

Bacterial Biofilms in Wounds

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Shriners Children's Texas

1

Financial Disclosures:

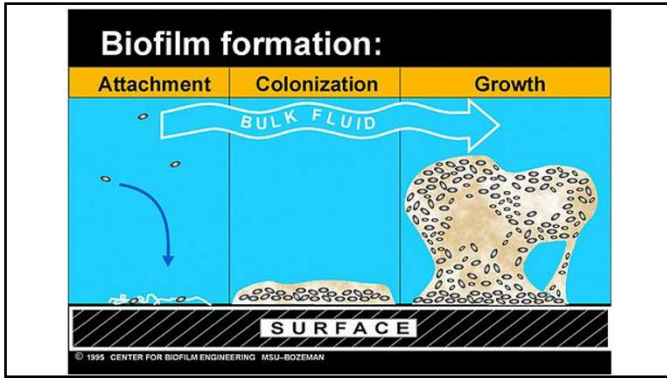
-Journal of Orthopaedic Research: Editorial or governing board
-JSOR: Editorial or governing board
-CDMRP Grant "Wound Stabilization for Prolonged Field Care"

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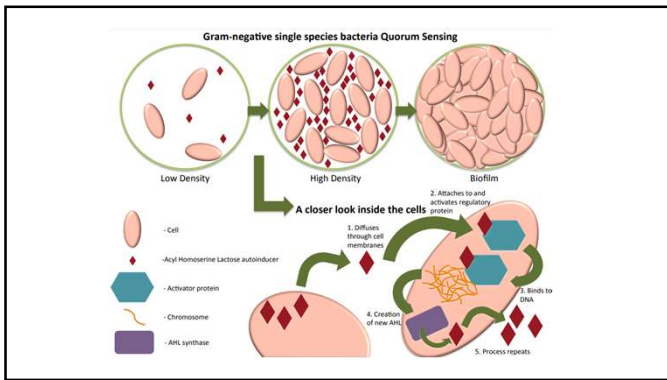
What is a biofilm?

- Bacterial phenotype (sessile form)
- Protected microbiological community found on surfaces
- Cells surrounded by extracellular polymeric substances (slime)
- Stress response to environmental factors
- Virulence factor
- Evidence they existed for 3.25 billion years
- Described in 17th century from scruff of teeth by van Leeuwenhoek
- Coined term in 1978 by Bill Costerton and introduced to medicine in 1985

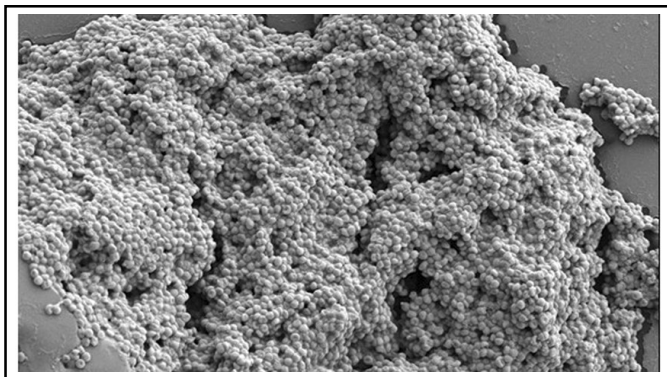
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Why do biofilms matter?

- Evidence for being primary reason for chronic and recalcitrant infections
- Protect microbes from immune cells
- They are **tolerant** to antibiotics

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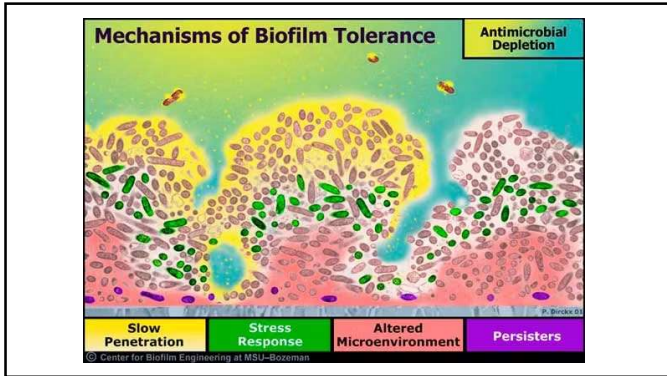
Antibiotic tolerance is the ability of bacteria to survive transiently under normally lethal antibiotic conditions.

