School Sores: Bacterial Pathogenesis

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The Case

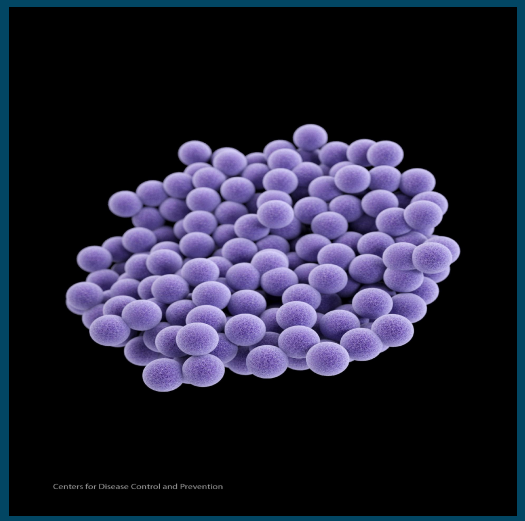
School Sores

6-year-old Stephanie O. has developed red sores around her mouth and nose. At the start of class her teacher noticed the rash and called her parents to take her home. Her parents take her to the family doctor who examines Steph. She is afebrile and does not have any swollen lymph nodes. There is no rash on her hands or feet or inside her mouth. He prescribes an antibiotic and tells her parents that she needs to stay at home for a couple of days. He swabs the rash and sends the swab to the Microbiology Laboratory.

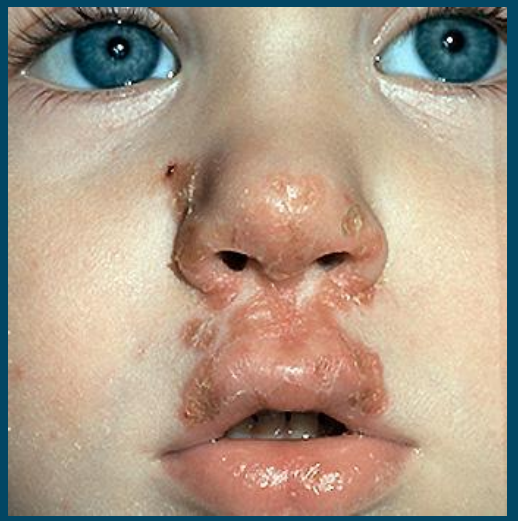
What could it be?

- Based on the signs that Stephanie presents, especially the red sores found around her nose and her mouth, it is likely that she has impetigo[1].
- The two main bacterial families that could have caused this include the Group A hemolytic *Streptococcus* and *Staphylococcus aureus* species[2].

Group A Streptococcus[3]



Staphylococcus aureus[4]

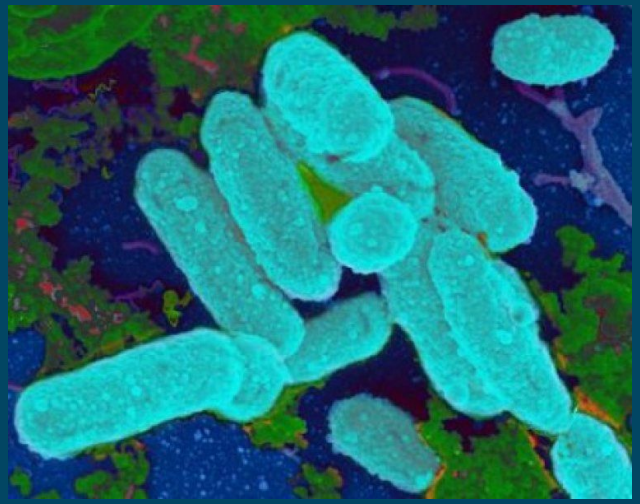


Impetigo[5]

Bacterial Encounter

In this section, we will address the following questions:

- Where do these organisms normally reside, geographically and host wise?
- What are the bacterial characteristics that leave them suited to these places of residence?
- How would our patient have come in contact with these bacteria?



Bacterial attachment[6]

Bacterial Encounter

Geographic location of Group A *Streptococcus*

- Group A *Streptococcus* infections can occur in both temperate and tropical climates, but upper respiratory tract infections predominate in temperate climates and impetigo predominates in tropical climates[8]
- The impetigo-causing or skin specialist type is commonly found in countries that have weather conditions which are warm and humid, such as New Zealand or tropical countries[7]
- In some countries such as the United States, where a warm and humid climate does not necessarily exist, infection can also occur during the summer (i.e. seasonal differences)[7,8]

Geographic location of *Staphylococcus aureus*

- Worldwide distribution[9]
- Methicillin-susceptible *Staphylococcus aureus* is more prevalent than Methicillin-resistant *Staphylococcus aureus*[10]

Group A. Streptococcus and S. aureus are prevalent worldwide[11]

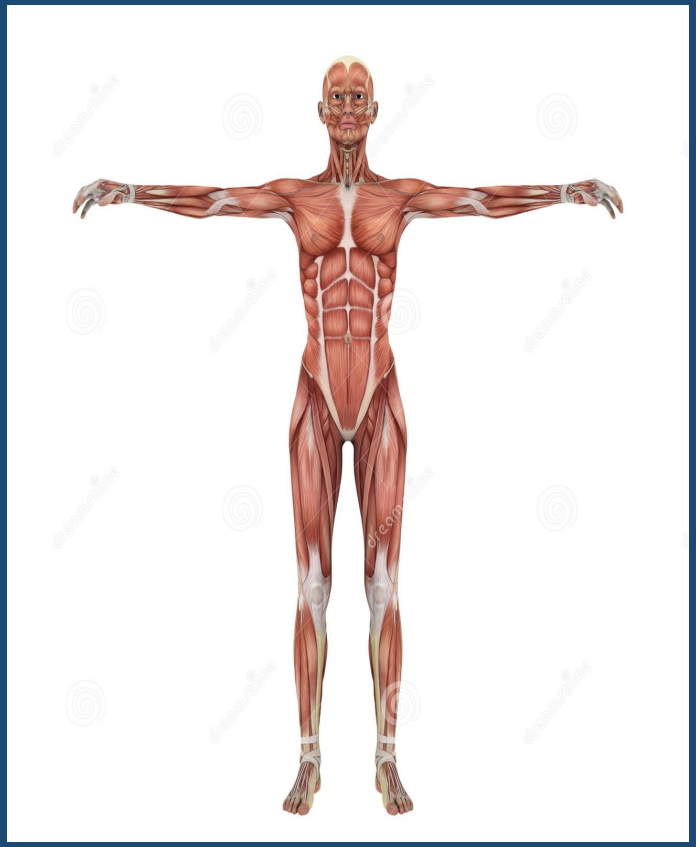
Bacterial Encounter

Tissue tropism of Group A *Streptococcus*

- Human specific pathogen[8]
- Majority of infections involve the epithelial surfaces of either the throat or the skin[8]
- Others locations include the nose, skin, and genital tract[12]

