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

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What Is Thought To Be The Problem?

- 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 presence of osteomyelitis significantly increases the individual’s chance of lower extremity amputation. Minor amputation rates reported as high as 35%. Major amputation rates as high as 16%.

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%. Patients who underwent toe amputation with joint disarticulation had a positive margin culture rate of 23.1%. Patients who underwent partial metatarsal or transmetatarsal amputation had a positive margin culture rate of 57.1%.

Reoccurrence Rates are High

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


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 used¹
- Recurrence appeared to be more likely for subjects treated with cefazolin (34.8%), vancomycin (53%)¹
- Vancomycin-treated infections were nearly three times more likely to recur¹

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%.
- When *P. aeruginosa* was the initially recovered pathogen, the risk of recurrences was more than twice that of *S. aureus* infections.
- There was also a strong correlation between *P. aeruginosa* and amputations.


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.
- The overall rate of residual osteomyelitis was 40.7%.


Biofilm/Recalcitrant Infection

What is Biofilm?

- Densely packed aggregations of microbes that attach to each other and to a surface.
- Enclosed in a self-synthesized extracellular polymeric substance (EPS).
- Composition estimated to be 5–25% bacterial and 75–95% EPS.
Biofilm/Recalcitrant Infection

Biofilm From the Beginning

100s to mid-1000s
Focus on single-species bacteria

Bacteria tend to grow on surfaces in industrial and ecological settings

1961 Biofilm on biofilm surface seen in medical literature

1981 Only known on your skin

2006 Molecular basis for biofilm in chronic wound

Biofilm/Recalcitrant Infection

Understanding the Bioburden Continuum

Aggressive Debridement Is Essential, but Biofilm Reforms Rapidly

Debridement

Day 1

Day 2

Day 3

Can reduce bacterial counts to <10^3 CFU/g of tissue

Biofilm regrows to reform within 24 hours

Enhanced biofilm formed within 3 days
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

PMMA Elusion vs. CaS/CaP Elusion

- 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 rate 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 bactericidal 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


Sustained Antifungal Elusion

Karr, JC, Lautetta J. In Vitro Antifungal Disc Activity of Calcium Sulphate and Hydroxyapatite Cerament™ Bone Void Filler Loaded with Amphotericin B or Voriconazole for Consideration in Adjunctive Osteomyelitis Management. JOPMB. 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
- Imipenem
- Cubacyn
- 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 levels obtained