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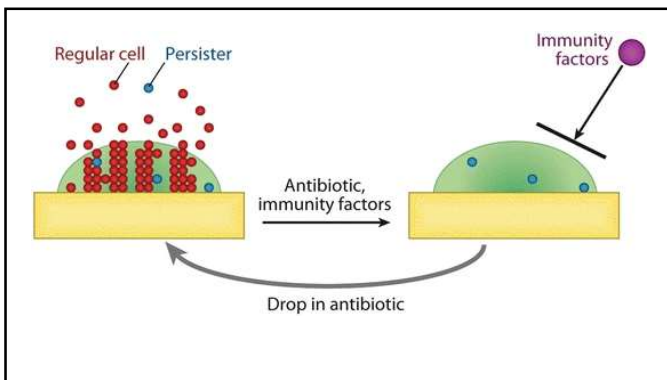
Antibiotic tolerance is the ability of bacteria to survive *transiently* under normally lethal antibiotic conditions.

Antibiotic resistance is genetic mutation (often through plasmid) that evolves bacteria to evade effects of antibiotics.

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Protected from immune response

Unlike planktonic bacteria, biofilm-associated bacteria benefit from **physical protection, altered physiology, immune evasion, and population heterogeneity**, making them far more difficult for immune cells to recognize, access, and eliminate.

12

1. Physical barrier of the extracellular matrix

The matrix impedes penetration of immune cells

2. Reduced immune cell access and phagocytosis

Immune cells have difficulty engulfing bacteria that are surrounded by matrix

3. Altered bacterial physiology

Many immune mechanisms (oxidative burst, antimicrobial peptides) are less effective against metabolically inactive or slow-growing cells

13

4. Masking of antigenic targets

Components of the EPS can mask pathogen-associated molecular patterns (PAMPs) to reduce recognition

5. Frustrated immune response and immune exhaustion

Immune cells may accumulate around biofilms but fail to clear them, leading to chronic inflammation causing tissue damage and immune cell dysfunction

14

Tolerance to antibiotics

Bacteria in biofilms survive antibiotics because the community creates **physical, chemical, and physiological barriers** that reduce drug penetration and kill-rate, and because a **subset of cells enter tolerant states (persisters)** that are intrinsically less affected by antibiotics.

15

1. Extracellular matrix limits antibiotic access

Microbes are embedded in an extracellular polymeric substance (EPS) that physically binds or slows diffusion of many antibiotics, lowering the concentration that reaches cells deep in the biofilm.

2. Reduced growth and metabolic activity

Cells deep in a biofilm often grow slowly or are metabolically inactive; **many antibiotics** (β -lactams, aminoglycosides, fluoroquinolones) **target processes active in growing cells**, so slow or dormant cells are intrinsically less susceptible.

3. Persister cells

Within biofilms a small fraction of cells become persisters—phenotypic variants that survive high antibiotic doses without genetic resistance. Persisters can repopulate the biofilm after treatment ends, causing relapse.

16

4. Chemical microenvironments that inactivate drugs

Gradients of oxygen, pH, and nutrients form across biofilm depth; low oxygen or acidic microenvironments can reduce the activity of some antibiotics or change bacterial physiology so drugs are less effective.