Tissue tropism of *Staphylococcus aureus*

- Infects humans and other animals[9]
- Human commensal that resides on skin surfaces, especially around openings of the body[13]
- Examples include the nose, mouth, genitals, and rectum[13]

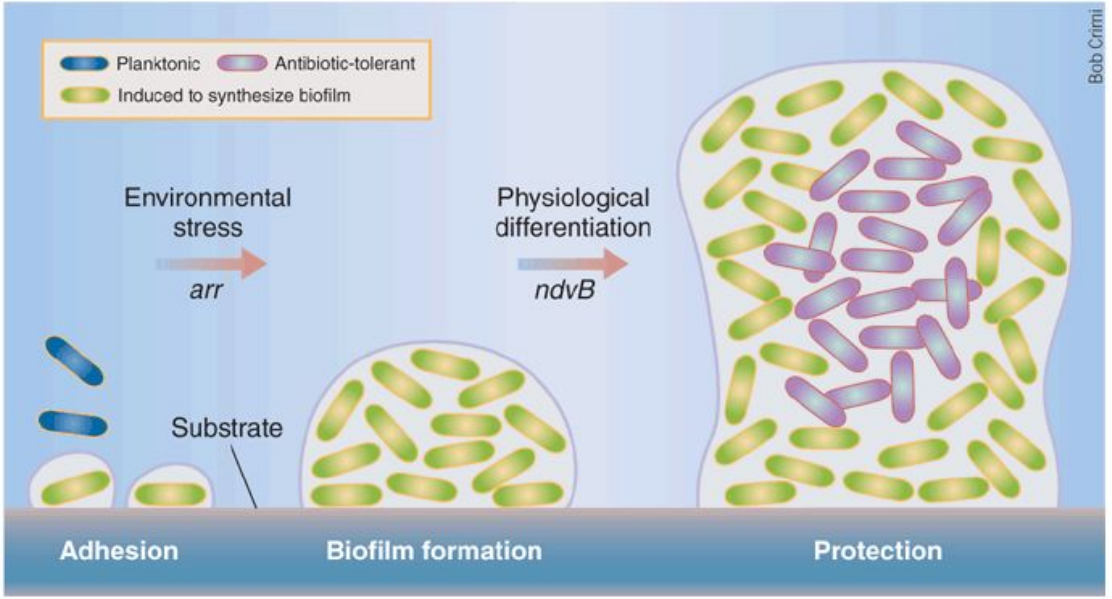


S. pyogenes and S. aureus colonize various sites on the human body[14]

Bacterial Encounter

Bacterial characteristics of Group A *Streptococcus* allowing for survival

- Geographically, it was originally believed that these bacteria rapidly die when outside of the human host; however, it has been shown that the formation of a biofilm allows these bacteria to stay viable for extended periods of time outside the host and remain infectious.[15]
- Inside the host, bacterial survival is linked to their ability to deter the host defenses by utilizing a hyaluronic capsule and surface M-proteins that prevent phagocytosis and also through the formation of a biofilm which allows for enhanced resistance.[15,16] Adherence to the host tissues through surface protein binding contributes highly to their colonization of these sites as well.[16]



The formation a biofilm aids in the colonization and survival of Group A Streptococcus bacteria and Staphylococcus aureus[17]

Bacterial Encounter

Bacterial characteristics of *Staphylococcus aureus* allowing for survival

- Geographically, *S. aureus* have may be able to colonize environments outside the human body through the formation of biofilms on these surfaces. A strain of S. aureus that is methicillin resistant, termed MRSA, is especially good at colonizing well sanitized locations as its methicillin resistance allows it to outcompete other microorganisms.[16]
- Inside the host, the bacteria's ability to form a biofilm, their ability to prevent phagocytosis by utilizing a capsule and protein A and surface proteins that enhance host cell adherence allow for suitable colonization and survival.[16]

Similar evolutionary adaptations in *S. pyogenes* and *S, aureus*, collectively allow both of these bacteria to outcompete other flora and flourish in their respective environments.

Bacterial Encounter

Group A *Streptococcus* transmission

- This bacteria is known to be highly communicable as a result of its ability to survive in many environments. Coming in direct contact with mucus from infected individuals on biotic and abiotic surfaces or infected cuts and wounds are common ways through which the bacteria can be spread.[18]

Staphylococcus aureus transmission

- The bacteria's ability to readily colonize sites on the human body as part of the normal flora allow it to be easily spread from these sites to damaged tissues. Additionally, they can also be contracted from other humans. The bacteria may be contracted by the infected individual through self-infection from nasal discharge or direct contact with other carriers and their contaminated hands or lesions.[9]

Stephanie could have come in contact with either of these bacteria through skin to skin contact with other infectious people. For the case of S. pyogenes however, she could have also contracted the bacteria from a fomite.

Bacterial Entry

In this section, we will address the following questions:

- How do both *S. aureus* and *S. pyogenes* enter the host?
- Where do they take up residence?
- What are the cellular, molecular and/or physiological factors at play?

