Biofilms in Human Disease
Dr. Ryan Jordan, Cytergy
A Webber Training Teleclass

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• Senior Research Engineer, Center for Biofilm Engineering at Montana State University (1995-2003)
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• Editor-in-Chief, Biofilms Online (1999-2003)
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About Cytergy
• Scientific e-Learning Packaged Courseware (www.Cytergy.com)
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Outline
1. Biofilm Fundamentals
2. Survey of Biofilms in Human Health
3. Therapeutic Strategies for Biofilm Control
4. Biofilms and Antimicrobial Resistance
5. Anti-Biofilm Medical Devices
6. New Frontiers: Intercellular Chemical Signaling

What is a Biofilm?
• A community of microorganisms attached to a surface
• Contrast to “planktonic” cells:
  – Individual cells suspended in a fluid medium

What Makes up a Biofilm?
• Living microorganisms
  – Bacteria, yeast, algae, protozoa
• Dissolved & solid organic byproducts
  – Polysaccharides, lipids, proteins
• Solid inorganic detritus
  – Minerals, soil
• Dissolved inorganics
  – Metal salts, cellular metabolism byproducts
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What are Key Features of Biofilm?
- Multicellular
- Multispecies
- Extracellular polysaccharide (EPS) matrix
- Three dimensional structure

How Does Biofilm Form?
- Three Key Processes:
  - Attachment
    - Adsorption / adhesion of a microbial cell to a solid surface
  - Colonization
    - Establishment of a microbial community at the site of attachment
  - Growth
    - Maturation of a three-dimensional biofilm community

Where are Biofilms Found?
- Natural environment
  - e.g., streambed
- Industrial systems
  - e.g., water distribution pipes
- Human body
  - e.g., mouth, stomach lining, skin
- Criteria for biofilm growth:
  - Any confluence of a water-based fluid, a surface, and microorganism
What Makes Biofilm Ubiquitous?
- Microorganisms are ubiquitous
- Biofilm is the preferred mode of growth
  - Individual & community efficiency
  - Survival mechanism
- Resistance to extreme conditions
  - Heat & cold
  - Starvation
  - Dessication
  - Resistance to toxic substances

2. Biofilms in Human Health
- Waterborne Illnesses
- Airborne Illnesses
- Foodborne Illnesses
- Household Biofilms
  - Medical Devices & Implants
    - Infectious Diseases
    - Dental Health

Medical Devices and Implants
- Catheterization
- Prosthesis
- Superficial Reconstruction
- Organ Transplant & Repair
- Wound Healing

Catheterization
- Catheters and other invasive devices are the #1 exogenous cause of hospital-acquired infections
- Central venous catheters
- Foley (urinary) catheters

Biofilm on Intravenous Catheter
Connecter 24 hours after Insertion

Prostheses
- Artificial limbs
- Prosthetic eyes
- Dentures
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Superficial Reconstruction  
- Epidermal infection  
- Subcutaneous infection

Organ Transplant & Repair  
- Kidneys  
  - transplant, dialysis*  
- Heart  
  - transplant, artificial organ, valve repair or replacement  
- Contamination during organ transfer

Wound Healing  
- Contamination from outside environment  
- Proliferation of infection in the wound  
- Proliferation of infection in the wound dressing

Infectious Diseases  
- The role of biofilms in originating, mediating, and proliferating infectious diseases is becoming more important (better understood) with an increasing number and variety of infections.

Biofilms are Indigenous to the Body  
- Healthy microflora exists in:  
  - Ear, nose, mouth, and throat  
  - Gastrointestinal tract  
  - Skin  
  - Vagina  
  - Bowels, colon  
  - Etc.

Biofilm Mediated Infectious Diseases  
- Eyes  
- Ear, Nose, and Throat  
- Heart & Lungs  
- Gastrointestinal Tract  
- Urinary & Sexual Function  
- Skin
Infectious Diseases of the Eye
- Conjunctivitis
- Dacryocystitis (infection of the lacrimal sac)
- Bacterial corneal ulcer (photo)

Infectious Diseases of the Ear, Nose, and Throat
- Tonsillitis & pharyngitis
- Sinusitis
- External otitis
- Bronchiolitis
- Diptheria

Otitis media
- Normal Eardrum
- Infected with acute Otitis media

Heart and Lungs
- Tuberculosis
- Whooping cough
- Myocarditis, pericarditis (e.g., meningococcal meningitis)
- Endocarditis

Pneumonia

Cystic Fibrosis
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Endocarditis

Other Biofilm Mediated Diseases
- GI Tract Infections
- Urinary Tract Infections
- Skin Infections

Dental Health
- Dental Caries
- Periodontal Disease
- Halitosis
- Dental Unit Waterlines

Dental Caries
- Description
  - Enamel-bound biofilm (plaque) metabolism of carbohydrates (sugars and starches), producing acids that dissolve tooth enamel
- Control
  - Plaque removal is extremely difficult after it has formed highly calcified deposits on the enamel surface
  - Physical removal of the biofilm (flossing, brushing, professional cleaning)
- Prevention
  - Antimicrobial rinses
  - Fluoride
  - Dental sealants

Periodontal Disease
- Definition
  - Infection of tissues surrounding and supporting the teeth; key cause of tooth loss in older adults
- Stages
  - Gingivitis (early)
  - Periodontitis (late)
- Role of biofilm
  - Biofilm colony infestation into the gum tissue
  - Remote location makes it extremely resistant to antimicrobial therapies
  - Emphasizes the need for debridement as the primary treatment
- Prevention
  - Development of rinse treatments that prevent biofilm colonization of gum tissues

