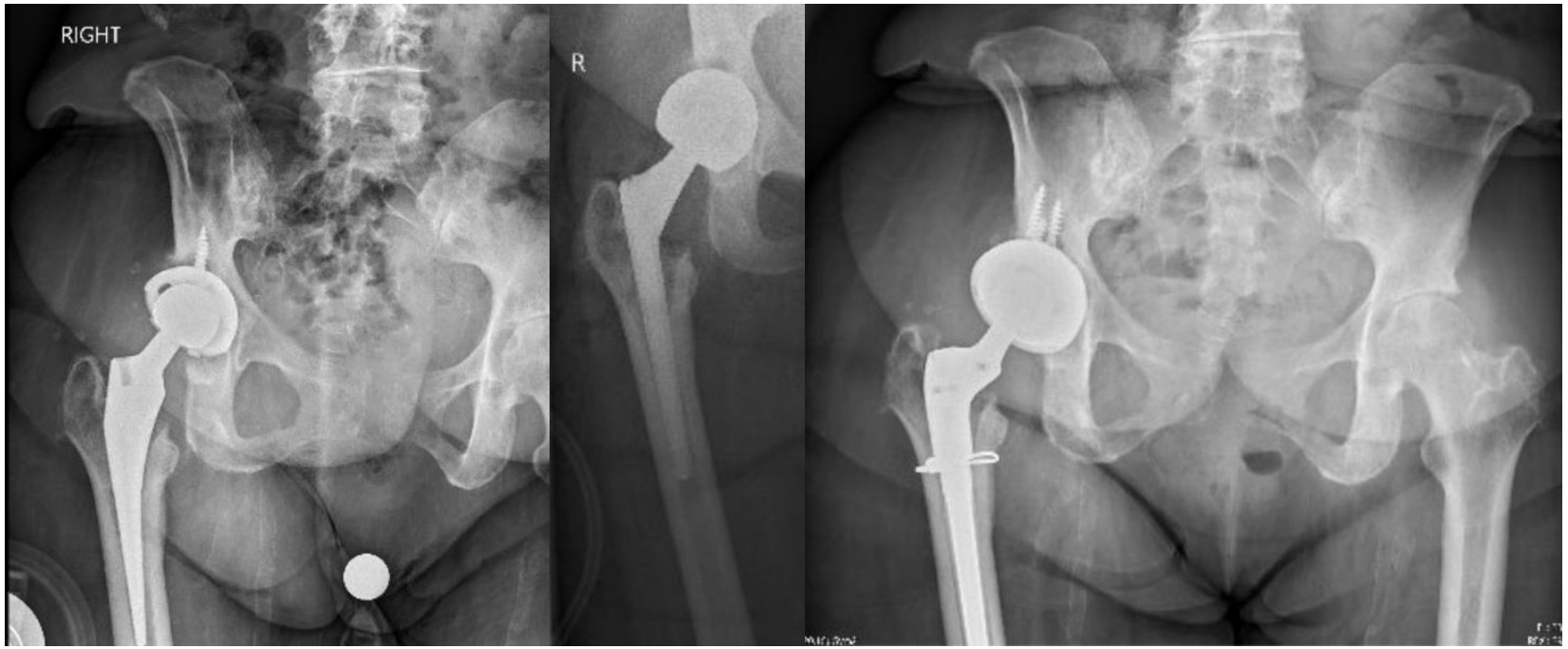
On behalf of the APEX Clinical Investigators

Carlos Higuera-Rueda, MD
Cleveland Clinic Florida

APEX and APEX-2 Study Investigators

Investigator	Institution
Brock Walker, MD	Banner – University Medical Center Phoenix
Steven Goldfarb, MD	Bethesda North Hospital
Carlos Higuera-Rueda, MD	Cleveland Clinic Florida
Nicolas Piuzzi, MD	Cleveland Clinic Ohio
John Cooper, MD	Columbia University Medical Center
Brian de Beaubien, MD	Covenant Medical Center
Lewis Moss, MD	Harbor-UCLA Medical Center
Kwan Park, MD	Houston Methodist Medical Center
Bradley Reddick, DO	Integris Southwest Medical Center
Edward Stolarski, MD	Gulf Coast Research Institute
Ran Schwarzkopf, MD	NYU Langone, New York Presbyterian
Bryan Springer, MD	OrthoCarolina
Max Courtney, MD	Rothman Orthopedic Institute
Roger Emerson, MD	Texas Health Presbyterian – Plano
Andrew Glassman, MD	The Ohio State University
Toan Le, MD	University of Cincinnati
Hari Parvataneni, MD	University of Florida Health
Stephen Duncan, MD	University of Kentucky Medical Center
Elie Ghanem, MD	University of Missouri
Kenneth Urish, MD	University of Pittsburgh Medical Center
Jeremy Gililland, MD	University of Utah Hospital
Ian Duensing, MD	University of Virginia Health
Katherine Harper, MD	Washington DC VA Medical Center

Case Example



Irrigation System

3 months f/u

Rapid 2-Stage protocol

7-Day Antibiotic Dosage	Total (mg)	Concentration (mcg/ml)
Tobramycin Sulfate	560	1,600
Vancomycin HCL	21,000	2,500

Stage 1 | 7-Day Interstage Treatment | Stage 2

Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7

Stage 1
- Debridement
- Implant removal
- Irrigation
- Spacer placement
- Irrigation
- Begin antibiotic instillation/drainage

Interstage Day N

Hour 0: Tobramycin Sulfate
- 2-hour soak: 80 mg in 50 ml NS
- 30-minute vacuum

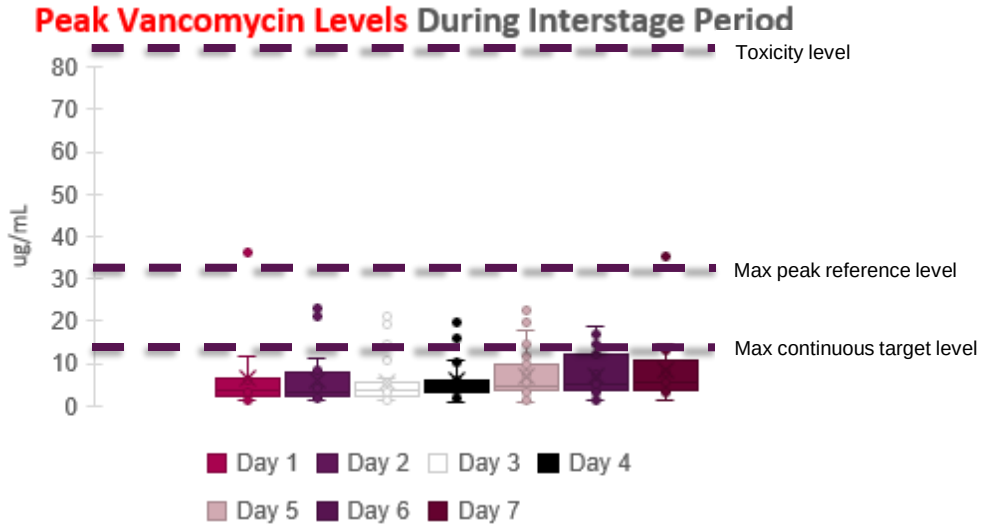
Hour 2- 24: Vancomycin HCL
- 30-minute soak: 125 mg in 50 ml NS
- 30-minute vacuum
- Repeat

150+ Cycles Over 7 Days

Stage 2
- Remove spacer
- Debridement
- Irrigation
- Prosthesis implantation
- Irrigation

Results

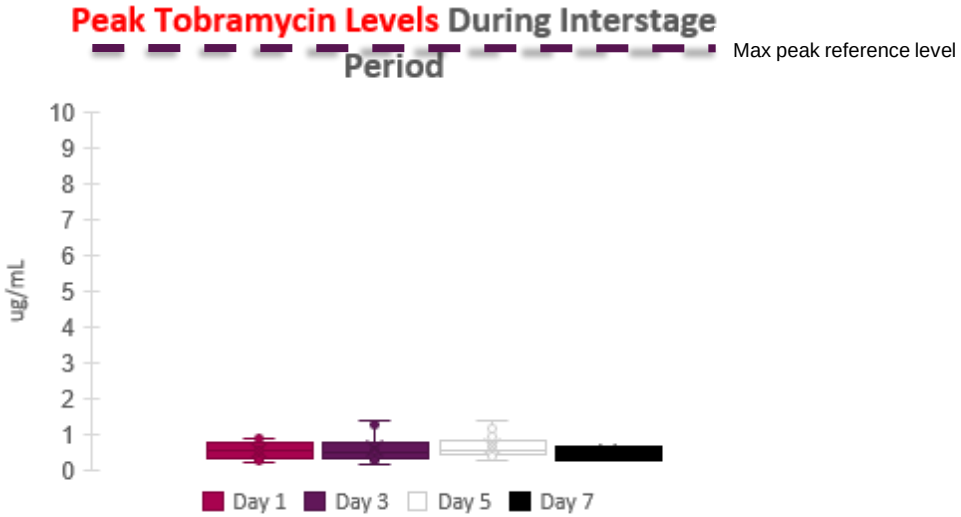
Vancomycin Serum Concentration Levels



- 62/226 measured vancomycin levels (27.4%) were below detectability.
- **All detectable values well below 80 mg/L (toxicity).**
- Highest measured peak vancomycin levels were from 2 subjects receiving IV vancomycin in addition to VT-X7 during interstage period.

Results

Peak Tobramycin Serum Concentration Levels



- 83/139 measured peak tobramycin levels (59.7%) were below detectability.
- **All detectable levels were <2 mg/L in peak testing with the majority <1 mg/L.**
- 99/118 measured trough tobramycin levels (83.8%) were below detectability.