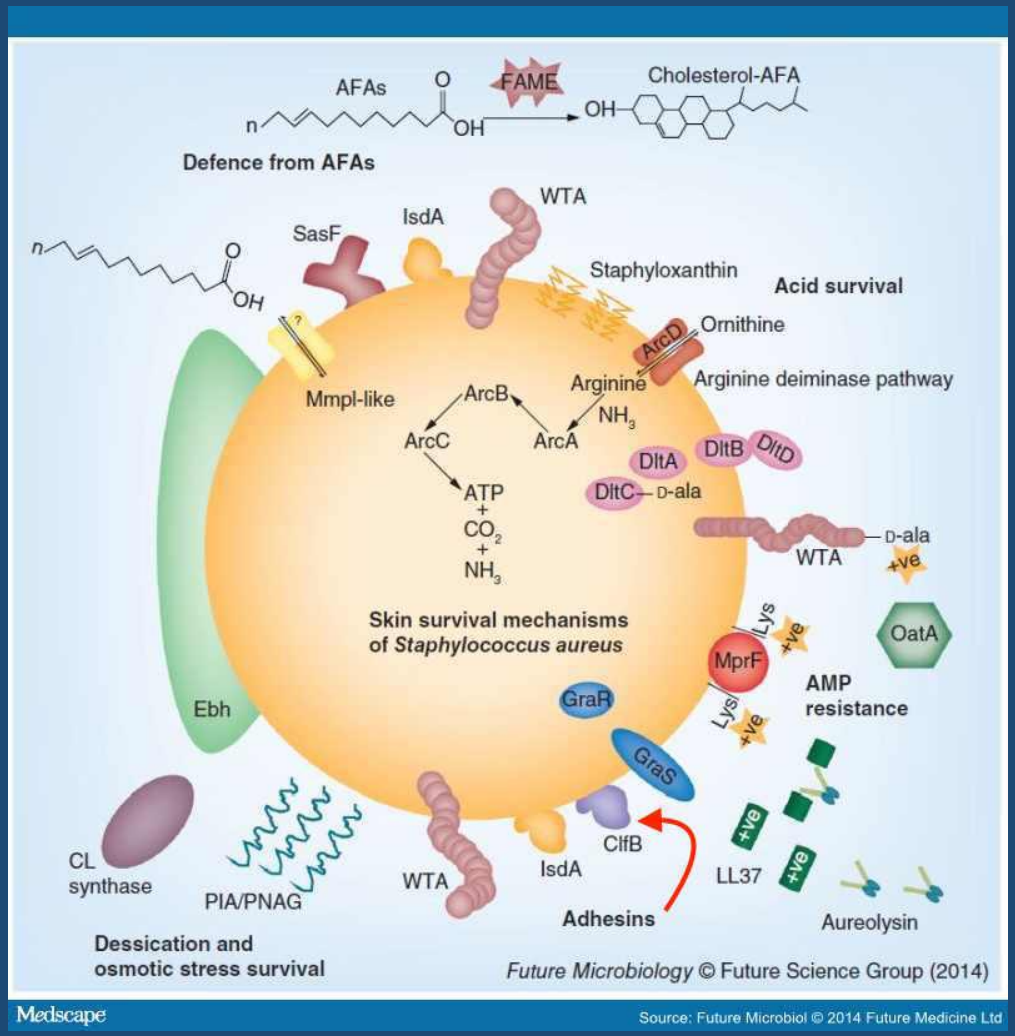
Bacterial Entry

1) *Staphylococcus aureus*

- In healthy conditions, *S. aureus* form a component of the human normal flora[16] .
  - They utilize specific adhesive molecules, termed MSCRAMMs, to bind to host epithelial cells[19]. Of these molecules, clumping factor B and wall associated teichoic acid facilitate this specific adherence to epithelial cells[19].
  - Virulence factors are not activated at this point[20]
- Breakage in the skin barrier, via injury, surgery or viral infection, may introduce the bacteria to internal surfaces[16]
  - This exposure to internal surfaces upregulates virulence factors, resulting in a pathogenic response[20]

Any breakage in the skin barrier, including cuts, can provide a portal of entry for S. aureus into the human host[21].

Bacterial Entry



Various molecules are important in the survival and attachment of S. aureus to epithelial cells. ClfB (Clumping factor B) which is indicated by the red arrow, is a MSCRAMM that facilitates attachment to fibronectins and laminins on host epithelial cells[22].

Bacterial Entry

1) *Staphylococcus Aureus*

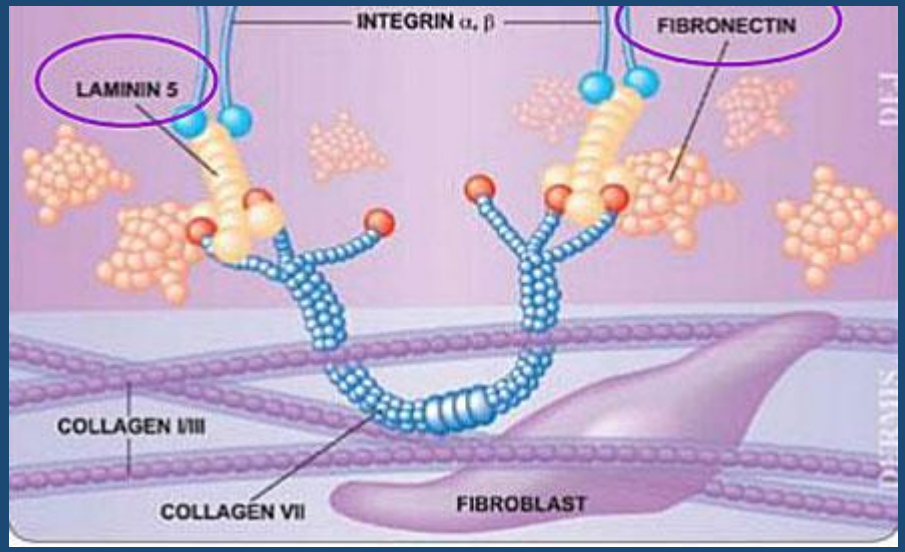
➢ When the bacteria are internalized, they can take up residence in 3 regions[19]:

- On traumatized tissue
- Extracellular matrix of the epithelial or endothelial surfaces
- Intracellular environment

Bacterial Entry

1) *Staphylococcus aureus*

- Initial adherence step following internalization:
  - The extracellular environment of the epithelial and endothelial surfaces and the endothelial cells express the proteins laminin and fibronectin[16,23].
  - *S. aureus* utilize the previously mentioned MSCRAMMs to attach to laminin and fibronectin on these surfaces[16,19].
    - Of these factors, clumping factor B and wall-associated teichoic acid are specifically utilized to attach to fibronectin and laminin[16,19]. This facilitates the initial adherence step following internalization.



Bacterial adherence in the host is facilitated by fibronectins and laminins, located on human epithelial cells and in the extracellular matrix of the host[24].

Bacterial Entry

1) *Staphylococcus aureus*

➢ Initial adherence step following internalization:

- Recent studies have shown that adherence to endothelial cells also requires some form of physiological trauma[23].
- Therefore, adherence to endothelial cells requires two conditions:
  - Some form of physiological trauma[23]
  - Attachment of clumping factor B and teichoic acid to fibronectin and laminin on endothelial cells[16,19].
- In the absence of these two conditions, *S. aureus* resides on traumatized tissue or in the extracellular environment.