Halitosis
- Cause
  - Metabolic activity of oral bacterial biofilm feeding on post nasal drip (back of tongue)
  - Protein metabolizers (in contrast to sugar metabolizers)
- Compounds produced
  - Hydrogen sulfide (rotten eggs)
  - Methyl mercaptan & skatole (feces)
  - Cadaverine (corpses)
  - Putrescine (decaying meat)
  - Isovaleric acid (feet)
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Dental Unit Waterlines

- Problem Scope
  - Biofilm growth in dental unit waterlines poses potential risk of pathogen exposure to patients
  - Exposure risk is highest to immunocompromised individuals

Dental Unit Waterlines

- Why are DUW’s are so susceptible to biofilm formation?
  - Flow is low volume, slow, and laminar
  - Small tube diameter, high SA/V ratio
  - Long tubing lengths
  - Room temperature or warmer
  - Plastic tubing

DUW Biofilm Control Strategies

- Cleaner source water (e.g., independent reservoir systems)
- Point of use microorganism filtration (e.g., reverse osmosis)
- Point of use disinfection (e.g., UV irradiation)
- Regular DUW maintenance
  - Chemical cleaning
  - Physical cleaning
  - DUW replacement

3. Therapeutic Strategies

- Disruption of biofilm cell function
- Disruption of biofilm structure
- Inhibition of biofilm growth

Disruption of Biofilm Cell Function

- Traditionally accepted method for antibiotic-based infection control
- Objective
  - Kill individual cells by targeting specific cell function
- Problem
  - Biofilms are notorious for their ability to “protect” individual cells in their community

Disruption of Biofilm Structure

- Traditional method in cleaning industrial manufacturing equipment
  - Soaps, detergents, surfactants, physical removal
- Problematic in-vivo due to potential for negative host response (side effects)
Disruption of Biofilm Structure

- Objectives
  - BIOFILM → PLANKTONIC
  - Disrupt the EPS matrix that binds cells together
  - Promote cell detachment from the surface
- Much room for R&D
  - Biofilm disrupting chemicals
  - Methods of implementing / delivery

Inhibition of Biofilm Growth

- Create either
  - An anti-biofilm surface
  - An anti-biofilm forming cell
- Antimicrobial coatings
  - Devices & implants
- In-vivo strategies for tissue infection prevention?

4. Antimicrobial Resistance

- Nosocomial infections
- Antibiotic resistant bacteria
- Mechanisms of antimicrobial resistance by biofilms

Nosocomial Infections

- Antibiotic resistant bacteria
- Hospital air & water systems
- Hospital staff sanitation
- Reusable device / instrument contamination
- Surgical procedures

The Nosocomal Troika

- Staphylococci
- Pseudomonads
- E. coli
- Note: These families of organisms are known to produce healthy, antimicrobial-resistant biofilms

Common Nosocomial Infections

- Nosocomial pneumonia
- Surgical wound infections
- Vascular access-related bacteremia

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Nosocomial Bacteria: The Problem
- Acquired antibiotic resistance
- Organism of greatest concern:
  - Vancomycin-resistant Staphylococcus aureus (VRSA)

Antibiotic Resistant Bacteria
- Hospitals, and especially, intensive care units (ICU’s), are a breeding ground for ARB’s
- The risk of leaving a hospital with an ARB infection is real
- More info:
  - http://www.cdc.gov/drugresistance/

Biofilms and Nosocomial Infections
- Biofilms are playing an increasingly important role in the spread of nosocomial infections because:
  - Renovation of aging hospitals increases risk of airborne fungal and bacterial pathogens present as biofilm in the infrastructure (molds, Legionella)
  - Increasingly aggressive medical and surgical interventions (implants, organ transplants, device use) places patients at a higher risk

Mechanisms of Antimicrobial Resistance by Biofilms
- Slow penetration
  - Failure of antimicrobial to penetrate biofilm structure
- Stress response
  - Failure of antimicrobial efficacy against a stressed microorganism
- Altered microenvironment
  - Reduced efficacy of antimicrobial agent in different parts of the biofilm
-Persisters
  - Survival of residual population following antimicrobial treatment

Slow Penetration
- Resistance results from the inability of the antimicrobial agent to reach all cells in a biofilm
  - Agent reacts with other components of the biofilm matrix
  - Concentration of agent is too low and remains diffusion-limited
Stress Response

- Some cells in a biofilm may be exposed to environmental stress (toxicity, lack of nutrients) and elicit a "stress response" that makes them less prone to attack by an antimicrobial agent.

Altered Microenvironment

- Localized microniches within a biofilm may harbor a microenvironment that may render an antimicrobial agent ineffective:
  - Changes in solution chemistry
  - Exudation of components that could neutralize the antimicrobial

Persisters

- Some of those little suckers just won't go away.
  - e.g., antibiotic resistant strains
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Mechanisms of Antibiotic Resistance in Biofilms
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Additional Resources (CD Courses)
http://www.Cytergy.com/
• "Biofilms"
  – An Introduction to Microbial Biofilm Science and Engineering Concepts, by Paul Stoodley
• "Medical Biofilm Microbiology"
  – The Role of Microbial Biofilms in Disease, Chronic Infections, and Medical Device Failure, by Bill Costerton
• "Battling Chronic Infections"
  – A State of the Science Review of Antimicrobial Resistance in Biofilms, by Phil Stewart

Additional Resources (Books)
http://www.Cytergy.com/
• "Advances in Biofilm Science and Engineering"
• "The Biofilm Laboratory"
  – Step-by-Step Protocols for Experimental Design, Analysis, and Data Interpretation, Ed. by M. Hamilton

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