Do We Need an Alternative Approach to the Management of Osteomyelitis?

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Chairman, Founder: The Osteomyelitis Center of Central Florida
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Former Medical Director of Education and Research: The Wound Care Center at LRH

What Is Thought To Be The Problem?

- Mayo Clinic in 2015 reported on the epidemiology of osteomyelitis in the United States between 1969 to 2009.
- The incidence remained relatively stable among children and young adults but almost tripled among individuals older than sixty years; this was partly driven by a significant increase in diabetes-related osteomyelitis from 2.3 cases per 100,000 person to 7.6 cases per 100,000 person
- The reasons for the increase in osteomyelitis between 1969 and 2009 are unclear but could comprise a variety of factors, including changes in diagnosing patterns or increases in the prevalence of risk factors (e.g., diabetes) in this population.

The Real Problem

Increasing Treatment Cost/Burden

High Reoccurrence Rates

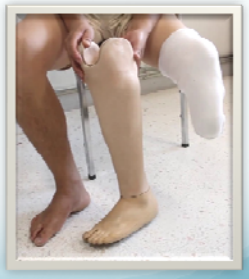
Recalcitrant Infection from Biofilm/Micro Disease

The Cost of Osteomyelitis

- For 2010 the annual yearly costs of diabetes in and its complications in the U.S. were $0.8 billion (type 1 diabetes), $10.1 billion (type 2 diabetes), and $10.9 billion (total).
- The average cost of a hospital admission in the US for osteomyelitis was estimated at US **$35,000.00.**
- The estimated osteomyelitis yearly cost is approximately 3.6% of the annual yearly costs of diabetes - **$392.4 million.**

The Cost of Osteomyelitis

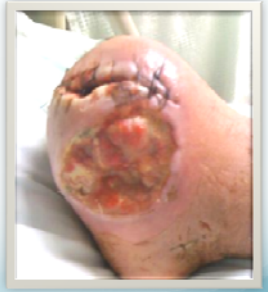
- The presence of osteomyelitis significantly increases the individual's chance of lower extremity amputation[1]
- Minor amputation rates reported as high as 35%[1]
- Major amputation rates as high as 16%[1]



Diabet Foot Ankle. 2012; 3: 10.3402/dfa.v3i0.18809.

The Cost of Osteomyelitis

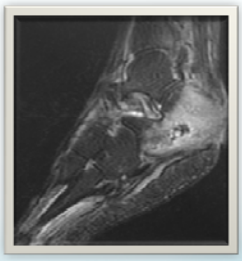
- Rate of Residual Osteomyelitis after Partial Foot Amputation in Diabetic Patients - The overall rate of residual osteomyelitis was 40.7%[1]
- Patients who underwent toe amputation with joint disarticulation had a positive margin culture rate of 23.1%[1]
- Patients who underwent partial metatarsal or transmetatarsal amputation had a positive margin culture rate of 57.1%[1]



1. JFAS Nov/Dec 2012. Volume 51, Issue 6, Pages 749–752

Reoccurrence Rates are High

- Despite advances in both antibiotics and surgical treatment, the long-term recurrence rate remains at approximately 20–30% [1]



1 Conterno LO, da Silva Filho CR. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev. 2009;3

Reoccurrence Rates are High

- There is no evidence that antibiotic therapy for more than 4–6 weeks improves outcomes compared with shorter regimens, and there is no evidence that prolonged parenteral antibiotics will penetrate the necrotic bone

Reoccurrence Rates are High – Are The Antibiotics to Blame?

- Outcomes for osteomyelitis caused by *S. aureus*, were also compared according to the antibiotic used[1]
- Recurrence appeared to be more likely for subjects treated with cefazolin (34.8%), vanco- mycin (53%)[1]
- Vancomycin-treated infections were nearly three times more likely to recur[1]

1. Tice et al *Journal of Antimicrobial Chemotherapy* (2003) **51**, 1261–1268

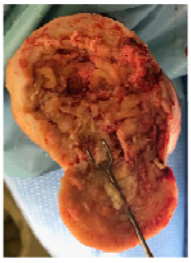
Reoccurrence Rates are High – Are The Bacteria to Blame?