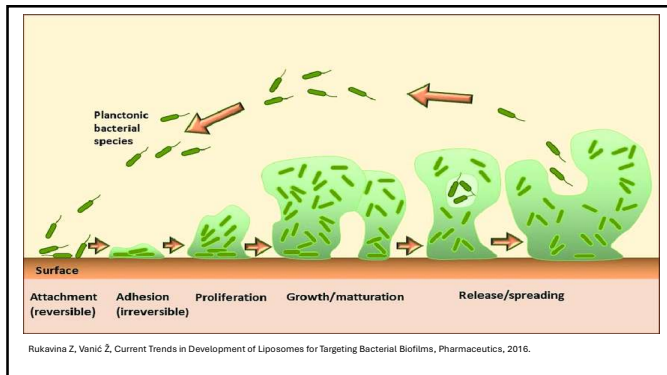
5. Active tolerance mechanisms and gene expression changes

Biofilm cells upregulate stress responses, efflux pumps, and other protective pathways that reduce intracellular antibiotic concentrations or repair damage, increasing survival without classical resistance mutations.

6. Enhanced horizontal gene transfer

The dense, matrix-rich community promotes exchange of plasmids and resistance genes, accelerating the spread of genetic antibiotic resistance within and between species in the biofilm.

17



18

How do we prevent biofilms?

19

Bill Costerton's advice:

Have a great surgeon.....and ideally administer appropriate antibiotics as soon as possible.

20

Surgical Practice

Surgeons discovered what works decades before knowing why it worked!

21


How to prevent biofilms?
Don't give them a surface to grow on!

22

THE VIRULENCE OF *STAPHYLOCOCCUS PYOGENES* FOR MAN.
A STUDY OF THE PROBLEMS OF WOUND INFECTION

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Received for publication 9 August, 1957



10⁶ Staphylococci **10² Staphylococci**

23

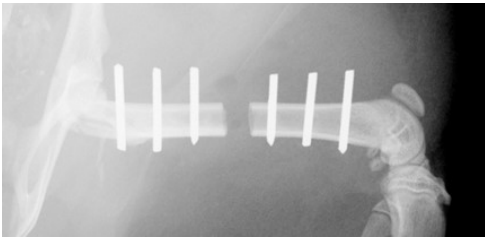
How to prevent biofilms?
Don't give them a surface to grow on!
-No implants in wound
-Thorough debridement, especially necrotic bone
-Consider how you treat the wound

24

How to prevent biofilms?

Reduce the bioburden early to prevent them from reaching a quorum

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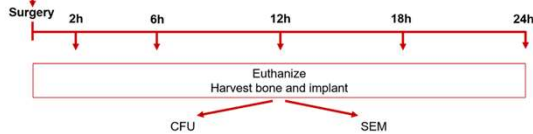


Plain radiograph of non-critical segmental defect in the femur. Fixation plates, radiolucent polyacetal, were fixed with threaded, stainless-steel K-wire.

26

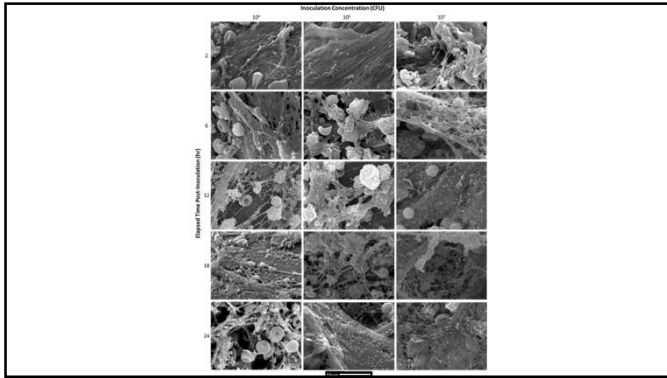


Staphylococcus aureus
10^X CFU in collagen matrix
X = 3, 5, 7

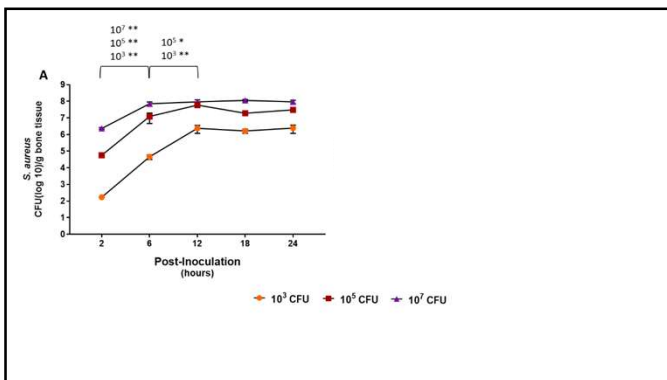


Experimental timeline of Experiment 1. Animals were inoculated with *S. aureus* bacteria (10³, 10⁵, or 10⁷ CFU) at surgery and subsequently euthanized and tissue harvested at the indicated time points.