Results

Initial Safety → Summary of Adverse Events

Event	Experimental (N=37)	Control (N=39)	p – value
Anemia	22 (59.5%)	16 (41.0%)	.11
Nausea/Vomiting	7 (18.9%)	5 (12.8%)	.47
Index Joint Dislocation/Fracture	5 (13.5%)	7 (17.9%)	.60
Urinary Retention	6 (16.2%)	3 (7.7%)	.26
Diarrhea	4 (10.8%)	2 (5.1%)	.36
Re-infection of Index Joint	3 (8.1%)	3 (7.7%)	.95
Wound Healing Issue	3 (8.1%)	2 (5.1%)	.60
Hyperkalemia	2 (5.4%)	3 (7.7%)	.69
Acute Kidney Injury	3 (8.1%)	0	.07
TOTAL	32 (86.5%)	31 (79.5%)	.42

No difference

- 2 events in 2 subjects related or possibly related to VT-X7 spacer device and procedure: irrigation line impingement
- 2 events in 1 subject possibly related to study antibiotics: hearing loss and chronic diarrhea
  - Occurred 6 wks post-Stage 2 while on IV Vanc

Results

Operative Details

Event	Experimental (N=37)	Control (N=39)	p-value
Total Procedure Time (min) (Stage 1 + Stage 2)	332.8 (N=37)	402.5 (N=33)	.02
Time to Stage 2 (days)	7.1 (N=37)	116.4 (N=33)	<.01
Patients Transfused (%)	56.8% (N=21)	41% (N=16)	.42
Reimplantation (%)	100% (N=37)	85% (N=33)	.014

Conclusions

- Interstage vancomycin and tobramycin levels demonstrate that local antibiotic concentrations associated with the VT-X7 dosing regimen produced serum antibiotic levels within established safe ranges
- The incidence of AEs are similar between Arms
- Low number of device- and procedure-related events in the Experimental Arm (2 events in 2 Experimental Arm subjects)
  - More transfusions
  - More renal failures
- Total Stage 1 and Stage 2 operating time and time to Stage 2 surgery significantly lower in the Experimental Arm compared to the Control Arm

J Arthroplasty. 2024 Apr 9:S0883-5403(24)00313-9. doi: 10.1016/j.arth.2024.03.069.
Online ahead of print.

Safety Profile of Seven-Day Intra-Articular Antibiotic Irrigation for the Treatment of Chronic Periprosthetic Joint Infection: A Prospective Randomized Phase II Comparative Study

Bryan D Springer [1], Carlos Higuera-Rueda [2], Brian de Beaubien [3], Kevin Warner [3], Andrew Glassman [4], Hari Parvataneni [5], Nicolas Piuzzi [6]

Affiliations + expand

PMID: 38604274 DOI: 10.1016/j.arth.2024.03.069

Initial Success of Seven-Day Intra-Articular Antibiotic Irrigation for the Treatment of Chronic Periprosthetic Joint Infection: Results from Two Prospective Randomized Comparative Studies (Apex 2).

On behalf of the APEX and APEX-2 Clinical Investigators:

Carlos Higuera-Rueda, MD
Cleveland Clinic Florida

MUSCULOSKELETAL INFECTION SOCIETY

34th Annual Open Scientific Meeting
August 2-3, 2024
Durham, NC

Study Rationale and Design

Objective:

Determine effectiveness of rapid (7-day) two-stage exchange arthroplasty with cyclic local antibiotic irrigation

Design:

- Prospective, randomized 1:1 vs. SOC two-stage exchange arthroplasty

- 12M follow-up with interim visit at 6M

Endpoints:

Success at 6M/12M using MSIS Tier 1 criteria:

1. Permanent prosthesis
2. No death
3. No post-Stage 2 PJI
4. No revision surgery
5. No continued antibiotics

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Study Rationale and Design

Major Eligibility Criteria

Inclusion:

- Knee or hip PJI per 2018 ICM criteria

Exclusion:

- 2 or more prior exchange arthroplasties
- 2 or more prior failed spacers
- Bacteremia within 30 days of enrollment
- Advanced renal insufficiency
- Immunodeficient

Enrollment:

Enrolled 152 subjects at 23 US centers

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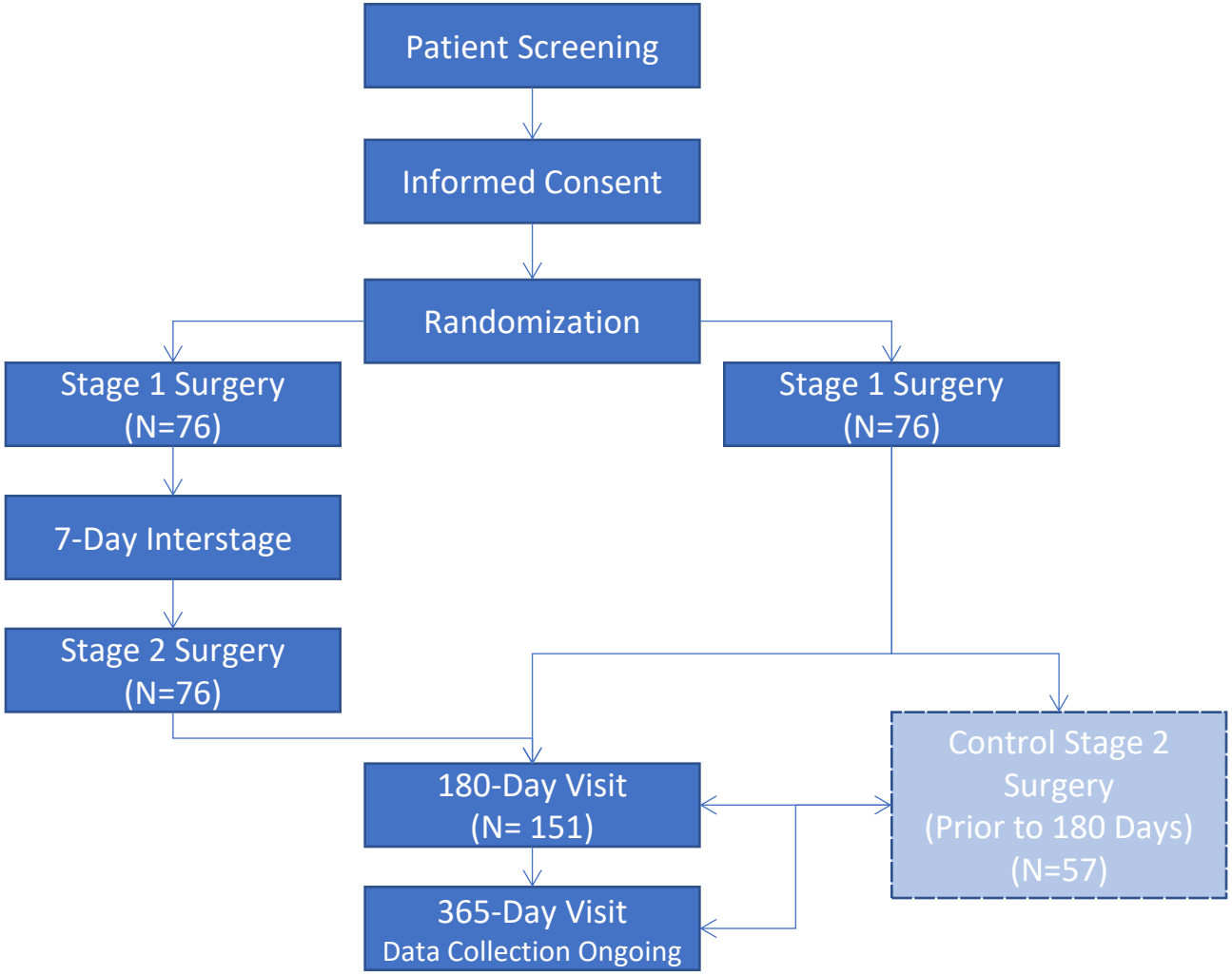
Study Flowchart



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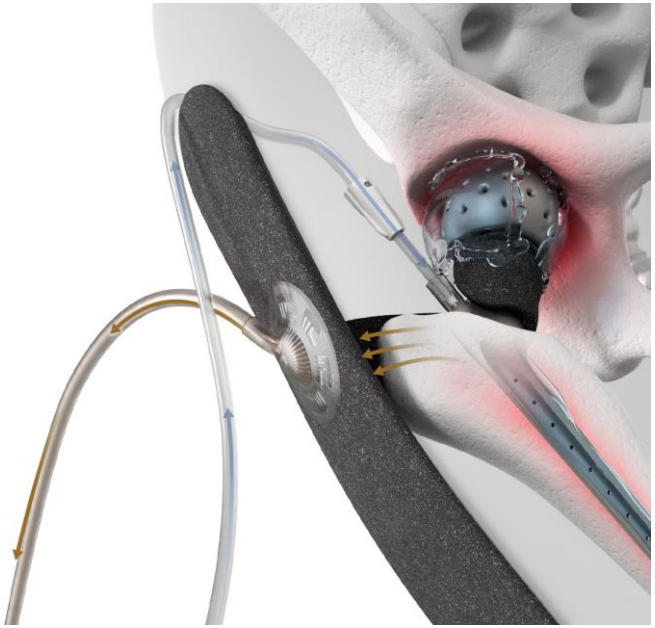
Investigational Product

Cyclic Local Antibiotic Irrigation



Photos courtesy Osteal Therapeutics. VT-X7 is an investigational product. Limited by federal law to investigational use.

- MBEC levels of broad-spectrum antibiotic combination
- Cyclically administered and removed from the joint
- Concentrations ~100X greater than MIC levels
- Bactericidal to microbes in biofilms
- Compresses the period between 2-stage exchange surgeries from months to days
- Patients complete exchange to a permanent prosthesis

Fenestrated Titanium Spacers

Tobramycin Sulfate and Vancomycin HCL

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Investigational Product

Rapid Two-Stage Exchange Protocol

7-Day Antibiotic Dosage	Total (mg)	Concentration (mcg/ml)
Tobramycin Sulfate	560	1,600
Vancomycin HCL	21,000	2,500

Stage 1
- Debridement
- Implant removal
- Irrigation
- Temporary spacer placement
- Irrigation
- Start of cyclic antibiotic administration

Interstage Day N

Hour 0: Tobramycin Sulfate
- 2-hour soak: 80 mg in 50 ml NS
- 30-minute vacuum

Hour 2-24: Vancomycin HCL
- 30-minute soak: 125 mg in 50 ml NS
- 30-minute vacuum
- Repeat

150+ Cycles Over 7 Days

Stage 2
- Spacer removal
- Debridement
- Irrigation
- Prosthesis implantation
- Irrigation

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Case 1

MSIS major criteria:
Two positive periprosthetic cultures with phenotypically identical organisms.
Sinus tract communicating with the joint/implant.