Bacterial Entry

2) Streptococcus pyogenes

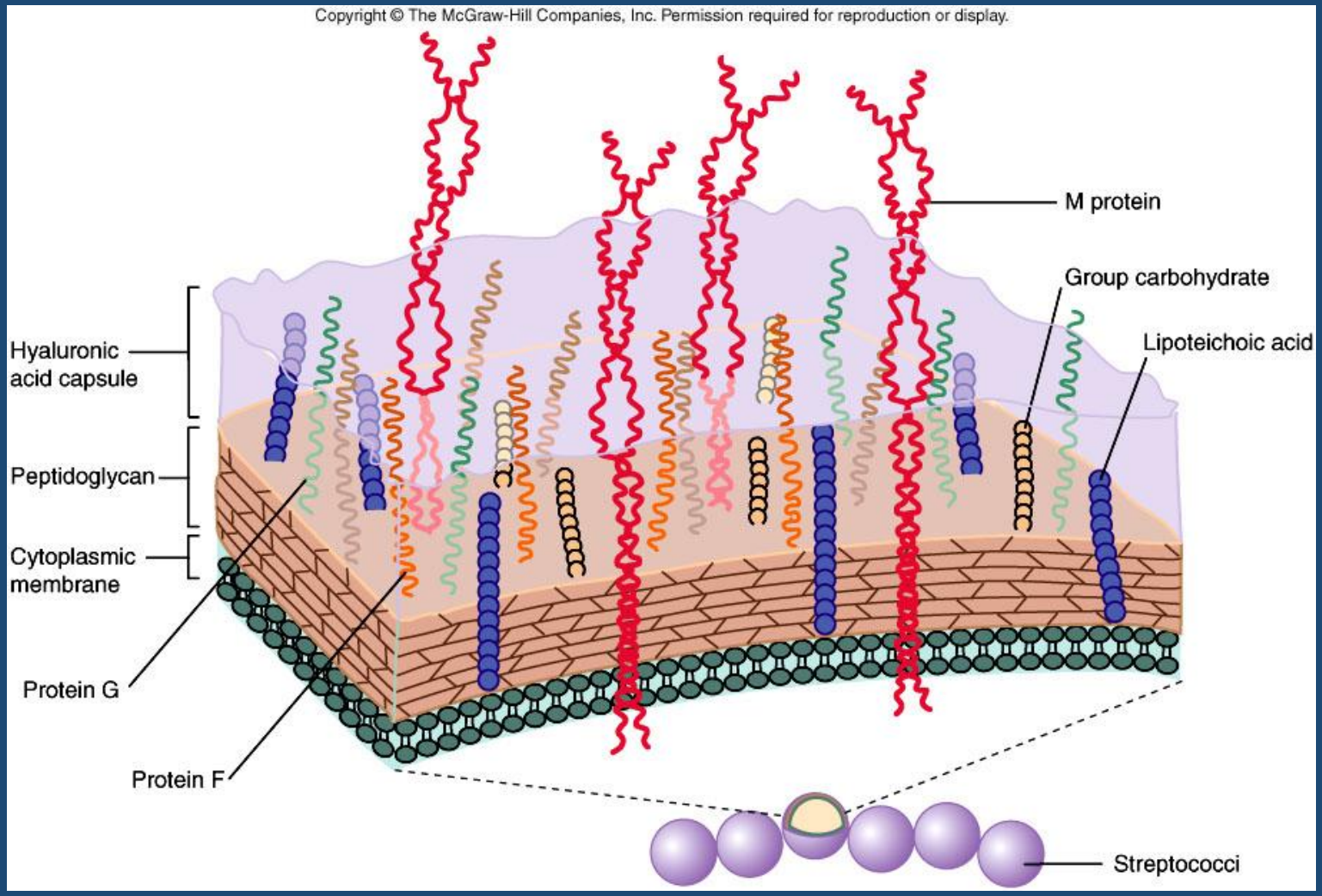
- Acts as an exogenous secondary invader or opportunistic pathogen that colonizes after disturbances in normal flora colonization and nonspecific host defenses [16].
  - Their pathogenic response is limited by competition from other microbes and host defense mechanisms[16].
  - When these initial defenses break down, they upregulate virulence factors and penetrate the epithelium to gain entry to the host[16].

Bacterial Entry

2) Streptococcus pyogenes

- Initial adherence step prior to internalization:
  - The initial adherence step involves attachment to epithelial cells through various molecular interactions:
    - Lipoteichoic acid (LTA), located on the bacterial cell wall, facilitates a weak, reversible interaction with epithelial cells[25].
    - Another bacterial cell wall protein, F1, forms an irreversible interaction with fibronectins located on the cell membrane of human epithelial cells[25].
    - The bacterial protein M6 helps to further mediate this irreversible interaction[16,25].

Bacterial Entry



The plasma membrane and cell wall of S. pyogenes is shown. Protein F, M protein and Lipoteichoic acid are important in bacterial attachment to epithelial cells [26].

Bacterial Entry

2) Streptococcus pyogenes

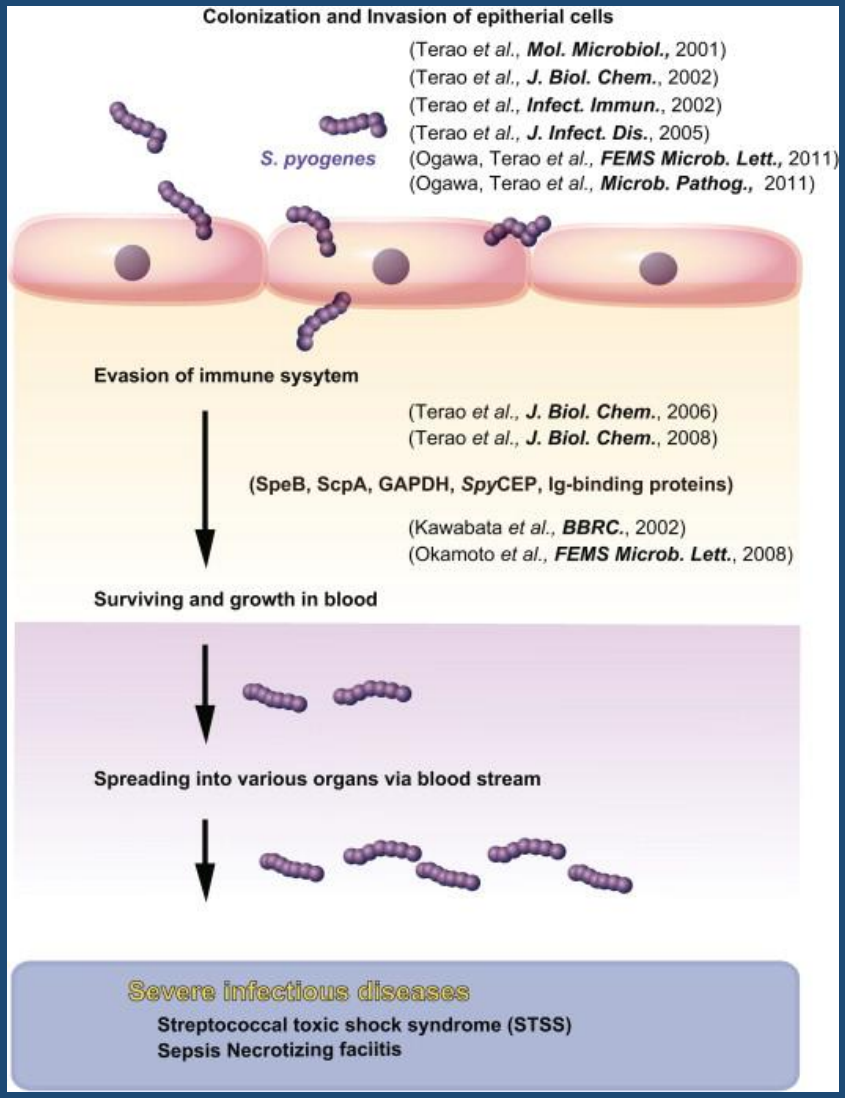
- Internalization following adherence:
  - Once the interaction between bacteria and the epithelial cells has been initialized, the bacteria are internalized by a process similar to phagocytosis[27].
    - This process is not entirely clear; however, actin polymerization is crucial to internalization[15].

