CASE 4–BACTERIAL PATHOGENESIS& *STAPHYLOCOCCUS AUREUS*

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Introduction

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1. **Encounter**: where does the organism normally reside, geographically and host wise, and what are the bacterial characteristics that leave it suited to these places of residence. How would our patient have come in contact with this bacteria?

2. **Entry**: what facilitates the entry of the bacteria into the human host? What are the molecular, cellular and/or physiological factors at play in the initial entry/adherence step from the point of view of the organism and the host?

3. **Multiplication and Spread**: does the organism remain extracellular or do they enter into cells and what are the molecular and cellular determinants of these events. Do the bacteria remain at the entry site or do they spread beyond the initial site i.e. are there secondary sites of infection and why do the bacteria hone in on these particular secondary sites?

4. **Bacterial Damage**: do the bacteria cause any direct damage to the host (or is the damage fully attributable to the host response, as indicated below) and, if so, what is the nature of the bacterial damage. Can it be linked to any of the signs and symptoms in this case?

The Case: A New Baby

Elizabeth's pregnancy and the birth of Amanda had gone well however, Elizabeth and Amanda were now **struggling with breastfeeding**. Elizabeth was aware from her prenatal classes of the various reasons why breastfeeding might be difficult. On the advice of a friend she made arrangements for a lactation consultant to visit her at home. She continued trying to 'latch' and feed Amanda in the days leading up to the visit but stopped when she **began to experience breast pain** and **noticed that her right breast was red all around the nipple**. She was **feeling stressed and tired**, along with a feeling of **general malaise** that she attributed to the stress associated with trying to breastfeed her newborn baby.

Based on Elizabeth's symptoms, the lactation consultant made a **preliminary diagnosis of mastitis and suggested that Elizabeth see her doctor for a full diagnosis and possible antibiotic treatment**. Do the symptoms that Elizabeth is experiencing concur with the preliminary diagnosis? What is the most likely bacterial cause and what are the antibiotics of choice to treat it?

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I.Encounter

Where does *S. aureus* reside and why?

S. aureus are gram-positive cocci that appear in grape-like cluster under microscope. As commensal bacteria, they are found to colonize the skin and mucous membranes of the nasal passages and axillae of ~30% of healthy adults. *S. aureus* are ubiquitous in the environment (sound in soil, drinking and waste water) and able to adapt to diverse habitats.

The nares:

- *S. aureus* resists attack from nasal secreted defensisn and cathlicidins, is resistant to lysozyme due to its peptidoglycan-specific-O-etyltransferase and binds to Igs to inactivate them
- Competes and replaces other bacterial populations

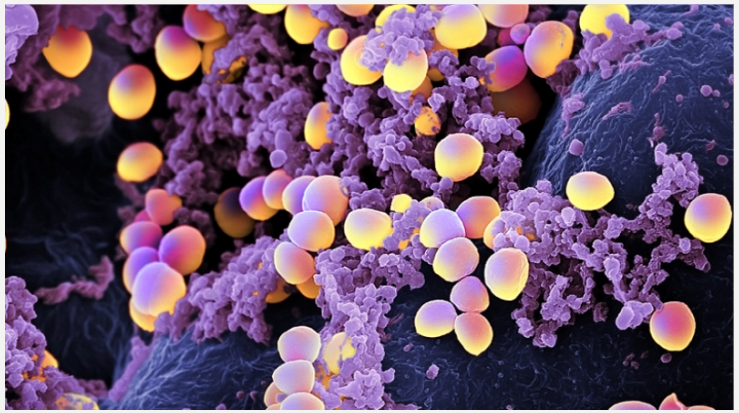
Human milk microbiome: one of many bacterial species in human milk; oligosacherides provide nourishment for growth

Other Animals: colonizes canine fur as well as other surfaces it is found on in humans

Inanimate surfaces: exists in biofilm on variety of clinical and home surfaces. Following signaling via quorum sensing, biofilms forms and consists of secreted polymeric substances providing the bacteria a safe environment conducive to its growth and survival

Other body surfaces: *S. aureus* is salt and sugar tolerant making it possible to live in different body environments

- Areas of skin, including nipples
- Respiratory tract: binds to cilia and mucin un the upper tract and protect itself from immune response
- Digestive tract: binds to intestinal mucus & forms biofilms; exploits saliva as a nutrient vehicle
- Vagina: will likely colonize a neonate during birth due to colonizing the vaginal canal



I.Encounter

How did Elizabeth come in contact with *S. aureus*?