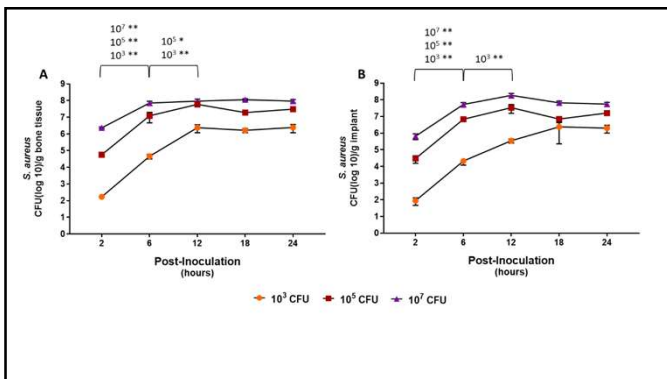
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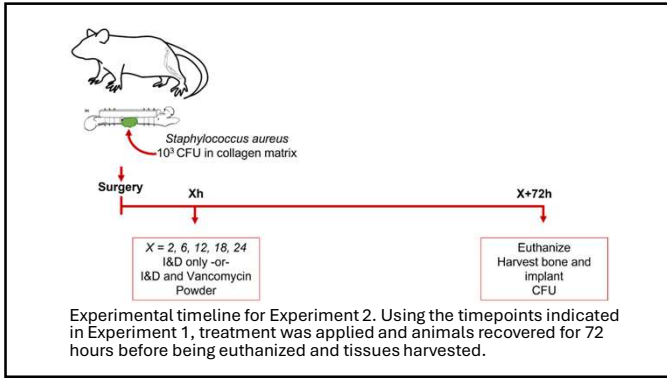
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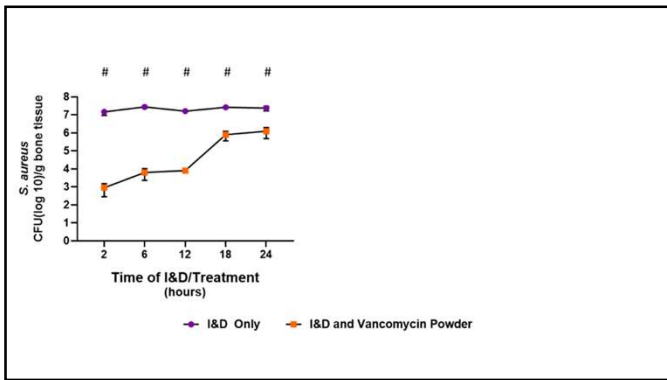
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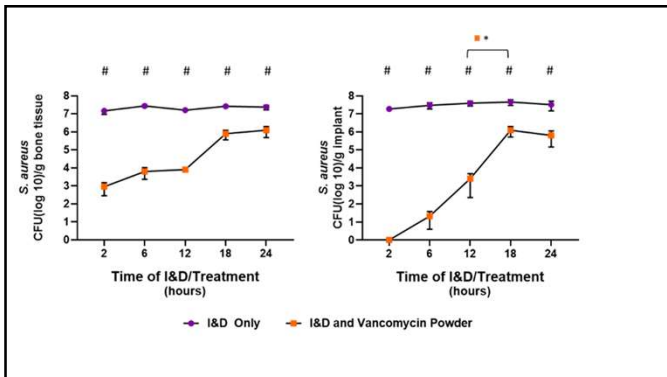
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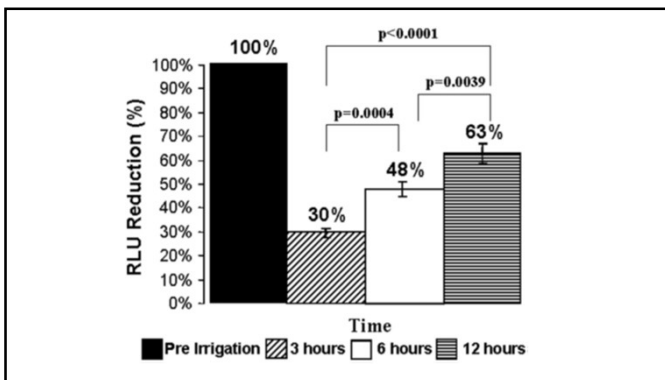