Bacterial Entry

2) Streptococcus pyogenes

- Following internalization, the bacteria have two main options:
  - They take up residence in the epithelial cells[27]
  - They exit the epithelial cells into the extracellular environment, where they can spread to various other sites, through the bloodstream[27].
- As they progress to other sites in the body, their interactions with internal surfaces and cells are mediated by the same adhesive molecules, including LTA, protein F and M protein[16, 25].

Bacterial Entry

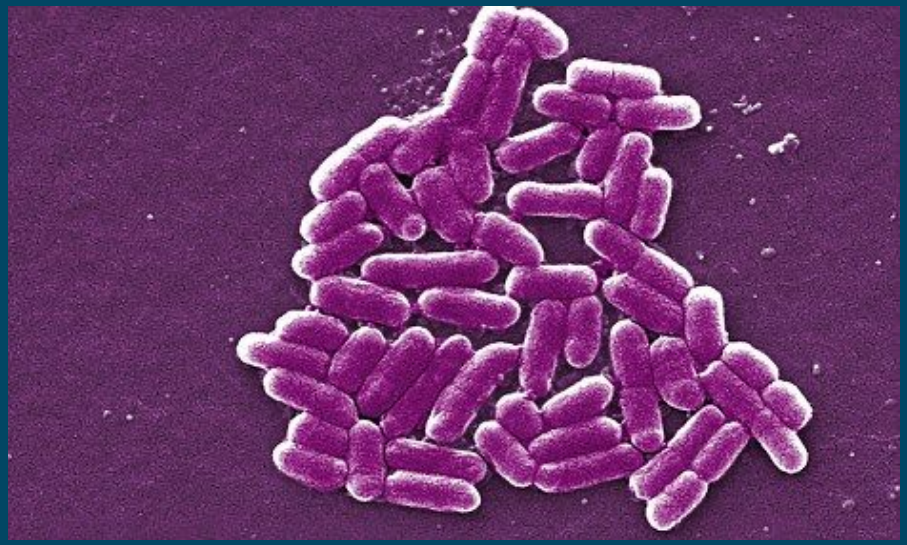


Following entry into epithelial cells, S. pyogenes can either survive and grow within the cells or exit into the extracellular environment[27].

Multiplication and Spread

In this section, we will address the following questions:

- Does *S. pyogenes* or *S. aureus* spread to other sites of the body?
- If so, what are some secondary diseases and sites of infection that can occur?
- Do the bacteria survive intracellularly or extracellularly?

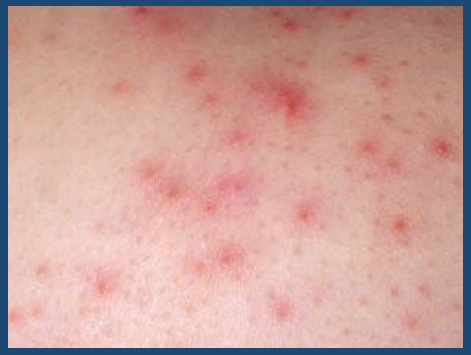


Bacterial Multiplication[28]

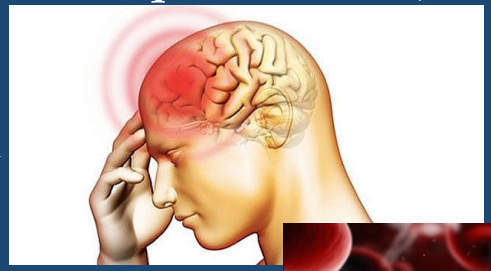
Multiplication and Spread

1) *Streptococcus pyogenes*

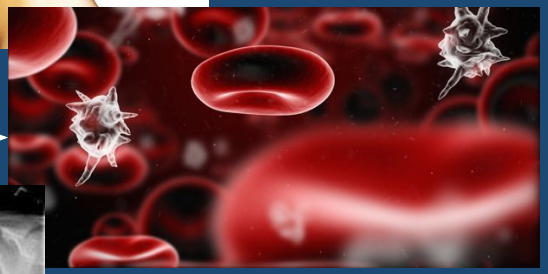
- Initially, *S. pyogenes* starts as a superficial skin infection but a variety of secondary infections exist[25]
- These secondary infections include sepsis, pneumonia, and meningitis, among others[25]
- It can also spread to deeper tissue, potentially resulting in necrotizing fasciitis[25]



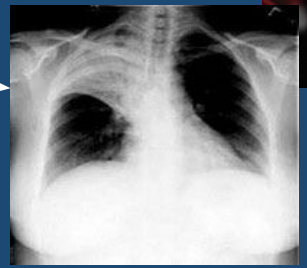
Skin Infection[29]



Meningitis[30]



Sepsis[31]



Pneumonia[32]

Multiplication and Spread

1) *Streptococcus pyogenes*

➢ Secondary infections will often be in relative proximity to the primary site[16]

- Colonization of the upper respiratory tract or pharynx can result in spreading to other portions of the upper or lower respiratory tract and this can ultimately cause infections of the middle ear, lungs, and sinuses[16]
- From the middle ear, meningitis can result[16]
- After pneumonia, the bacteria can also spread to the meninges from the bloodstream through bacteremia[16]

Multiplication and Spread

1) *Streptococcus pyogenes*

- *S. pyogenes* generally survive extracellularly[33]
- Some serotypes also have the ability to survive and persist intracellularly[33]
- Factors that contribute to the bacterium's survival within host cells include the following:
  - Immune evasion[27]
  - Trafficking mechanisms to facilitate the establishment of secondary infections[27]