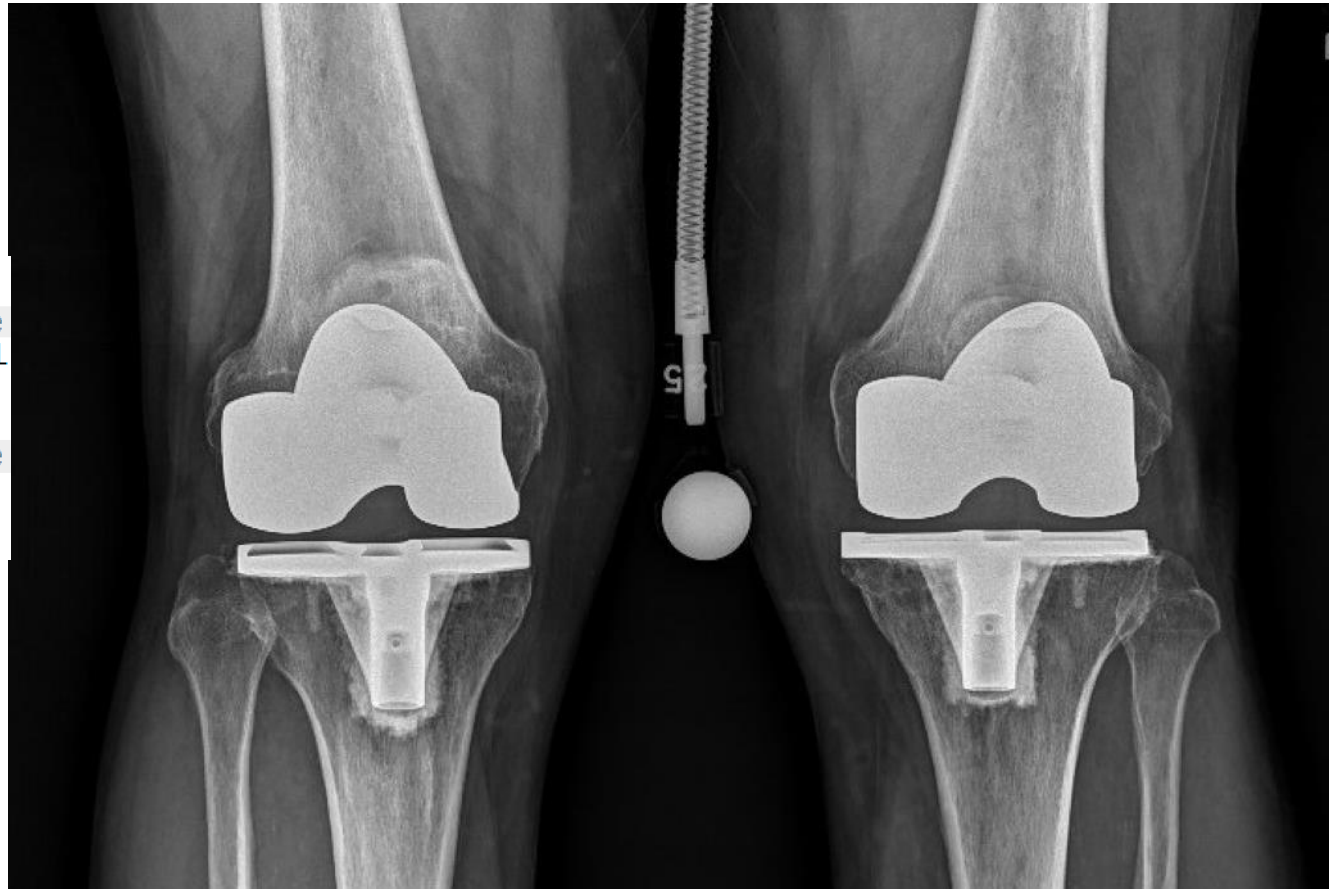
MSIS minor criteria:
Elevated serum C-reactive protein level and erythrocyte sedimentation rate. - YES
Elevated synovial fluid white blood cell count - YES
Elevated synovial fluid polymorphonuclearneutrophil percentage. - YES
Positive histologic analysis of periprosthetic tissue.
Single positive culture from periprosthetic tissue or fluid.

54 y/o Male

Left knee pain

***Left TKA July 2020**

***Right TKA June 2020**



CRP

Date	Value	Ref Range
02/22/2022	1.1 (H)	<0.9 mg/dL

WSR

Date	Value	Ref Range
02/22/2022	24 (H)	0 - 15 mm/hr

2/22/2022 Knee Aspiration

TNC 53052
PMN 94%

Cultures NEGATIVE

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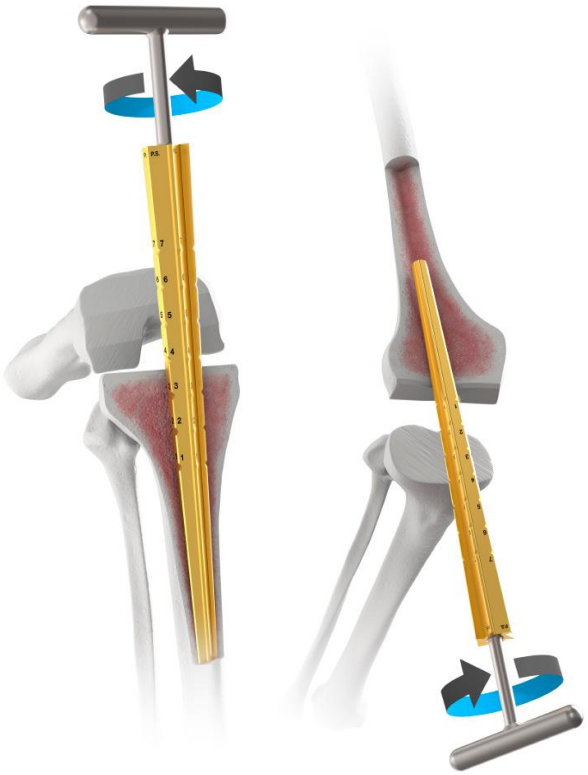
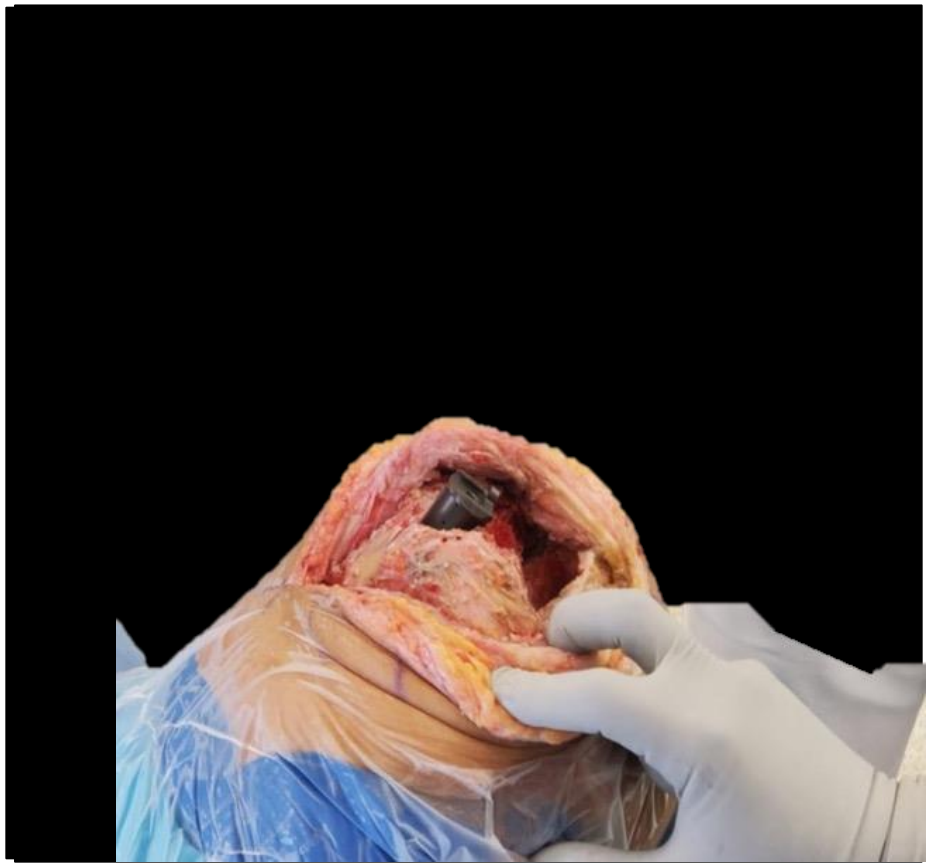
Courtesy of Nicolas S. Piuzzi, MD

