***Dr.Thanaa Rasheed 2nd lec. Systematic Bacteriology***

**Gram-Positive Cocci:**

**Introduction**

***Staphylococcus* and *Streptococcus****.* Two of the most important human pathogens are **gram-positive cocci , non motile** and do **not form spores,** but they are distinguished by two main criteria:

1. **Microscopically,** staphylococci appear in grapelike clusters, whereas streptococci are in chains.
2. **Biochemically,** staphylococci produce **catalase** (i.e., they degrade **hydrogen peroxide H2O2 into O2 and H2O),** whereas **streptococci do not**. Catalase is an important virulence factor because **H2O2 is microbicidal** and its degradation **limits the ability of neutrophils to kill.**

***Staphylococcus***

***Sta. aureus, Sta. epidermidis,* and *Sta. saprophyticus***

**Important properties**

1. ***Sta. aureus*** produce **coagulase**. **Coagulase** is an **enzyme** that causes **plasma to clot** by **activating prothrombin to form thrombin**. **Thrombin** then catalyzes the activation of **fibrinogen** to form the **fibrin clot**. ***Sta. epidermidis* and *Sta. saprophyticus*** are **coagulase-negative staphylococci**
2. ***Sta. aureus*** produces a **carotenoid pigment** called **staphyloxanthin,** which imparts a **golden color to its colonies**. This **pigment enhances** the **pathogenicity** of the organism by **inactivating the microbicidal effect of superoxides** and **other reactive oxygen species** within **neutrophils.** ***Sta. epidermidis*** does not synthesize this pigment and **produces white colonies**.
3. ***Sta. aureus* usually ferments mannitol** and **hemolyzes red blood cells**, whereas the **others do not**.

***Sta. aureus* has several important cell wall components and antigens:**

1. **Protein A** is the **major protein in the cell wall**. It is an **important virulence factor** because it **binds** to the **Fc portion of IgG at the complement-binding site**, and forms a "**coagglutinate**" with **antigen–antibody complexes**. Thereby **preventing the activation of complement**. As a consequence the **opsonization and phagocytosis are greatly reduced.** Protein A is used in **certain tests** in the **clinical laboratory.** The **coagulase-negative staphylococci** **do not produce protein A**.
2. **Teichoic acids** are **polymers of ribitol** **phosphate**. They mediate **adherence of the staphylococci** to **mucosal cells** and **play a role** in the **induction of septic shock.**
3. **Polysaccharide capsule** is also an **important virulence factor**. There are 11 serotypes based on the antigenicity of the capsular polysaccharide, but **types 5 and 8** cause **85% of infections**.
4. **Surface receptors** for **specific staphylococcal bacteriophages** permit the "**phage typing**" of strains for epidemiologic purposes. **Teichoic acids** make up **part of these receptors**.
5. **The peptidoglycan** of *Sta. aureus* has **endotoxin-like properties**, i.e., it can **stimulate macrophages to produce cytokines** and can **activate the complement and coagulation cascades**.

**Transmission**

* **Humans** are the **reservoir** for staphylococci. The **nose is the main site of colonization of** ***Sta. aureus***. **The skin**, especially **of hospital personnel** and **patients**.
* **Hand contact** .
* *Sta. aureus* is also **found in the vagina** of approximately **5% of women**, which predisposes them to **toxic shock syndrome**.
* Additional sources of staphylococcal infection are **shedding from human lesions and fomites** such as **towels and clothing contaminated by these lesions**.
* *Sta. aureus* is favored by a heavily contaminated environment (e.g., **family members with boils**) and a **compromised immune system**.
* Reduced **humoral immunity**, including **low levels of antibody**, **complement, or neutrophils**, especially predisposes to staphylococcal infections.
* **Diabetes and intravenous drug** use **predispose to infections** by *Sta. aureus.* Patients with **chronic granulomatous disease (CGD**), a disease characterized by **a defect in the ability of neutrophils** to kill bacteria, are especially prone to *Sta. aureus* infections
* ***Sta. epidermidis*** is found primarily on the **human skin** and can enter the **blood stream** at the site of **intravenous catheters**.
* ***Sta. saprophyticus*** is found primarily on **the mucosa of the genital tract** in **young women** and from that **site can ascend into the urinary bladder** to cause **urinary tract infections.**

**Pathogenesis**

***Sta. aureus*** causes disease both by **producing toxins** and **by inducing pyogenic inflammation**. The typical lesion is an **abscess.** Abscesses **undergo central necrosis** and usually **drain to the outside** (e.g., **furuncles and boils**), but organisms may **disseminate via the bloodstream** as well. **Foreign bodies,** such as **sutures and intravenous catheters**, are important **predisposing factors** to infection by *Sta. aureus.*