Multiplication and Spread

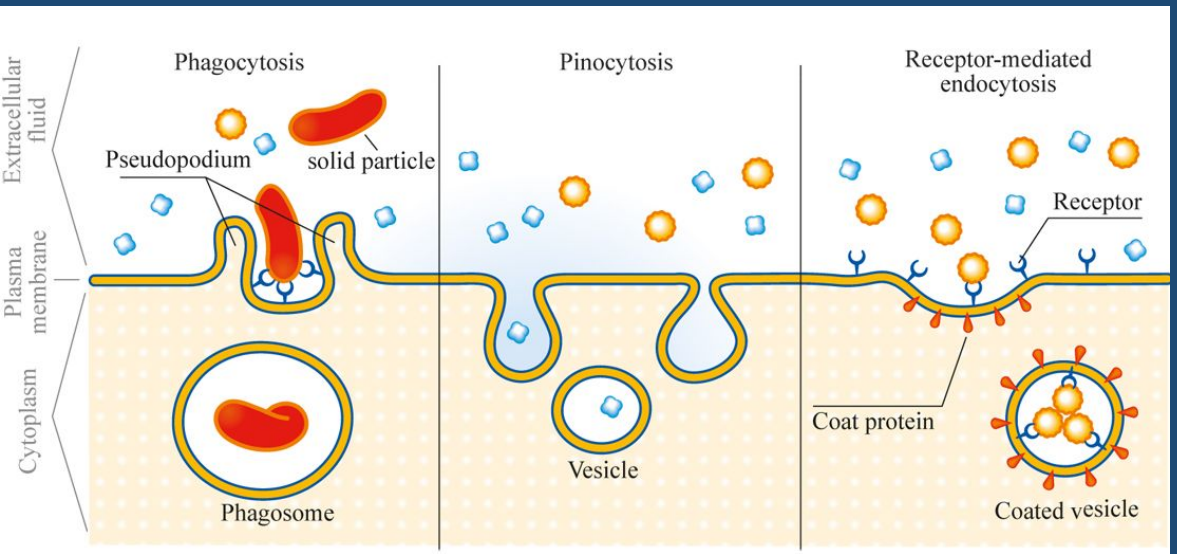
2) Staphylococcus aureus

- Infections involving *S. aureus* are generally localized to the initial site of invasion[16]
  - This is because once the bacteria are in the host, they often have a relatively difficult time fighting the immune system[16]
  - The most serious complication associated with *S. aureus* infection is bacteremia[16]
    - This occurs when the bacterium enters the bloodstream, which can prove to be fatal for the patient.

Multiplication and Spread

2) Staphylococcus aureus

- This bacterium has the ability to survive both intracellularly and extracellularly[19]
- In order to survive intracellularly (whether in endothelial cells or macrophages for example), this bacterium relies on two primary prerequisite conditions[19]:
  - Some form of physiological trauma[34]
  - Receptor-mediated endocytosis[34]



Methods of internalization[35]

Bacterial damage to the Host

In this section, we will address the following questions:

- What kind of damage does this bacteria do to the host?
- Are these damages linked to any signs and symptoms in this case?

Bacterial damage to the Host

1) *Staphylococcus aureus*

- Cause damage to host directly or indirectly via toxin-mediated responses
- Can be cytotoxic (direct) or immune (indirect)
- Induced by exotoxins

- What is produced?
  - Membrane damaging toxins
  - Superantigens
  - Enzymes
  - Epidermolytic Toxin

Bacterial damage to the Host

1) *Staphylococcus aureus*

- **Membrane damaging toxins** cause pore formation
  This includes α-toxin, β-toxin, δ-toxin, γ-toxin, and leukocidin
  - **α-toxins (direct)[38]**
    - receptor-mediated toxins
      - Hemolysins - lyse RBCs (composed of γ-toxin subunits A&B)
      - Leukotoxins - lyse WBCs (γ-toxin subunits B&C)
    - forms pore in target cells → allow cations to enter cell
    - platelets and monocytes are targeted due to their high affinity sites for α-toxin
      - specific targeting results in release of **eicosanoids** and **cytokines** → generates symptoms associated with septic shock
  - **Leukocidin (direct)[23]**
    - Pore forming toxin that targets leukocytes
    - Causes **dermonecrosis**
    - Triggers inflammatory responses via neutrophil activations[23]
    - Neutrophil lysis by PSMa peptides and LukAB leukotoxins after being taken up[39]