Case 1 → Surgery 1

4/11/2022





Incision Start: 1:36 PM
Incision Stop: 3:46 PM

Courtesy of Nicolas S. Piuzzi, MD

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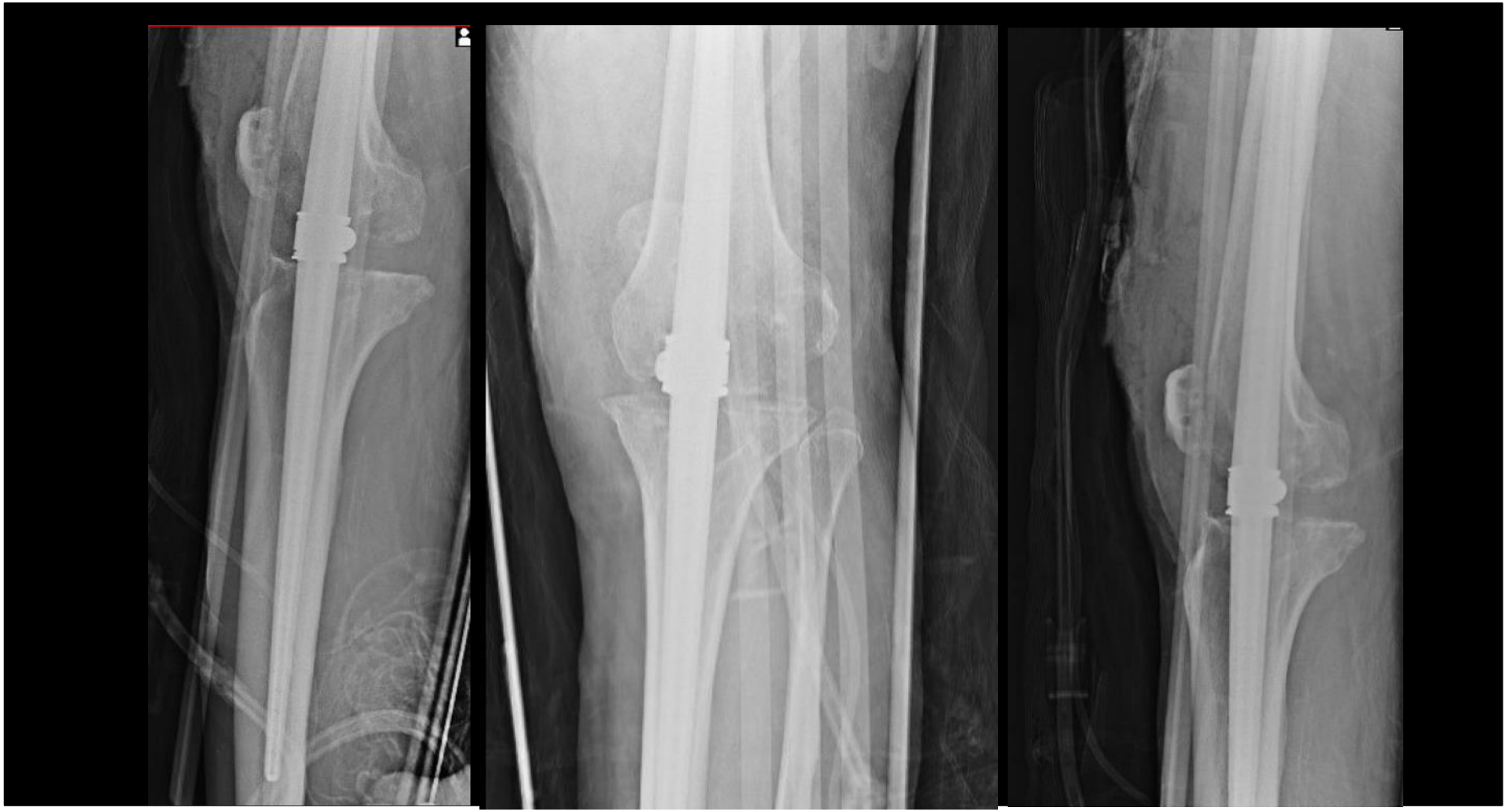
Case 1 → Surgery 1

4/11/2022

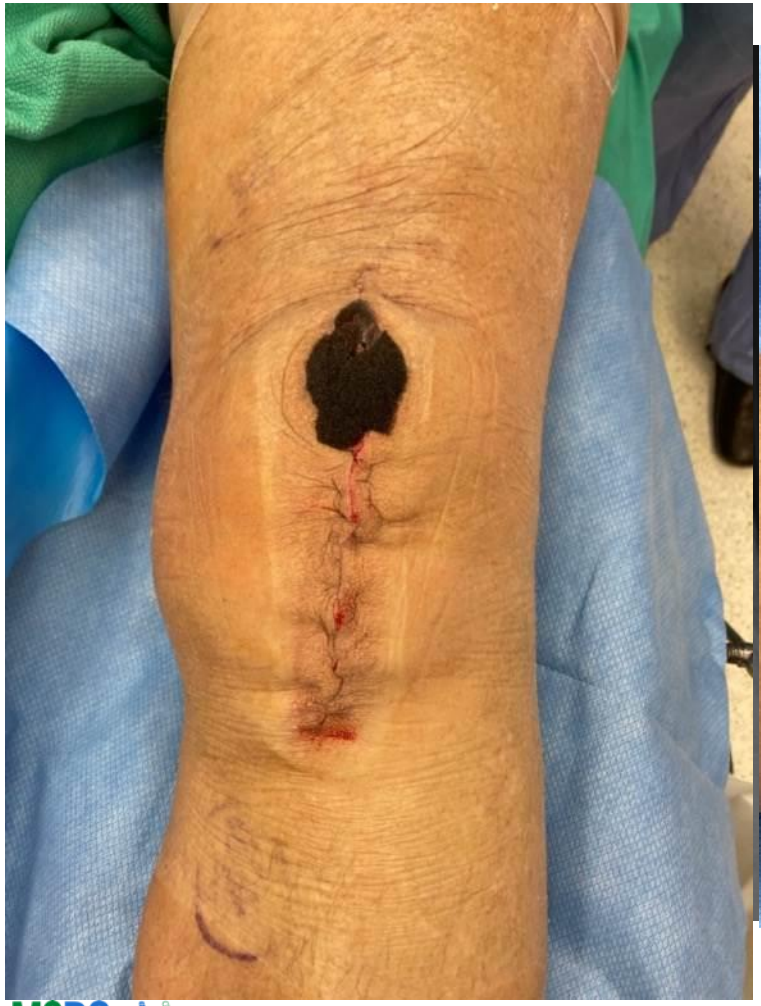


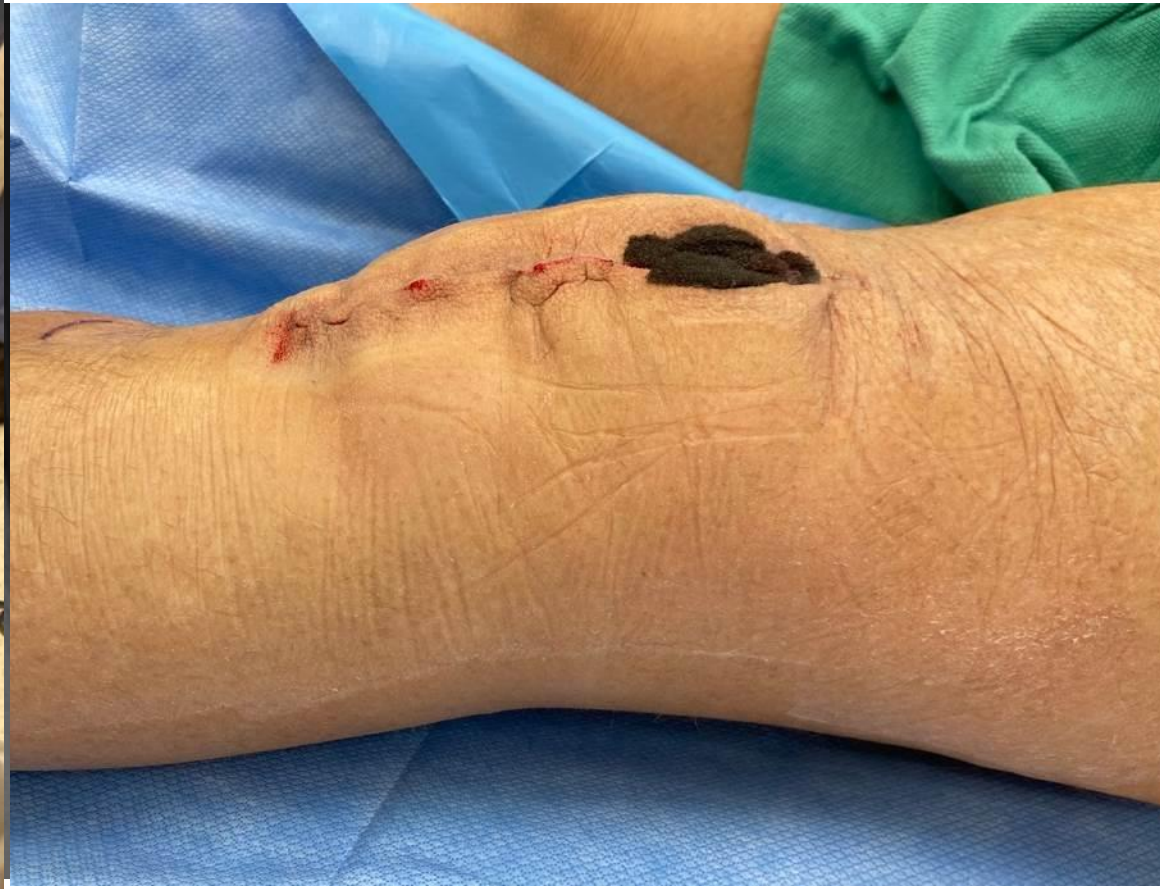
Incision Start: 1:36 PM
Incision Stop: 3:46 PM