Human or home contact: Being a part of the normal flora for many individuals, *S. aureus* may have already colonized Elizabeth's skin and when the opportunity presented, entered through a fissure; it may have been transferred to her from someone in the home or from surfaces in the home.

Hospital: *S. aureus* may be found on different medical instruments and is responsible for a large portion of nosocomial infections. It may also be shed by an infected individual or be found in hospital dust, aerosols or dirt.

Other animals or food products: Other animals, especially cows, are reservoirs of *S. aureus*. The bacteria may contaminate meat and dairy products and result in food poisoning.

Milk pumps: Breastfeeding devices are often not sterilized properly and as such, the bacteria may colonize milk pumps that serve as a mode of transmission.

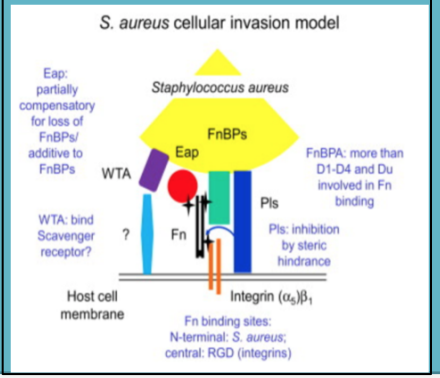
2. Entry

Factors Promoting Adhesion

Microbial Surface Components Recognizing Adhesive Matrix Molecules: an umbrella term for adhesins produced by *S. aureus*. Structures have 3 domains (bacterial-surface binding domain, membrane spanning domain, & extracellular binding domain)

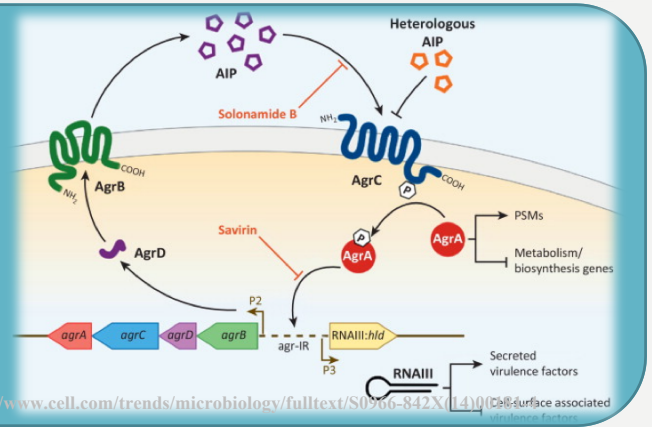
Adhesins binding to collagen allows colonization of bone and joints leading to osteomyelitis and septic arthritis

Fibronectin-binding proteins (FnBP-A and FnBP-B): bind to fibronectin in the extracellular matrix



Clumping factors (composed of fibrinogen binding proteins): fibrinogen is a clotting factor in blood; "clumping" promotes adherence

Quorum Sensing: is encoded in the bacterial genome and promotes adhesion (the accessory gene regulator (agr) system promotes adhesin production to bind fibronectin)

