Cardiovascular Device Infection and the Role of Biofilm

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Dr. Robert Padera declares he has NO conflict of interest to disclose.

Outline

• Case of medical device infection
• Medical device infections and biofilm
• Biofilm formation and biology
• Potential therapies and interventions

Case – Medical Device Infection

• 62F with coronary artery disease and old myocardial infarction
• Developed end-stage heart failure – listed for transplant
• HeartMate II ventricular assist device as bridge to transplant

Case – Medical Device Infection

• Presented 6 months later – fever, malaise and drainage/dehiscence of driveline – prior driveline site trauma
• Blood and driveline cultures grew Staphylococcus epidermidis
• Driveline site debrided, vacuum drain placed, and appropriate antibiotics started
• Improved, discharged home after 10 day hospital course
• Re-presented 2 weeks later after mechanical fall with head strike
• Prior to this had several days of progressive fatigue, weakness, drowsiness and increased drainage from driveline
• Blood and driveline cultures grew Staphylococcus epidermidis
• Fall resulted in fatal subdural hematoma

Driveline Exit Site
Pump Pocket

Driveline Healing

Well healed
Poorly healed (our case)

Gram Stain

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Infections and Biomaterials

- Elek and Cohen (1957) – foreign body decreased the threshold infection-causing inoculum from $10^8$ to $10^2$ for *S. aureus*
- Common organisms in biomaterial-related infections
  - Staph. epidermidis
  - Staph. aureus
  - Strep. viridans
  - Enterococcus faecalis
  - Pseudomonas aeruginosa
  - Proteus mirabilis
  - Escherichia coli
  - Klebsiella
  - Candida
  - Aspergillus

Gram positive bacteria

Gram negative bacteria

Fungus

Medical Device Infections and Biofilm

- Biofilm implicated in 65% of hospital infections
- Cost estimates ~$25 billion per year in US (~2 “Walls”)
- Current treatment – antibiotics and device removal
Biofilm

- Biofilm: Multicellular consortium of microbial cells, irreversibly associated with a surface and enclosed in a self-produced extracellular matrix composed primarily of polysaccharides
- Natural process—environmental, industrial and medical systems
- Overwhelming majority of earth’s microbial biomass exists as biofilm rather than in free-floating (planktonic) form

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Biofilm Formation

1: Initial attachment
2: Matrix production for enhanced adherence
3: Early biofilm development
4: Biofilm maturation and differentiation
5: Organism dispersion

Stoodley et al., Anna Rev Microbiol 2002; 56:187-209

Why Bother? – Advantages of Biofilm

- Protection from external environment
  - Desiccation, chemical/osmotic shifts
  - Protozoa, host macrophages and neutrophils
  - Bactericidal molecules made by other organisms, antibiotics
- Cooperation, diversity, division of labor
  - Specialization, conservation of resources
  - Horizontal transfer of beneficial genetic material
  - “Persister” cells

Donlan and Costerson, Clin Microbiol Rev 2002; 15:167-93

Attachment to Surface

- Conditioning film formation on material surface
  - Host adhesive molecules (e.g., fibronectin, proteoglycans)
- Binding to conditioning film or to bare biomaterial
  - Organism surface molecules (e.g., Staphylococcal surface protein-1, autolysin E, fibrinogen binding protein FbpA)
- Practice – 3.5-3.6 billion years
- Reversible attachment
- Still behaving like planktonic bacteria
  - Not yet committed to biofilm lifestyle

Matrix Production and Early Biofilm Formation

- Fundamental switch in gene expression reflects commitment to biofilm lifestyle
  - Upregulate ECM production for irreversible attachment
  - Change in modes of locomotion (pili replace flagella)
  - Change in intercellular interactions (upregulate polysaccharide intercellular adhesin (PIA))
  - How do they know when it is time to make this switch?
**Quorum Sensing**

- HSL - N-acyl-L-homoserine lactone
- [HSL] reflects number and proximity of organisms; perception of a threshold concentration indicates a certain density of organisms
- Provides cell density-dependent gene regulation

**Quorum Sensing**

- Communication system for microorganisms to monitor population density and establish cooperative behavior
- *Vibrio harveyi* bioluminescence

**Quorum Sensing**

- Signaling molecules are species-specific
- Allows for “jamming” other organisms signals

**Biofilm Maturation**

- Radically different phenotype than planktonic organisms in *P. aeruginosa* studies
  - 50% of proteome with at least 6-fold difference in expression, including 300 new proteins not expressed by planktonic forms
- Generation of complex architecture – nutrient-driven
- Variation in growth rates – detection
- Redistribution and differentiation of cells
- Persister cells – stem-like properties

**Persister Cells**

- Cells resistant to a lethal dose of antibiotics (or other lethal stresses) with the ability to re-grow the biofilm
- Likely why only effective therapy is removal of infected device

**Persister Cancer Stem Cells**

- Cells resistant to a lethal dose of antibiotics, chemotherapy, radiotherapy (or other lethal stresses therapies) with the ability to re-grow the biofilm tumor
Cheats
- Biofilm provides benefit to population of individual organisms
- Exploitation by “cheats” – individuals that avoid the cost of producing goods while benefiting from those produced by others

Organism Dispersion
- Release of cells or groups of cells from biofilm
- Least well understood of biofilm processes
- Likely mediated by quorum sensing, nutrient depletion
- Mechanical/hydrodynamic forces in cardiovascular device infections
- Change in gene expression back to planktonic program with release of matrix degrading enzymes

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Potential Therapies/Interventions
- Prevent bacterial adhesion
- Disrupt quorum sensing – extracellular and intracellular signaling pathways – mother nature
- Degrade/disrupt extracellular matrix
- “Trojan horse” – introducing cheats, lytic bacteriophage
- Mechanical disruption - ultrasound
- Device design (e.g., smaller, eliminate driveline)
- Combination of all of the above and more

Potential Therapies/Interventions
- Promote healing – “race to the surface”

Take Home Points
- Medical device infections are predominantly caused by biofilm-forming organisms
- Organisms behave very differently in biofilm vs. free-floating (planktonic) forms
  - Quorum sensing
  - Changes in gene expression
  - Persister cells
- By understanding mechanisms of disease, novel therapeutic strategies to prevent and treat these infections can be designed

Gristina AG. Science 1987; 237:1588-95
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