Courtesy of Nicolas S. Piuzzi, MD

Case 1 → Surgery 2

4/18/2022





Incision Start: 10:40 AM
Incision Stop: 1:43 PM

Courtesy of Nicolas S. Piuzzi, MD

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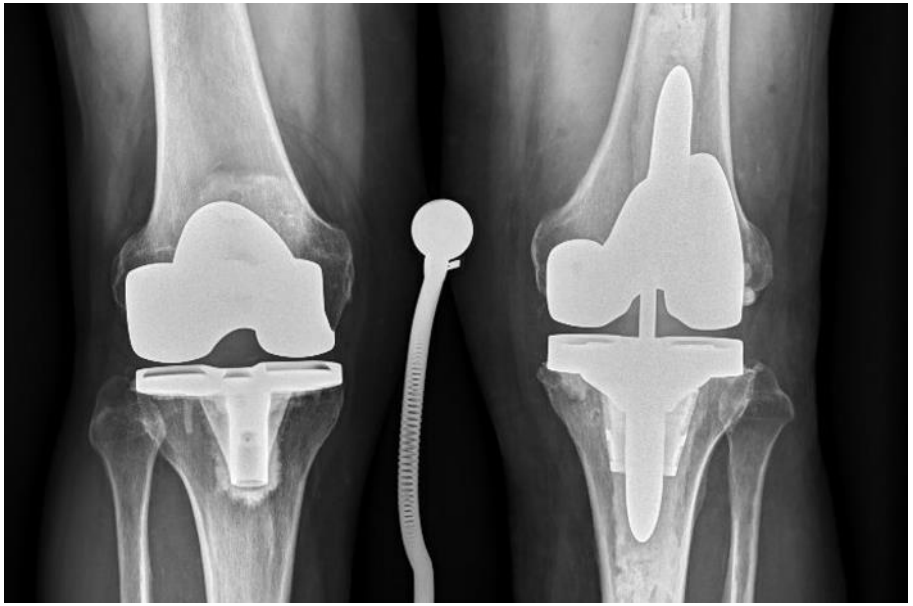
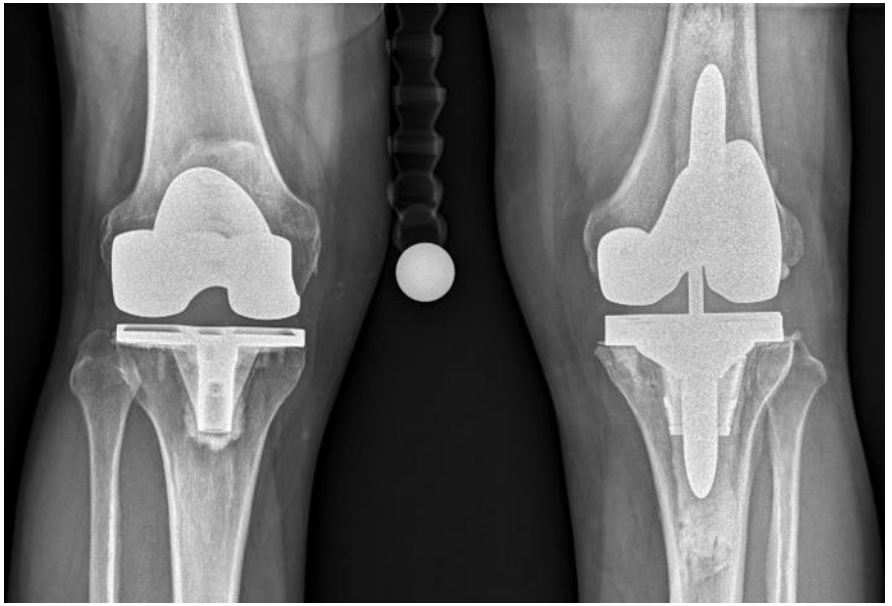
Case 1 – Follow up



1 month



12 months

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Courtesy of Nicolas S. Piuzzi, MD

Subject Demographics

No differences were noted in any subject baseline demographics including age, sex, BMI, or race between the study groups.

Demographics and Socio-Economic Characteristics in the ITT Population		
	Experimental (N = 76)	**Control (N = 76)**
Age at Consent (Years)		
Mean ± SD (n) Range	67.0 ± 8.3 44-83	65.3 ± 9.8 39-82
Sex, n (%)		
Male	44 (58%)	51 (67%)
Female	32 (42%)	25 (33%)
BMI (kg/m^2)		
Mean ± SD (n) Range	31.8 ± 7.1 17.7-45.9	33.8 ± 6.7 19.9-50.5
Race, n (%)		
American Indian	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	0 (0.0%)
Black or African	6 (7.9%)	4 (5.3%)
Native Hawaiian	0 (0.0%)	0 (0.0%)
Other	1 (1.3%)	2 (2.6%)
Unknown	1 (1.3%)	1 (1.3%)
White	68 (89.5%)	69 (90.8)
Index Joint		
Knee	43 (56.6%)	48 (63.2%)
Hip	33 (43.4%)	28 (36.8%)

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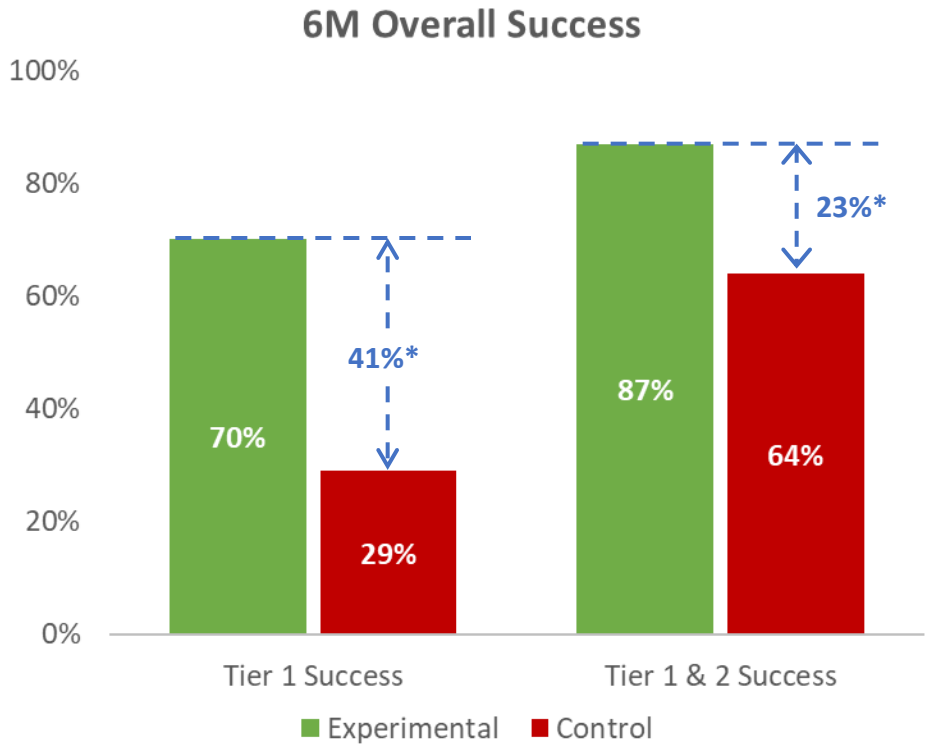
Study Results

Statistically Significant Net Treatment Effect at 6M of 41% (MSIS Tier 1) and 23% (MSIS Tier 1 & 2)



*p<0.01

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Study Results

Outcome Success by MSIS Tier Reporting (First Mode of Failure)

Outcome	Experimental (n=76)	Control (n=75)	Statistical Significance
MSIS Tier 1 Infection Control w/o ABX	69.7% (n=53)	29.3% (n=22)	p<0.01^
MSIS Tier 2 Infection Control w/ ABX	17.1% (n=13)	34.7% (n=26)	p=0.014^
MSIS Tier 3			
3A: Aseptic revision > 1 year	NA	NA	NA
3B: Septic revision > 1 year	NA	NA	NA
3C: Aseptic revision ≤ 1 year	5.3% (N=4)	6.7% (N=5)	1.00*
3D: Septic revision ≤ 1 year	5.3% (N=4)	6.7% (N=5)	1.00*
3E: Amputation	0.0% (N=0)	0.0% (N=0)	NA
3F: Retained spacer	0.0% (N=0)	20.0% (N=15)	p<0.01^
MSIS Tier 4 Death within 1 year	2.6% (N=2)	2.7% (N=2)	1.00*
Ad-Hoc Outcome Success Tier 1/2 Success and: - No Death (Tier 4) - No Septic Failure (Tier 3D, 3E)	92.1% (n=70)	70.7% (n=53)	p<0.01^

^ Chi-Square Test
* Fisher's Exact Test

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Study Results*

Total Surgery Time – Stage 1 + Stage 2 (mins)

Experimental: 304

Control: 364

% of Subjects Completing Stage 2 by 6M

Experimental: 100%

Control: 75%

Median Time to Stage 2 (days)

Experimental: 7

Control: 102

% of Subjects on ABX at 6M

Experimental 22%

Control 45%

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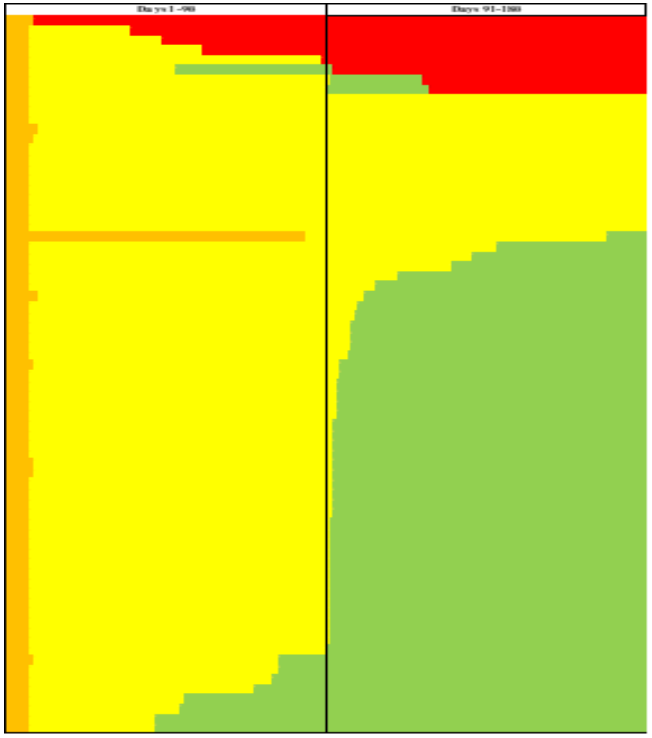
*All results statistically significant with a p-value <0.01