Bacterial damage to the host

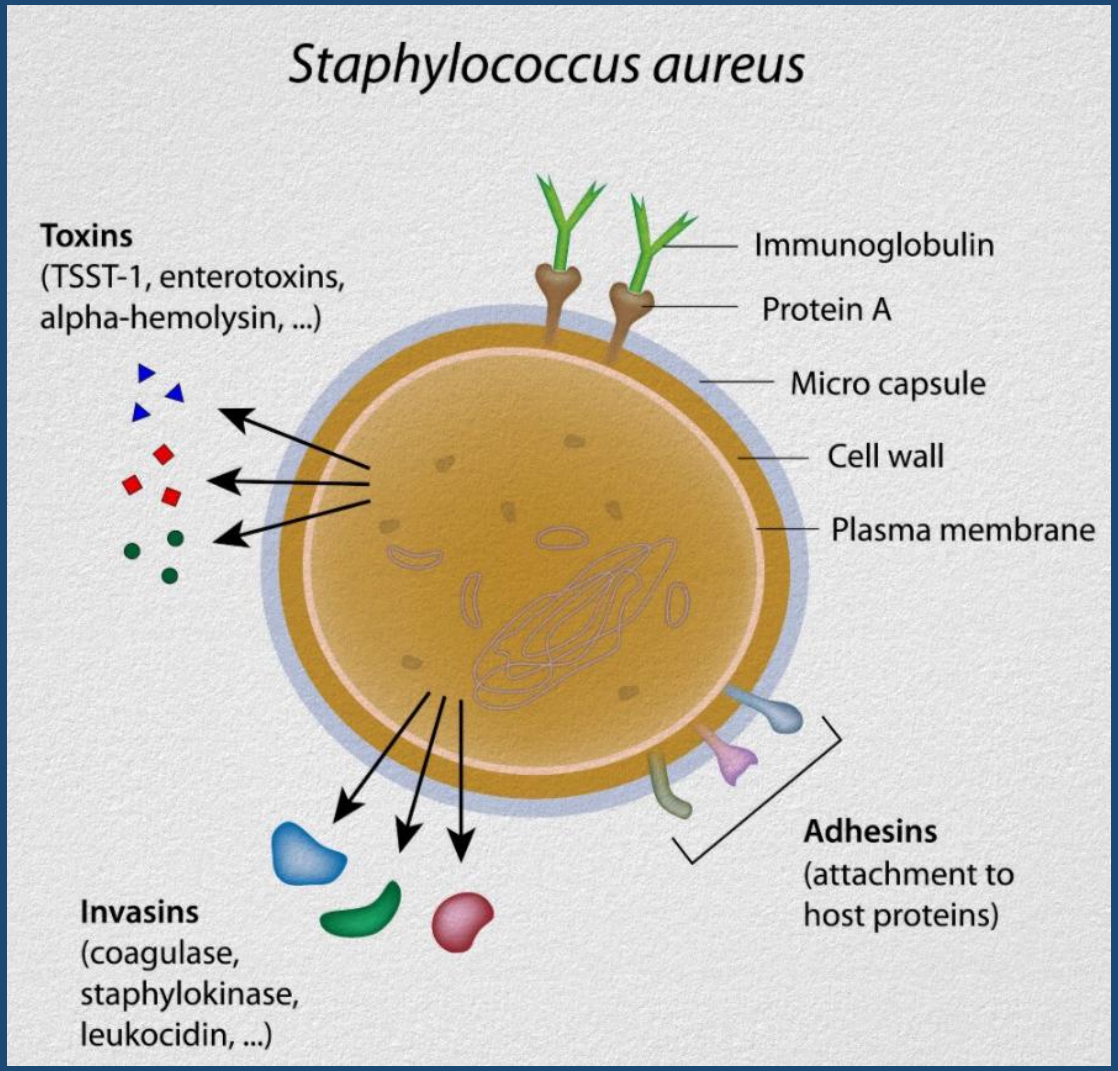


Figure: Leukocidin and hemolysins provide some examples of substances released by S. aureus, which induce direct or indirect damage upon the host[36].

Bacterial damage to the Host

1) *Staphylococcus aureus*

➢ **Superantigens** - 2 types that are produced[39]
- Enterotoxins (6 serotypes; A/B/C/D/E/G)
  - result in cytokine release (cytokine storm) leading to cell death
  - known cause of toxic shock syndrome
- Toxic shock syndrome toxin (TSST-1)
  - Primary cause of toxic shock syndrome
  - The result of the lack of specific host neutralizing antibodies
- May bind to MHC II and T cell receptor to create a massive cytokine storm → toxic shock syndrome

Bacterial damage to the Host

1) *Staphylococcus aureus*

- **Enzymes (direct)[39]**
  - produced enzymes can degrade/interfere with host cells
    - Proteases; degrade host proteins
    - Collagenase; degrade collagen
    - Staphylokinase; degrade fibrin clots and nucleases

- **Epidermolytic Toxin (ET) (indirect)[39]**
  - Bacteria produces this and causes blistering and loss of skin[38]
    - This explains the red sores observed around Stephanie's mouth
  - Toxin causes inflammatory response that is seen to affect Stephanie

Bacterial damage to the Host

2) *Streptococcus pyogenes*

- Cause damage to host directly/indirectly via toxin-mediated response[40]
- Can be cytotoxic or immune induced

- What is being produced?
  - Hemolysins
  - Pyrogenic exotoxins
  - Enzymes

Bacterial damage to the Host

2) *Streptococcus pyogenes*

- **Hemolysins - 2 types are produced[16, 40]**
  - Streptolysin O
    - Oxygen-labile leukocidin
    - Targets a wide range of cells
    - Highly immunogenic
  - Streptolysin S
    - Oxygen-stable leukocidin
    - Targets polymorphonuclear leukocytes
    - Targets subcellular organelles
    - Not immunogenic

Bacterial damage to the Host

2) *Streptococcus pyogenes*

- **Pyrogenic Exotoxins**[16]
  - 4 main types, called Streptococcal Pyrogenic Exotoxins A,B,C,F (SPE A, B, C, F)
  - Results in rash present in scarlet fever and potentially impetigo
  - Able to function as superantigens
    - can cause febrile response, T cell proliferations and cytokine release and synthesis
  - This is due to their ability to bind to both T cell and MHC II receptors[40]

Bacterial damage to the Host

2) *Streptococcus pyogenes*

➢ **Enzymes**[40]
- Nucleases (A,B,C,D)
  - helps with pus liquidation
  - generate substrates used for growth
- NADases which are leukotoxic
- Streptokinases which are proteolytic
- Hyaluronidases which degrade host connective tissue, hyaluronic acid and the bacteria's own capsule

Toxins can cause proteolysis of epidermal/sub-epidermal tissue layers[40]

- Causes blisters and pus-filled lesions of Impetigo, which is seen in the case with Stephanie