**Toxins** **and enzymes**

Are produced by *Sta. aureus.*

1. **Enterotoxin** causes **food poisoning** characterized by
2. Prominent **vomiting and watery, nonbloody diarrhea**.
3. It acts as a **superantigen** within the gastrointestinal tract to **stimulate the release of large amounts of interleukin-1 (IL-1) and interleukin-2** (IL-2) from **macrophages and helper T cells**, respectively. The prominent **vomiting** appears to be **caused by cytokines** released from the **lymphoid cells**, which **stimulate the enteric nervous system** to **activate the vomiting center in the brain**.
4. **Enterotoxin** is fairly **heat-resistant** and is therefore **usually not** **inactivated by brief cooking.**
5. It is resistant **to stomach acid and to enzymes** in the stomach and jejunum.
6. There **are six immunologic types of enterotoxin**, types **A–F**.
7. **Toxic shock syndrome toxin** (**TSST**)
8. Causes **toxic shock**, especially in **tampon-using menstruating women** or in **individuals with wound infections**.
9. Toxic shock also occurs in patients with **nasal packing used to stop bleeding from the nose.**
10. **TSST is produce**d **locally** by *Sta. aureus* in the **vagina, nose**, or **other infected site.**
11. The toxin **enters the bloodstream**, causing **a toxemia**.
12. **Blood cultures** typically **do not grow *Sta. aureus****.*
13. TSST is **a superantigen** and causes **toxic shock by stimulating the release of large amounts of IL-1, IL-2**, and **tumor necrosis factor (TNF**).
14. Approximately **5% to 25%** of isolates of *Sta. aureus* **carry the gene** for TSST.
15. Toxic shock occurs in people who do not have **antibody against TSST**.
16. **Exfoliatin** causes "**scalded skin**" **syndrome in young children**.

It is "**epidermolytic"** and acts **as a protease** that **cleaves desmoglein** in **desmosomes,** leading to the **separation of the epidermis** at the **granular cell layer**.

1. **Leukocidins**: Several toxins can **kill leukocytes**, and cause **necrosis of tissues in vivo.** Of these:
2. **Alpha toxin,** One of the most important toxins which causes **marked necrosis of the skin and hemolysis**. The **cytotoxic effect of alpha toxin** is attributed to the **formation of holes in the cell membrane** and the **consequent loss of low-molecular-weight substances from the damaged cell.**
3. **P-V leukocidin,** a second important toxin, is **a pore-forming** toxin that **kills cells**, especially **white blood cells**, by **damaging cell membranes.** The **two subunits** of **the toxin assemble** in the cell membrane to form **a pore through** which cell **contents leak out**. The gene **encoding P-V leukocidin** is located on a **lysogenic phage.**The **importance of P-V leukocidin** as a **virulence factor** is indicated by the **severe skin and soft tissue infection caused by MRSA strains that produce this leukocidin**. **A severe necrotizing pneumonia** is also caused by strains of *Sta. aureus* that **produce P-V leukocidin**. Approximately **2% of clinical isolates** of *Sta. aureus* produce **P-V leukocidin.**
4. **The enzymes** include **coagulase,** **fibrinolysin, hyaluro-nidase, proteases, nucleases, and lipases**. **Coagulase,** by **clotting plasma**, serves to **wall off the infected site**, thereby **retarding the migration** of **neutrophils into the site**. **Staphylokinase** is a **fibrinolysin that can lyse thrombi.**

***Staphylococcus epidermidis* & *Staphylococcus saprophyticus***

Unlike *Sta. aureus,* these **two coagulase-negative staphylococci** **do not** **produce exotoxins**. Thus, they do not cause **food poisoning or toxic shock syndrome.** They do, however, **cause pyogenic infections**. For example, ***Sta. epidermidis*** is a prominent cause of **pyogenic infections** on **prosthetic implants** such as **heart valves and hip joints**.

**Clinical Findings**

Can be divided into two groups:

**Pyogenic and toxin-mediated**. In the following list, **the first seven** are **pyogenic** in origin, whereas the **last three are toxin-mediated**.