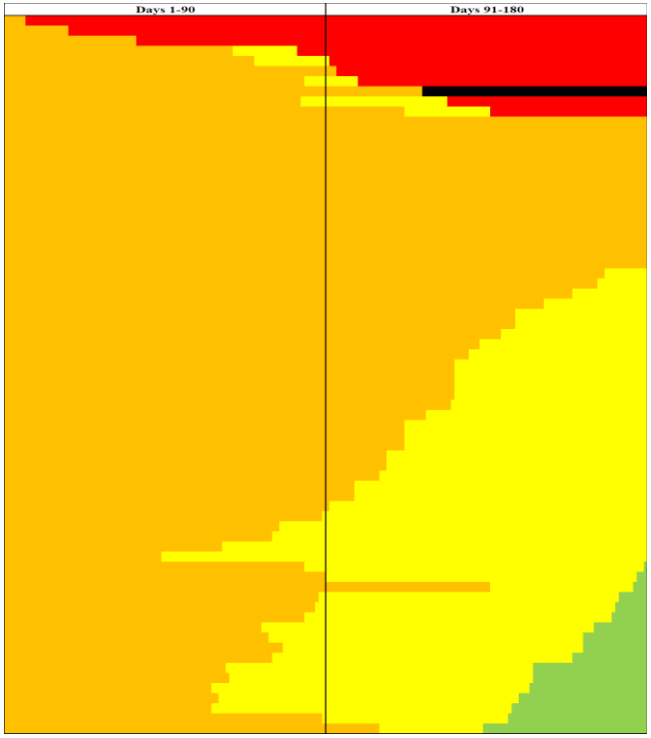
Study Results

Patient Journey at 6 Months

Experimental Arm



Control Arm



Mean Days in Treatment

- Exp: 105
- Control: 161

Mean Days as a Success

- Exp: 63
- Control: 5

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Conclusions

- Experimental Arm subjects had a statistically significant better Overall Success rate (Tier 1 and Tier 1 & 2) at 6M compared to Control Arm subjects.
- Experimental Arm subjects had a statistically significant better Overall Success when considering Tier 1 & 2 without death or septic failure.
- All Experimental Arm subjects and 75% of Control Arm subjects completed Stage 2 surgery by 6M.
- Total Stage 1 and Stage 2 operating time and time to Stage 2 surgery were significantly lower in the Experimental Arm compared to the Control Arm.
- Experimental Arm subjects spent an average of 12x more days as a success compared to Control Arm subjects (63 vs. 5) through 6M despite having less days in treatment (105 vs 160).

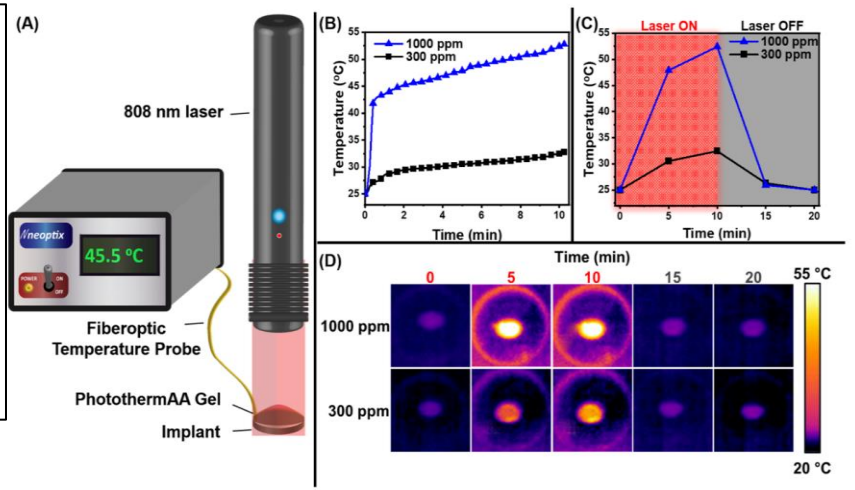
Variable	Experimental (VT-X7 Group)	Control (2-Stage Group)	P value
Hospital length of stay, Mean in days (range)	14.4 (9 - 47)	11.0 (6 - 22)	0.4
Total charges, Mean in US dollars (range)	1 (1 - 1)	+ 31% (+ 35% to + 42%)	0.049*
Total costs, Mean in US dollars (range)	1 (1 - 1)	+ 32% (+ 19% to + 52%)	0.06
Total fixed costs, Mean in US dollars (range)	1 (1 - 1)	+ 28% (+ 8% to + 52%)	0.1
Total indirect costs, Mean in US dollars (range)	1 (1 - 1)	+ 32% (+ 22% to + 55%)	0.1
Total variable costs, Mean in US dollars (range)	1 (1 - 1)	+ 36% (+ 34% to + 52%)	0.028*
Total direct costs, Mean in US dollars (range)	1 (1 - 1)	+ 32% (+ 25% to + 51%)	0.038*

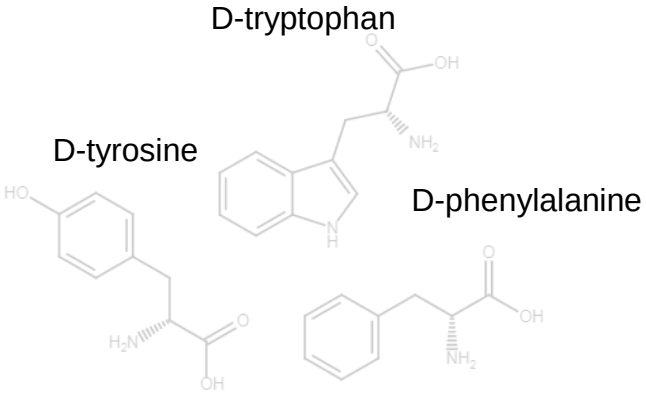
Data shown for the experimental (VT-X7 spacer) group represents all days of hospitalization (single hospitalization) while data for the control group accounts for 2 hospitalizations. Because charges and costs (including ranges) from the control group were found consistently higher, the percentage increase is shown using a reference value of 1 for the experimental group. * Significantly different.

PhotothermAA gel – anti-biofilm Treatment keeping the components in place

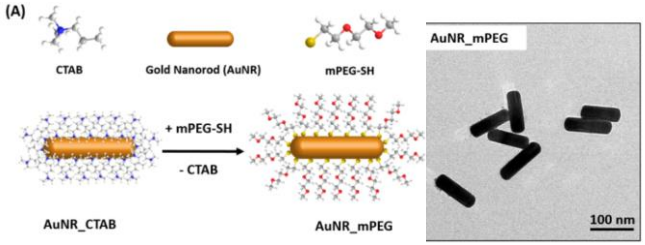
PhotothermAA gel Components

1. D-amino acids (D-trp, D-try, D-phe)
2. PEGylated gold nanoparticles – thermoresponsive
3. Glycol chitin hydrogel

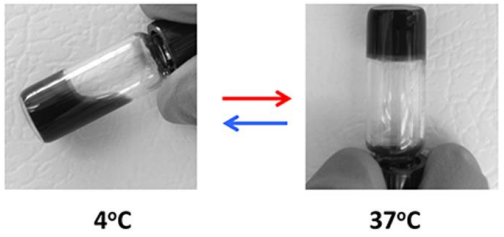




D-amino acids



Gold nanoparticles



Hydrogel properties

Wickramasinghe S. et. al. *ACS Appl. Nano Mater*. 2020, Milbrandt N. et. al. *ACS Appl Bio Mater.* 2023

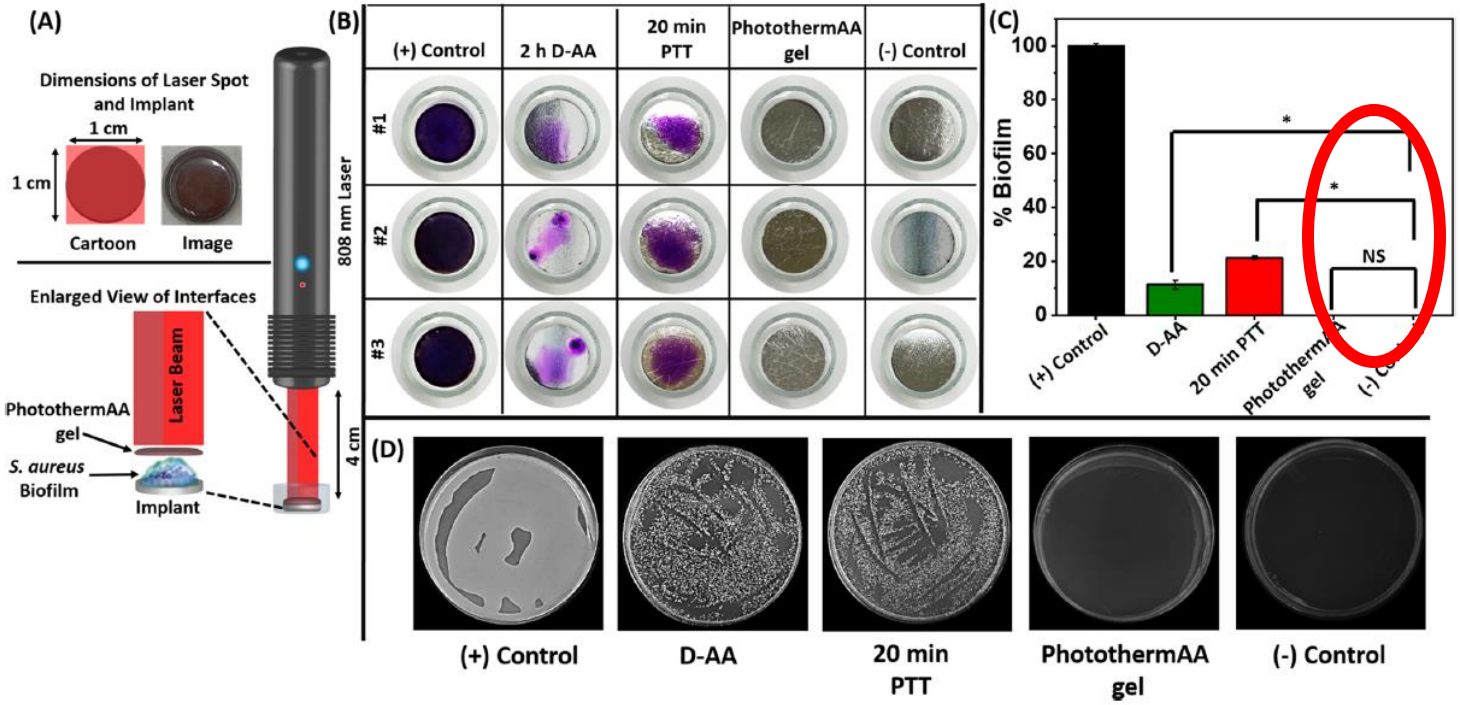
Photoactivated Gold Nanorod Hydrogel Composite Containing D-Amino Acids for the Complete Eradication of Bacterial Biofilms on Metal Alloy Implant Materials