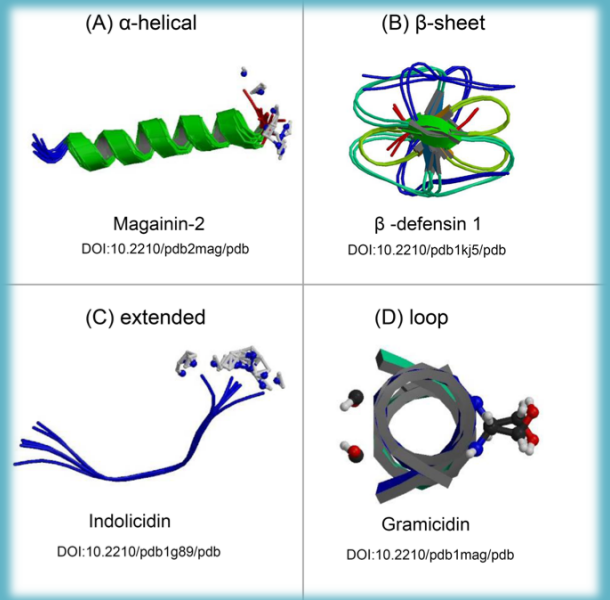


http://www.cell.com/trends/microbiology/fulltext/S0966-842X(14)00034-4

Factors Preventing Adhesion

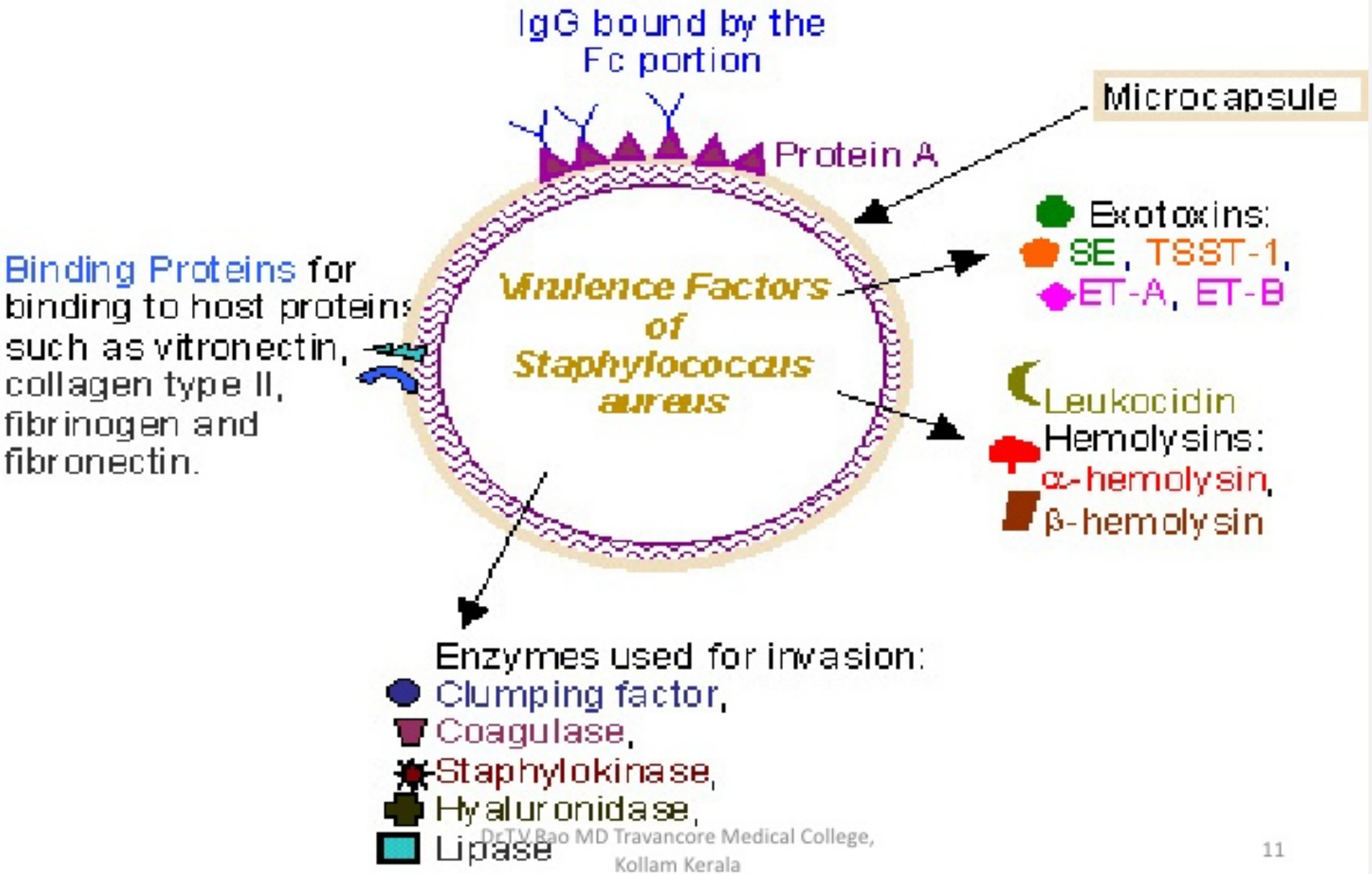
Antimicrobial Peptides (AMPs) = components of innate immunity secreted by keratinocytes, hair bulb cells, sebocytes & eccrine sweat glands