|  |
| --- |
| ***Staphylococcus aureus:* Pyogenic Diseases**   1. **Skin infections** . These include **impetigo**, **furuncles, carbuncles, paronychia, cellulitis**, **folliculitis, conjunctivitis, eyelid infections (blepharitis and hordeolum),** and **postpartum breast infections** (**mastitis**). **Lymphangitis** can occur, especially on the **forearm** associated with an **infection on the hand.** **Severe necrotizing skin** and **soft tissue infections** are caused by **MRSA strains**. These infections are typically **community-acquired rather than hospital-acquired**. 2. **Septicemia (sepsis)** can **originate from any localized lesion**, especially **wound infection**, or as a result of **intravenous drug** **abuse**. 3. **Endocarditis** may occur on **normal or prosthetic heart valves** (**Prosthetic valve endocarditis** is often caused by ***Sta. epidermidis.*)** 4. **Osteomyelitis** and **arthritis** may **arise either by hematogenous** **spread or locally at a wound site** especially in children. 5. **Postsurgical wound** **infections**: ***Sta. aureus*** are an important cause of **morbidity and mortality in hospitals**. 6. **Pneumonia** can occur in **postoperative patients** or **following viral respiratory infection,** especially **influenza.** **Staphylococcal pneumonia often leads to empyema or lung abscess**. In many **hospitals it is the most common cause of nosocomial pneumonia** in general and especially of **ventilator-associated pneumonia** in **intensive care units.** **CA-MRSA** causes **a severe necrotizing pneumonia.** 7. **Conjunctivitis typically presents** with **unilateral burning eye pain**, **hyperemia o**f the **conjunctiva, and a purulent discharge**. The organism is transmitted to the eye by contaminated fingers. 8. **Abscesses** can occur in **any organ** when the **organism circulates in the bloodstream (bacteremia).** These abscesses are often called "**metastatic abscesses**" because they occur by the **spread of bacteria from the original site.**   ***Staphylococcus aureus:* Toxin-Mediated Diseases**   1. **Food poisoning (gastroenteritis**) is caused by **ingestion of enterotoxin,** which is **preformed in foods** and hence has a **short incubation period (1–8 hours**). In staphylococcal food poisoning, **vomiting is typically more prominent than diarrhea.** 2. **Toxic shock syndrome** is characterized by **fever; hypotension**; a **diffuse, macular, sunburn-like rash that goes on to desquamate**; and **involvement of three or more of the following organs**: **liver, kidney, gastrointestinal tract**, **central nervous system, muscle, or blood.** 3. **Scalded-skin syndrome** is characterized by **fever, large bullae, and an erythematous macular rash**. **Large areas of skin slough**, **serous fluid exudes**, and **electrolyte imbalance** can occur. **Hair and nails can be lost.** **Recovery** usually **occurs within 7–10 days**. This syndrome occurs most **often in young children.**   ***Staphylococcus aureus:* Kawasaki Syndrome**  **Kawasaki syndrome (KS)** is a disease of **unknown etiology** ,its features **resemble toxic shock syndrome** caused by the **superantigens of *Sta. aureus* (and *Str. pyogenes*).** KS is a **vasculitis** involving **small and medium-size arteries, especially the coronary arteries.**  **Clinically,** KS is characterized by a **high fever of at least 5 days'** duration; **bilateral nonpurulent conjunctivitis**; **lesions of the lips and oral mucosa (such as strawberry tongue, edema of the lips, and erythema of the oropharynx)**; a **diffuse erythematous**, **maculopapular** **rash; erythema** and **edema of the hands and feet** that often ends with **desquamation**; and **cervical lymphadenopathy**.  The **most characteristic clinical finding** is **cardiac involvement**, especially **myocarditis, arrhythmias, and regurgitation involving** the **mitral or aortic valves**. The main cause of morbidity and mortality is **aneurysm of the coronary arteries.** It is a disease of **children younger than 5 years of age**. It occurs worldwide but is much more **common in Japan.**There is **no** **definitive diagnostic laboratory test** for KS. **Effective therapy** consists of **high-dose immune globulins (IVIG),** which **promptly reduces the fever and other symptoms** and, most importantly, significantly **reduces the occurrence of aneurysms**.  ***Staphylococcus epidermidis* & *Staphylococcus saprophyticus***  These are two **coagulase-negative staphylococci** of **medical importance***. Sta. epidermidis* infections are almost always **hospital-acquired**, whereas ***Sta. saprophyticus*** infections are almost always **community-acquired.**  ***Sta. epidermidis*** is part of **the normal human flora** on **the skin** and **mucous membranes** but can enter the **bloodstream (bacteremia**) and cause **metastatic infections**, especially at **the site of implants.