Sameera Wickramasinghe, Minseon Ju, Nathalie B. Milbrandt, Yu Hsin Tsai, Monica Navarreto-Lugo, Anabelle Visperas, Alison Klika, Wael Barsoum, Carlos A. Higuera-Rueda,* and Anna Cristina S. Samia*

Cite This: https://dx.doi.org/10.1021/acsanm.0c01018

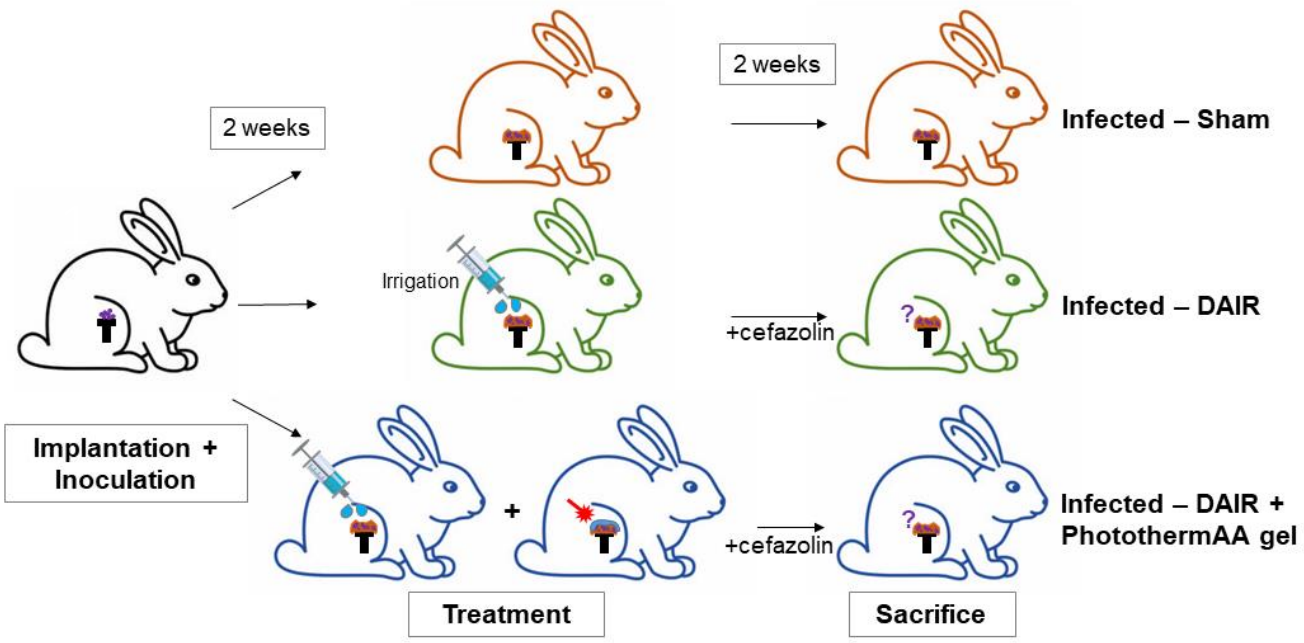
Read Online

ACS APPLIED NANO MATERIALS



Methods: Experimental Schematic for PhotothermAA Gel Testing

Higuera, et al. JBJI, 2022.



SHAM TREATMENT (n=6)

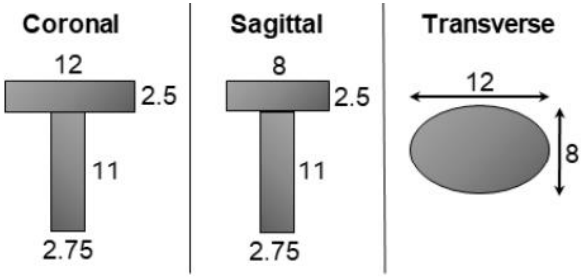
DAIR (n=6)

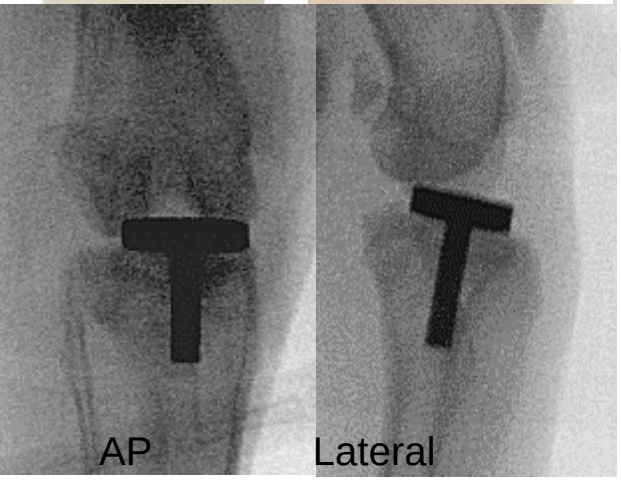
- Radical debridement
- 50mL saline irrigation
- Mechanical brushing for 1 minute
- 50mL saline irrigation

PhotothermAA gel (n=9)

- Coat surface with gel
- Incubate for 2 hours
- Laser heat using 808nm laser for 10 minutes
- Wash off

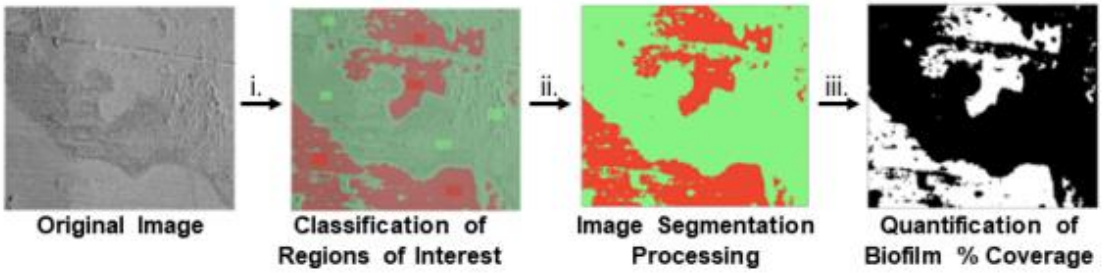
Titanium hemiarthroplasty was cemented into the tibia of New Zealand white rabbits and inoculated with $5x10^6$ CFU Staphylococcus aureus



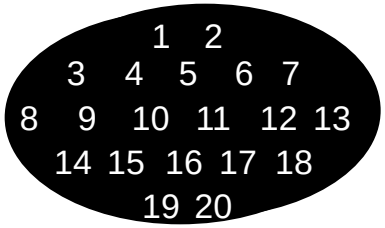


Outcomes

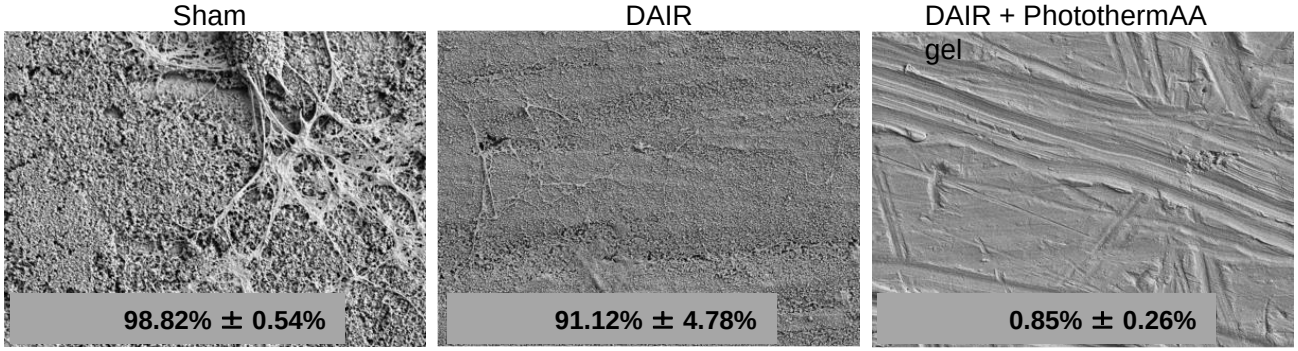
- 1ry: Implant Biofilm Coverage (SEM)
- 2ry: 4 samples
  - –Cultures
  - –Colony Forming Units (CFU)



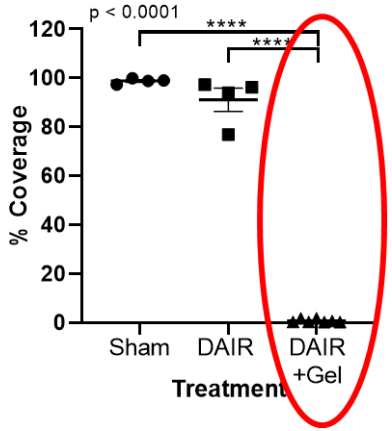
Results: DAIR + PhotothermAA gel significantly decreases biofilm coverage