Bacterial damage to the host

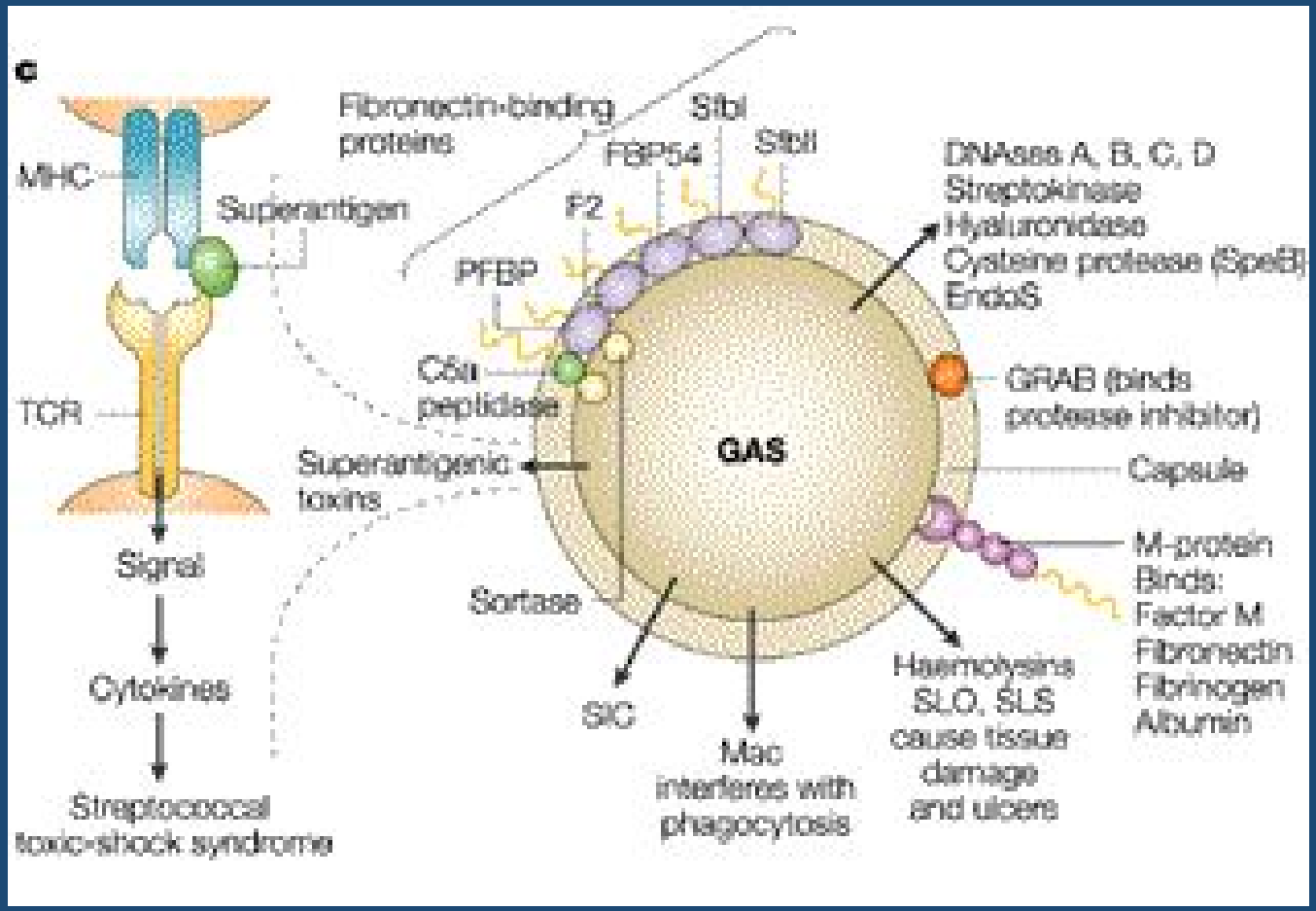


Figure: An overview of the some of the toxins released by S. pyogenes. The mechanism through which STSS occurs is also shown[37].

SUMMARY SLIDES

Compare and contrast the bacterial pathogenesis of *Streptococcus* pyogenes and *Staphylococcus* aureus

Bacterial Encounter

Streptococcus pyogenes

- Infection occurs mainly in temperate and tropical climates including summers with upper respiratory tract infections predominating in temperate climates and impetigo predominating in tropical climates
- Colonizes the throat, skin, nose and genital tract and is a human specific pathogen
- Able to stay viable outside the human body through the formation of biofilms
- Survival inside the human body due to surface proteins allowing for adherence to tissues and prevention of phagocytosis and the ability to form biofilms
- Highly communicable and can be transmitted through direct contact with contaminated surfaces

Staphylococcus aureus

- Infections occur worldwide in all environments
- Human commensal that readily colonizes opening such as the nose, mouth, genitals and rectum and infects both humans and other animals
- Formation of biofilms may allow for colonization of environments outside the human body and methicillin resistance allows for survival in even well-sanitized locations
- Inside the host, ability to form a biofilm and their ability to use surface proteins to prevent phagocytosis and enhance host cell adherence allow for suitable colonization and survival
- As part of the human flora, can be spread to damaged tissues through self-infection by transferring the bacteria or contact with other carries and their contaminated hands or lesions

Bacterial Entry

Streptococcus pyogenes

- Acts an opportunistic pathogen that colonizes when there are disturbances in the host's defense mechanisms
- When the defenses are down, upregulation of virulence factors allows for pathogenesis
- Surface molecules such as lipoteichoic acid, cell wall protein F1 and protein M6 mediate adherence to host cells
- Internalization of the bacteria after adherence is mediated by a process similar to phagocytosis utilizing actin polymerization
- Once internalized, the bacteria take residence in epithelial cells or exit into the extracellular environment to be spread through the bloodstream to other sites utilizing similar adherence steps to infect more host cells

Staphylococcus aureus

- Readily colonize the human body as part of the human normal flora
- Breakage in the skin allows for introduction of the bacteria to internal surfaces which causes upregulation of virulence factors
- Utilize adhesive surface molecules termed MSCRAMMs to bind to host cells
- Once internalized can reside on traumatized tissues, the extracellular matrix of epithelial or endothelial cells and intracellularly
- Bind to epithelial and endothelial cells by using MSCRAMMs such as clumping factor B and teichoic acid that bind to laminin and fibronectin on host cell surfaces
- Binding to endothelial cells also requires the presence of physiological trauma

Multiplication and Spread

Streptococcus pyogenes

- Resulting in an initial superficial skin infection, secondary infections such as sepsis, pneumonia, meningitis and deep tissue necrotizing fasciitis can occur
- Most secondary infections stay close to the initial site of infection such as upper respiratory colonization spreading to other parts of the upper and lower respiratory tract
- Infection of the middle ear and bacteremia resulting from pneumonia due to secondary infection may result in infection of the meninges
- The bacteria can survive extracellularly as well as intracellularly by using mechanisms such as immune evasion and trafficking mechanisms

Staphylococcus aureus

- Most infections are localized to the initial site of invasion as the bacteria due to pressure from the immune system
- A secondary complication that rarely occurs is bacteremia when the bacteria may enter the bloodstream
- The bacteria have the ability to survive extracellularly and intracellularly
- Intracellular invasion and survival is the result of physiological trauma and receptor-mediated endocytosis

Bacterial damage to the Host

Streptococcus pyogenes

S. pyogenes causes bacterial damage both directly and indirectly through cytotoxic or immune induced responses resulting from:

- Two types of hemolysins produced called Streptolysin O which targets a wide range of cells and is highly immunogenic and Streptolysin S which targets polymorphonuclear leukocytes and subcellular organelles and is not immunogenic.
- Four types of pyrogenic exotoxins causing rash from scarlet fever and potentially impetigo are able to function as superantigens to cause a febrile response, T cell proliferation and cytokine release.
- Enzymes secreted by the bacteria that cause damage through degradation or interference include nucleases, NADases, streptokinses and hyaluronidases
- These toxins can cause proteolysis of epidermal and subepidermal tissue layers which result in the characteristic blisters and pus-filled lesions of Impetigo

The signs observed on Stephanie of sores and inflammation may be the result of the proteolysis of the tissue layers due to the toxins or the pyrogenic toxins acting as superantigens

Staphylococcus aureus

S. aureus also utilizes a number of methods to cause bacterial damage both directly and indirectly through cytotoxic or immune induced responses such as:

- Membrane damaging toxins causing pore formation in the membrane of host cells. Examples are α-toxins and leukocidins.
- Superantigens such as enterotoxins and Toxic Shock Syndrome toxin resulting in cytokine release resulting form binding to MHC II and T cell receptors
- Enzymes that degrade or interfere with host cells such as proteases, collagenase and staphylokinase.
- Epidermolytic Toxin causes blistering and loss of skin

The signs observed in Stephanie may result from the effects of some of these toxins namely red sores from epidermolytic toxin and inflammation due to superantigens.

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