- In adult contiguous focus osteomyelitis the most common bacteria is *S. aureus* methicillin-susceptible (52%) with *P. aeruginosa* accounting for about 4.5%[1]
- When *P . aeruginosa* was the initially recovered pathogen, the risk of recurrences was more than twice that of *S. aureus* infections[1]
- There was also a strong correlation between *P. aeruginosa* and amputations.[1]

1. Tice et al *Journal of Antimicrobial Chemotherapy* (2003) 51, 1261–1268

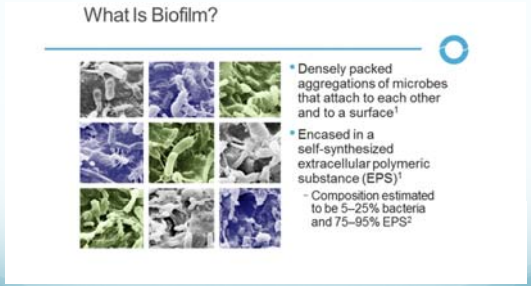
Reoccurrence Rates are High – Is Surgery to Blame?

- This study evaluated 27 diabetic patients who had a forefoot amputation (toe, partial ray, or trans-metatarsal) for osteomyelitis to determine if bone margins were negative for residual osteomyelitis.[1]
- The overall rate of residual osteomyelitis was 40.7%[1]



1. Atway S et al., The Journal of Foot & Ankle Surgery 51 (2012) 749–752

Biofilm/Recalcitrant Infection



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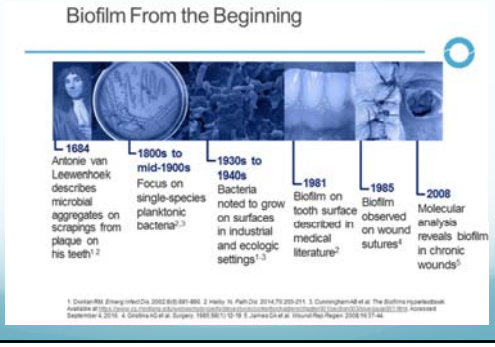

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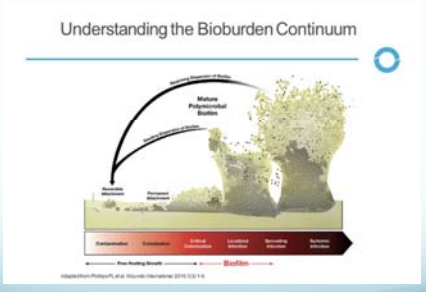

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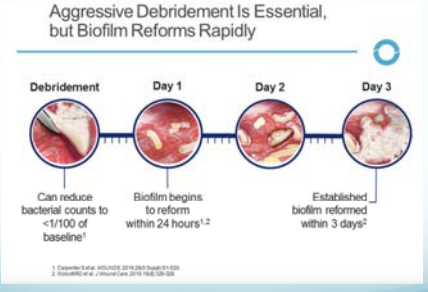

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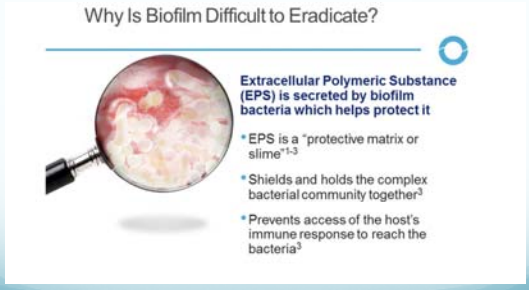
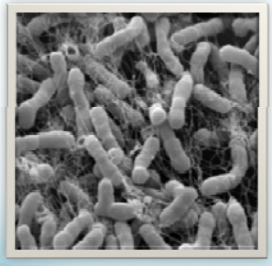
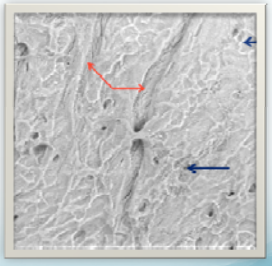