- **Exist in a variety of forms but are similar in their cationic nature, which allows binding to anionic bacterial surface components (e.g. LPS)**
- **Some peptides insert into the bacterial membrane and form pores promoting lysis**
- **May be involved in cell-cell signaling and activation of the adaptive immune cells**



http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1001067

Virulence factors of Staphylococcus aureus



3 Multiplication & Spread

Evasion of Immune Response for Safety

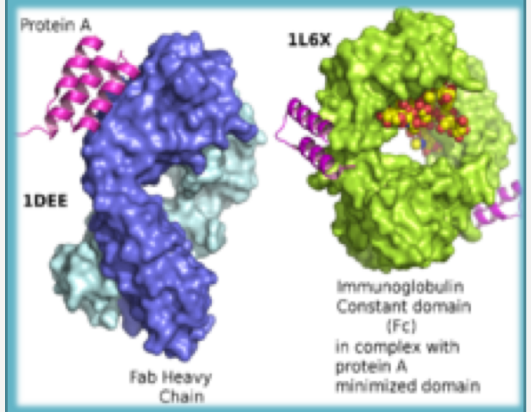
Leukocidin	•A pore-forming toxin expressed by some strains of *S. aureus* that acts on PMN leukocyte membranes (e.g. neutrophils)
Microcapsule	•Most clinically isolated *S. aureus* express a microcapsule that plays a role in avoiding phagocytosis
Protein A	•If the bacteria enter the bloodstream they are vulnerable to the humoral response; this protein prevents IgG (the most abundant antibody in blood) from opsonizing the bacteria
Staphyloxanthin	•A pigment that is released by the bacteria to evade death by Reactive Oxygen Species by its antioxidant action
Biofilm	•Formation of biofilm is a significant method of avoiding phagocytosis
SepA	•A protease that degrades AMPs and the AMP sensor/regulator; has a significant impact on resisting elimination by neutrophils

Replication Invasion & Spread

PIA/PNAG and poly-y-glutamic acid	•An important component of S. aureus biofilm that helps avoid phagocytosis and promotes growth
Coagulase & Staphylokinase	•Coagulase binds to prothrombin (staphylothrombin) to form a localized clot. The clot is a protection against immune cells and can be dissolved by staphylokinase after bacteria have replicated and can further spread
Membrane-Damaging Toxins	•Alpha-hemolysin associates with host cells to form pores causing the cell to "leak". This allows deeper spread of the bacteria
Phenol Soluble Modulins	•Proinflammatory cytolysins that selectively exert antimicrobial activity against other organisms. May also contribute to biofilm maturation

4. Bacterial Damage

Protein A (SpA): binds to Fc portion of IgG, TNFR-1 and vWf increasing local infectiousness, and attracting proinflammatory cytokines and chemokines (manifesting as redness, swelling and pain)



https://en.wikipedia.org/wiki/Protein_A

Sbi: binds to IgG analogously and also contributes to inflammation

Membrane Damaging Toxins: cause pore formation in host cell membranes leading to disruption of electorchemical gradients, loss of membrane integrity and cell death; cytotoxins induce proinflammatory responses as well

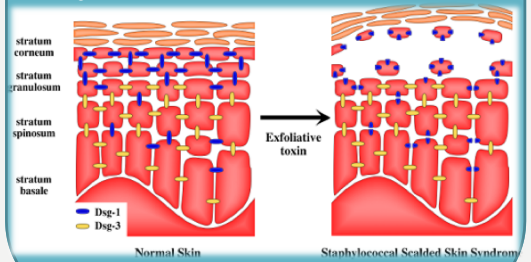
- **Alpha-hemolysin** is the major cytotoxic agent of S. aureus

Alpha-toxin: https://en.wikipedia.org/wiki/Staphylococcus_aureus_alpha_toxin

- **Leukocidin and gamma-toxin** create transmembrane pores in leukocytes
- **Beta toxin**

Enterotoxins & Toxic Shock Syndrome Toxin (TSST-1): toxins with superantigen activity (i.e. ability to activate T cells without antigen recognition) and are associated with fatal infections

Exfolative toxin: leads to skin erythema, separation and blistering causing Staphylococcal Scalded Skin Syndrome



http://www.mdpi.com/2072-6651/2/5/1148

Enzymes that disrupt host signaling pathways: E.g. proteases, lipase, DNase, and FAME/fatty acid modifying enzyme and staphylikinase (disrupts normal clotting)