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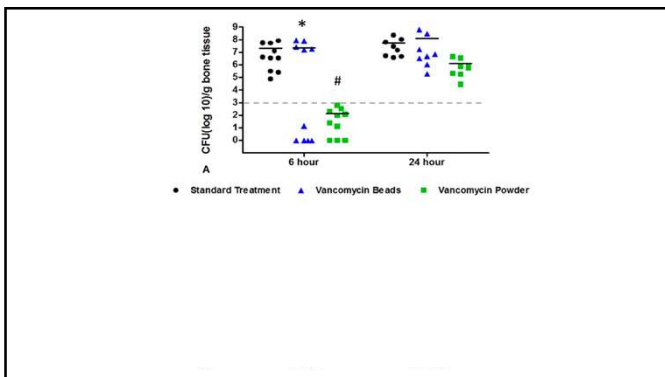
How to prevent biofilms?

Treat and give antibiotics early...while the bacteria are still susceptible

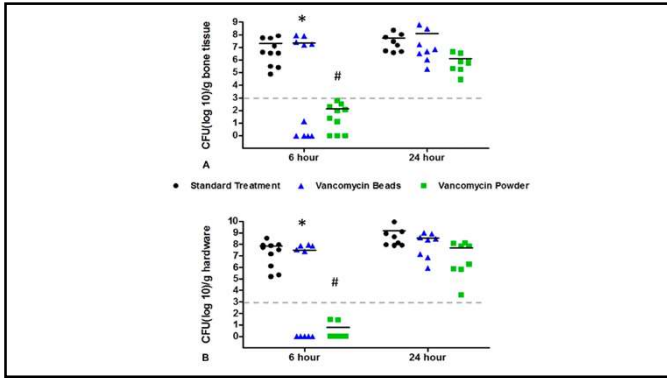
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36



37

Emerging Therapies

Antibiofilm immune protein and antibodies

38

Agrilogics Animal Health

REPAIR
WOUND TREATMENT



Innate immune-derived veterinary wound care powder that gives veterinarians an effective alternative to antibiotics

39

Powered by MIIP-E2, a multifunctional **immune glycoprotein** found naturally in mammals, REPAIRD forms a protective barrier that accelerates wound closure and **inhibits biofilm adhesion.**

40

Benefits for Veterinarians and Patients:

- Can reduce treatment time
- Supports a moist wound environment
- Protects against contamination
- Congeals exudate and blood quickly for efficient treatment
- Covers and shields wounds to support natural scab formation
- Safe for use in dogs, cats, horses, pigs, and cattle
- No refrigeration, special handling, or advanced training required

41

TRL1068, antibiofilm antibody from Trellis Bioscience

High affinity antibody
 Binds to protein required to form and maintain biofilms
 Multiple peer reviewed articles on preclinical success
 Currently in Phase 2 clinical trial for prosthetic joint infections

42

Summary

Biofilm phenotype is a normal response of bacteria to environment that protects them from lack of nutrients, host immune response, and antibiotics.

Eliminating implants and necrotic tissue, reducing the initial bioburden, and early administration of antibiotics while bacteria are still susceptible are ideal approaches for preventing formation of biofilms.

Many efforts on developing treatments that address biofilms with some promising ones emerging.
