The *Most Important* Paper I Have Read This Year

*COA Annual Meeting: June 1, 2014*

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Chief, Orthopaedic Trauma Service
Stanford University School of Medicine
 Advances in Treatment and Understanding of Musculoskeletal Infections

David W. Lowenberg, MD

My disclosure is in the Final Program and in the AAOS Orthopaedic Disclosure program.

- My disclosure is:
- Consultant: Stryker Orthopaedics
- Board of Directors: Foundation for Orthopaedic Trauma
Dr. Harry J. Buncke
(1922 – 2008)

“The Father of Microsurgery”
Dr. George Cierny, III
(1947 – 2013)

“The Father of Osteomyelitis Surgery”
“Can We Trust Intraoperative Culture Results in Nonunions?”

Can We Trust Intraoperative Culture Results in Nonunions?
Palmer, Michael P; Altman, Daniel T; Altman, Gregory T; Sewecke, Jeffrey J; Ehrlich, Garth D; Hu, Fen Z; Nistico, Laura; Melton-Kreft, Rachel; Gause, Trent M III; Costerton, J William

Journal of Orthopaedic Trauma., POST ACCEPTANCE, 26 December 2013
Can We Trust Intraoperative Culture Results in Nonunions?. OBJECTIVE: To identify the presence of bacterial biofilms in nonunions comparing molecular techniques (multiplex PCR and Ehrlich, Garth D PhD
Search PubMed:
“Infected Nonunion”

- 1964 to March 8, 2014
- 276 Articles
Search PubMed:

“Infected Nonunion”

- 74 articles actually on infected nonunions.
- 68 of them are retrospective case reviews.
- 3 are review articles.
- 1 is a “Mo Review”.

74 articles actually on infected nonunions.
Texts on the Subject
Search PubMed:  
“Infected Nonunion”

- **2 Articles actually studying the entity:**


- Utility of pre-op inflammatory markers in diagnosing infection.
Search PubMed: “Infected Nonunion”

“Can we trust intraoperative culture results in nonunion?”

- Took 34 nonunions and cultured swabs and tissue from the nonunion site.

- Also sent these tissue specimens for *Rapid Sequence PCR in line with Mass Spectometry* (Ibis, Plex ID System, Carlsbad, CA)

- Then confirmed results for those Plex ID system positive results with *Fluorescence in situ hybridization* (FISH).
Microbe Identification

- Unfortunately, **Tissue Cultures** still remain the Gold Standard.

- In chronic musculoskeletal infections there is often poor recovery of microbes, might be that they are more difficult to grow with current plating techniques when they are in **Sessile State (Biofilm)**.

- Culture & plating remains an inefficient modality, with a low sensitivity but high specificity.
Plex ID System

- Utilizes Rapid PCR combined with Mass Spectrometry.
- Uses mass spectrometry to measure characteristic genome weights after amplification with PCR.
Plex ID System

- 98% sensitive and specific for 188 microbial genomes in 6 hours.
“Can we trust intraoperative culture results in nonunion?”

- 8/34 prospective nonunions Cx+ at surgery
- 30/34 Bacterial DNA + by Plex ID
- All 8 Cx + also Plex ID + and for at least the same organisms
- All Plex ID + confirmed by FISH
“Can we trust intraoperative culture results in nonunion?”

Culture + by Plex ID:

- 62% polymicrobial +
- 41% S. aureus +
- 21% Treponema species +
Distributed Genome Hypothesis

- DNA in biofilm (especially in musculoskeletal & oral infections) can be polymicrobial.

- This represents a potential “supragenome” that acts as a pool for microbe adaptation.

- This represents another method for microbes to overcome host defenses in the biofilm.
Implications

- As with otitis media and prostatitis, probably most infected nonunions are polymicrobial in nature.

- The bacterial flora is in the sessile and persister cell state, therefore hard to culture and hard to eradicate.
The Battle

- Prokaryotes vs. Eukaryotes
Ratio of cell types in our “Biosphere”

Prokaryotes : Eucaryotes

• 10 to 1

Viruses : Prokaryotes

• 10 to 1

Viral particles : Us = 100 to 1

400 microbial genes for each human gene in the body
Pathogen … What is it??

- “…many pathogens did not initially evolve as pathogens, but simply take on this role as a result of a lack of ability of the host to maintain homeostasis.”

“To beat microbes we first must learn to think like microbes”
Importance of Bacterial “Phase” in the Host

**Planktonic**
- This represents the initial innoculum phase.
- The bacteria have a high metabolic rate.
- They are “free floating”.

**Biofilm**
- This represents the semi-dormant bacterial phase where the microbe is “trying” to live in a symbiotic state.
- Low metabolic rate.
- Adherent to the biofilm.
- $10^3$ times less sensitive to most antibiotics.
Bacteria are smarter than we are
Importance of Biofilm State

- Difficulty with antibiotic penetration.
- Stress Response - Dormant State
- Bacteria protected in the biofilm.
- *Persister Cells*
Why else does bacterial adaptation occur so rapidly?

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>GENERATIONAL CYCLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria (planktonic)</td>
<td>20 – 30 minutes</td>
</tr>
<tr>
<td>Bacteria (sessile, in biofilm)</td>
<td>hours to a day</td>
</tr>
<tr>
<td>Man</td>
<td>20 – 30 years</td>
</tr>
</tbody>
</table>
“Plex ID Evaluation of Articular Cartilage in the Arthritic Knee”

Ehrlich GD, et al

- Took 10 patients at time of TKA and harvested remnants of articular cartilage.
- Ran the samples through the Plex ID system.
“Plex ID Evaluation of Articular Cartilage in the Arthritic Knee”

Ehrlich GD, et al

- 8/10 (80%) Plex ED + for microbial DNA.
- All these 8 Plex ID + for Treponema.
Heresy

The specifics of the microbe are less important than the specifics or condition of the host.
Thank You