Biofilm/Recalcitrant Infection

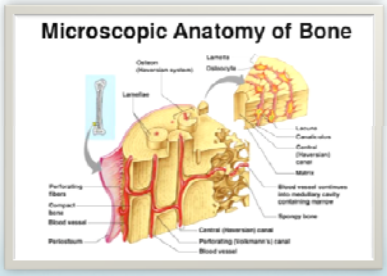
Biofilm



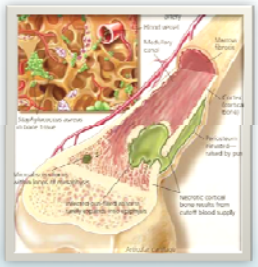
Micro Disease



Normal Bone Anatomy



Biofilm/Recalcitrant Infection



Compounding The Problem

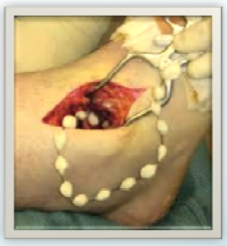
Antibiotic Carrier Vehicle Limitations

Limited Antibiotic Selection

Limited Antibiotic Elusion

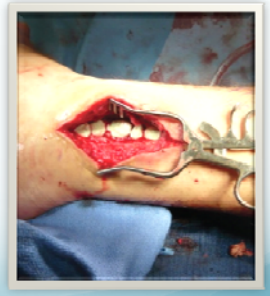
Antibiotic Carrier Vehicles – PMMA Limitations?

- Release of antibiotics contained within PMMA bone cement relies on surface elusion
- Prolonged low-level release of antibiotics below the minimum inhibitory concentration needed to eradicate organisms creates multi-drug resistant organisms
- Once the antibiotic levels are too low to kill organisms the PMMA itself can become colonized and organisms are able to form a biofilm upon its surface



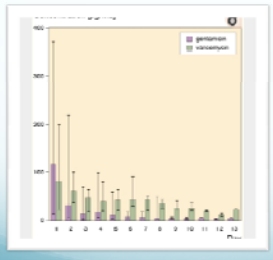
Antibiotic Carrier Vehicles – PMMA Limitations?

- Limited compatibility due to the exothermic polymerization reaction
- Requirement of a secondary surgery for removal

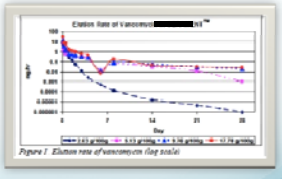


Antibiotic Carrier Vehicles – PMMA Limitations?

PMMA Elusion



CaS/CaP Elusion

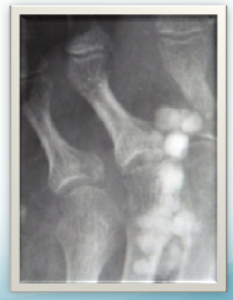


Antibiotic Carrier Vehicles – PMMA Limitations?

- The elusion of a drug from a carrier vehicle is paramount to the successful delivery of that drug to the bacteria and the subsequent eradication of those bacteria.
- Calcium sulphate/phosphate BVF vancomycin elusion concentration initial release was at 10+ mg/hr vs. about 0.25 mg/hr for the PMMA vancomycin elusion rates. The tail concentration plateau elusion rates for BVF was maintained at 0.5 mg/hr for four weeks vs. 0.05 mg/hr for the PMMA

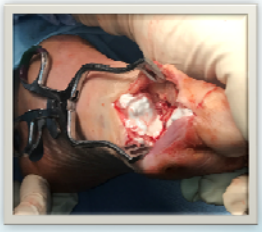
Antibiotic Carrier Vehicles – Calcium Sulfate Limitations?