20 standardized images – SEM (1,500X) + Trainable Weka Segmentation



96% 81% 1.8%

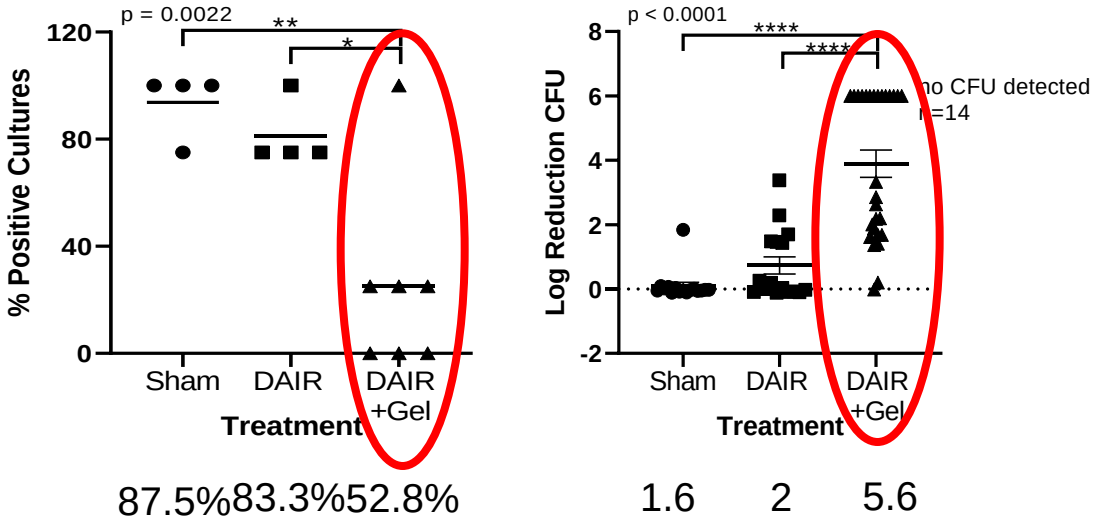


n=4 sham
n=4 DAIR
n=7 DAIR + Gel

Visperas et. al. *JBJI* 2022

DAIR + PhotothermAA gel significantly decreases soft tissue infection

Samples – 3 periprosthetic tissues + synovial fluid
1 week culture regrow + overnight plating



n=4 sham
n=4 DAIR
n=7 DAIR + Gel

87.5% 83.3% 52.8%

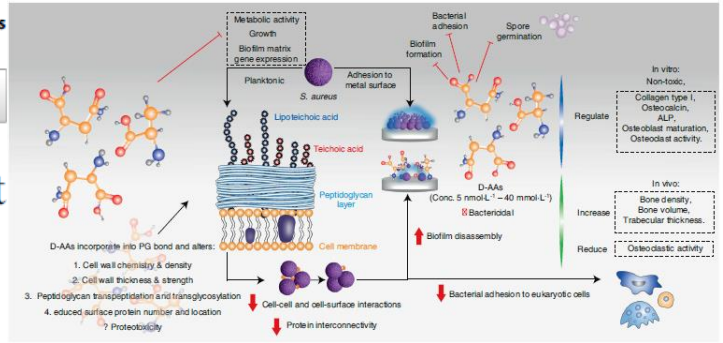
1.6 2 5.6

Discussion

- DAIR + PhotothermAA gel significantly decreases:
  - Biofilm coverage when assessed 2 weeks after treatment
  - Bacterial burden in soft tissue

Bone Research

www.nature.com/boneres



REVIEW ARTICLE OPEN

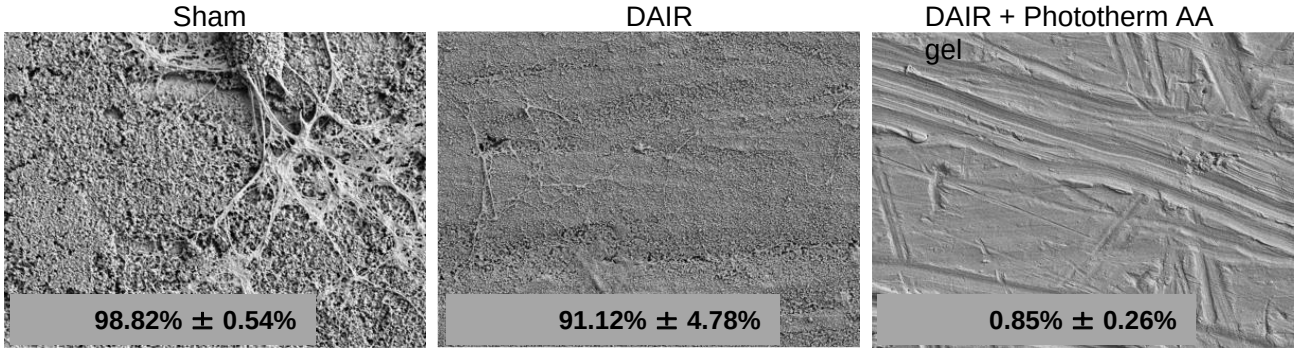
Promising applications of D-amino acids in periprosthetic joint infection

Matthew Caldwell[1], Megan Hughes[2], Fei Wei[1], Christopher Ngo[1], Raven Pascua[3], Abinaya Sindu Pugazhendhi[1] and Melanie J. Coathup[1]✉

Bone Research (2023)11:14 ; https://doi.org/10.1038/s41413-023-00254-z

Study Limitations

- Small sample size
- SEM quantification
  - % coverage, does not account for the thickness of biofilm
- Biofilm in soft tissue and bone was not assessed
- Relationship with full eradication still needs to be measured



Conclusion

DAIR + PhotothermAA gel treatment significantly decreases biofilm coverage on infected knee implants and soft tissue infection in a rabbit PJI model

The Journal of Arthroplasty xxx (2024) 1–7

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

2024 Knee Society Award

The Mark Coventry Award: PhotothermAA Gel Combined With Debridement, Antibiotics, and Implant Retention Significantly Decreases Implant Biofilm Burden and Soft-Tissue Infection in a Rabbit Model of Knee Periprosthetic Joint Infection

Carlos A. Higuera-Rueda, MD [a], Nicolas S. Piuzzi, MD [b, c], Nathalie B. Milbrandt, PhD [d], Yu Hsin Tsai, BS [d], Alison K. Klika, MS [b], Anna Cristina S. Samia, PhD [d], Anabelle Visperas, PhD [b, c, *]

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[b] Department of Orthopaedic Surgery, Cleveland Clinic Adult Reconstruction Research (CCARR), Cleveland Clinic, Cleveland, Ohio
[c] Department of Bioengineering, Cleveland Clinic, Cleveland, Ohio
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Periprosthetic joint infection and immunity: Current understanding of host–microbe interplay

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REVIEW

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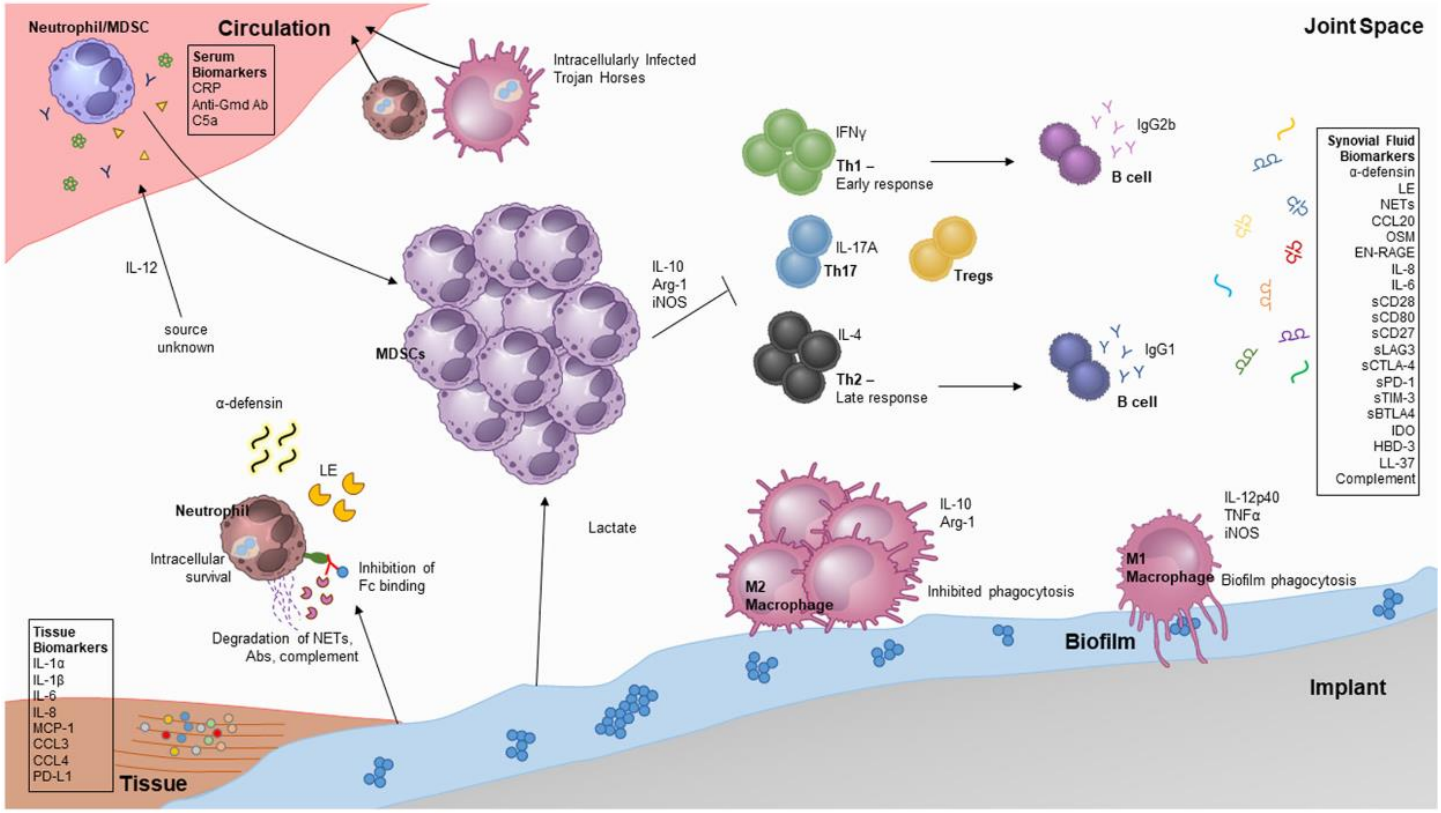

Summary

- PJI is a devastating complication that increases mortality, morbidity and cost
- 1 and 1.5 stage revision utilization is on the rise – clearer indications
- Extensive Debridement, Clean and Dirty set up, Vanco IO and tailor antibiotics locally and systemically – Keep in mind principles
- Time for reimplantation is still unclear
- New advances in technology may change the way we treat PJI in the near future

Thank You !

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