- The beads are brittle and are reabsorbed quickly as the beads are hydrolyzed.
- The bead dissolution occurs at a faster when antibiotics are added



Antibiotic Carrier Vehicles – Ceramic Limitations - Leakage?

- Unable to maintain the bone void filler with antibiotics in the dysvascular and avascular bone to allow complete bacteria-drug interaction/contact

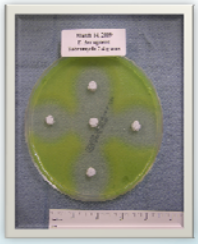


So What Is A Solution?

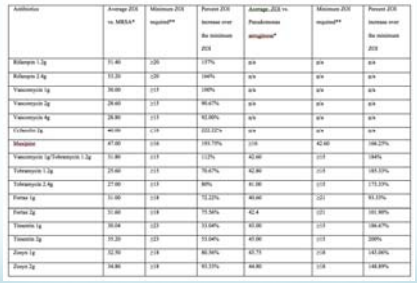
- Antibiotic sustained elusion at a sufficient concentration to have a bacterial-cidal effect on biofilm
- Able to Use a wide choice of antifungal and AB's
- Absorbable carrier vehicle
- We need a carrier vehicle that does all of this!

Sustained Drug Elusion

- Yes! - A carrier vehicle that can deliver antibiotics at extremely high levels well beyond minimal inhibitory concentrations to eliminate biofilm colonies within the disvascular and avascular infected bone surfaces.

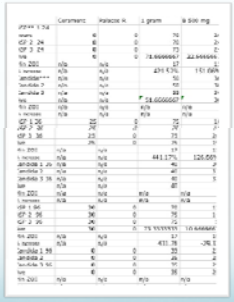


Sustained AB Elusion



Karr, JC, Keriazes G, Lautetta J. In Vitro Antimicrobial Activity of Calcium Sulfate and Hydroxyapatite (Cerament™| Bone Void Filler) Discs Utilizing Heat Sensitive and Heat Non-Sensitive Antibiotics against Methicillin Resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa. Journal of American Podiatric Medical Association Journal. Vol 101, No. 2, March/April 2011.

Sustained Antifungal Elusion



Karr, JC, Lautetta J. In Vitro Anti-fungal Disc Activity of Calcium Sulfate and Hydroxyapatite (Cerament™| Bone Void Filler) Loaded with Amphotericin B or Voriconazole for Consideration in Adjunctive Osteomyelitis Management. JAPMA Feb 105(2) 2015

Need to Be Able to Use a Wide Choice of AB's and Antifungal

Antibiotics Used

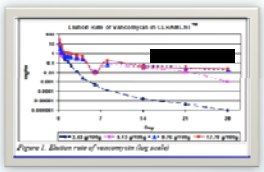
- Tobramycin
- Maxipime
- Vancomycin
- Zosyn
- Timentin
- Fortaz
- Cefazolin
- Rifampin
- Inipenim
- Cubacin
- PolyMyxin B

Antifungal/Yeast Used

- Voriconazole
- Amphotericin B

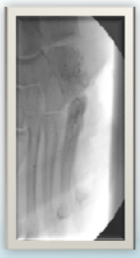
Improving AB elusions

- The tail concentration plateau elusion rates for BVF was maintained at 0.5 mg/hr for four weeks vs. 0.05 mg/hr for the PMMA



Problem Solved? – Find A Carrier Vehicle That Is:

- **Absorbable** - does not require removal after surgery and releases all of the antibiotics
- **Isothermic**, able to utilize multiple antibiotics and antifungal drugs
- **Flowable –** To penetrate dysvascular and avascular bone allowing complete bacteria-drug interaction/contact
- **Flowable option**
- Significant **drug elution** with therapeutic drug **inhibitory leve**ls obtained



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Thank You