** It commonly **infects intravenous catheters and prosthetic implants**, e.g., **prosthetic heart valves (endocarditis), vascular grafts, and prosthetic joints (arthritis or osteomyelitis)**. ***Sta. epidermidis*** is also a major cause **of sepsis in neonates** and of **peritonitis in patients** with **renal failure** who are **undergoing peritoneal dialysis through an indwelling catheter**. It is the **most common bacterium** to cause **cerebrospinal fluid shunt infections.**  **Strains of *Sta. epidermidis*** that produce a **glycocalyx** are more likely to **adhere to prosthetic implant materials** and therefore are **more likely to infect these implants** than strains **that do not produce a glycocalyx**. **Hospital personnel are a major reservoir for antibiotic-resistant strains of *Sta. epidermidis.***  ***Sta. saprophyticus*** causes **urinary tract infections**, particularly in **sexually active young women**. This organism **is second to *Escherichia coli* as** a cause of **community-acquired urinary tract infections** in young women.  **Laboratory Diagnosis**   1. **Smears from staphylococcal lesions** reveal **gram-positive cocci** in **grapelike clusters**. 2. ***Sta. aureus*** is **coagulase-positive.** 3. **Cultures** of *Sta. aureus* typically **yield golden-yellow colonies** that are usually **β-hemolytic**. Cultures of **coagulase-negative staphylococci** typically yield **white colonies** that are **nonhemolytic** 4. **Mannitol-salt agar** is a commonly used screening device for *Sta. aureus.*. 5. The **two coagulase-negative staphylococci** are **distinguished** by their reaction to the **antibiotic novobiocin**: ***Sta. epidermidis* is sensitive**, whereas ***Sta. saprophyticus* is resistant**. 6. There are **no serologic or skin tests used for the diagnosis of any acute staphylococcal infection.** 7. In **toxic shock syndrome**, **isolation of *Sta. aureus* is not required** to **make a diagnosis** as long as the **clinical criteria are met**. Laboratory findings that support a diagnosis of toxic shock syndrome include the **isolation of a TSST-producing strain of *Sta. aureus*** and **development of antibodies to the toxin during convalescence**, although the latter is **not useful for diagnosis during the acute disease**. 8. For **epidemiological purposes**, *Sta. aureus* can be **subdivided into subgroups** based on the **susceptibility of the clinical isolate to lysis by a variety of bacteriophages.**   **Treatment**  In the United States, **90% or more of *Sta. aureus* strains** are **resistant to penicillin G.** Most of these strains produce β**-lactamase.** Such organisms **can be treated with β -lactamase–resistant penicillins**, e.g., **nafcillin or cloxacillin**, some **cephalosporins, or vancomycin**. Treatment with a combination of **β -lactamase–sensitive penicillin**, e.g., **amoxicillin, and a β -lactamase inhibitor, e.g., clavulanic acid, is also useful.**The **drug of choice for MRSA or NRSA is vancomycin**, to which **gentamicin is sometimes** added. **Daptomycin** is also useful. **Trimethoprim-sulfamethoxazole or clindamycin** can be used to treat **non–life-threatening infections** caused by these organisms.  **VISA strains and VRSA** strains have been isolated from patients. These strains **are typically methicillin-/nafcillin-resistant as** well, which makes them very difficult to treat. **Daptomycin (Cubicin**) and **Quinupristin-dalfopristin (Synercid)** is another **useful choice**.  **The treatment of toxic shock syndrome** involves **correction of the shock by using fluids, pressor drugs**, and **inotropic drugs**; **administration of β-lactamase–resistant penicillin such as nafcillin**; and **removal of the tampon or debridement of the infected site** as needed. **Pooled serum globulins**, which contain **antibodies against TSST**, may be useful.  **Mupirocin** is very effective **as a topical antibiotic** in **skin infections** caused by ***Sta. aureus****.* It has also been used to **reduce nasal carriage of the organism in hospital personnel and in patients with recurrent staphylococcal infections.**  Some strains of staphylococci exhibit **tolerance,** i.e., they **can be inhibited by antibiotics but are not killed. Tolerance may result from failure of the drugs to inactivate inhibitors** of **autolytic enzymes** that **degrade the organism**. Tolerant organisms should be **treated with drug combinations.**  **Drainage (spontaneous or surgical)** is the **cornerstone of abscess treatment.** Previous infection provides only partial immunity to reinfection.  ***Sta. epidermidis*** is **highly antibiotic resistant.** Most strains **produce β-lactamase** and many **are methicillin-/nafcillin-resistant**. The drug of choice is **vancomycin**, to which either **rifampin or an aminoglycoside** **can be added**. **Removal of the catheter or other device is often necessary**. ***Sta. saprophyticus*** **urinary tract infections can** be treated with **a quinolone, such as norfloxacin**, or with **trimethoprim-sulfamethoxazole.**  **Resistance**  More than **90%** of *Sta. aureus* strains contain **plasmids that encode β-lactamase**, the enzyme that **degrades** many, **but not all**, **penicillins.** Some strains of *Sta. aureus* are **resistant to the β-lactamase–resistant penicillins**, such as **methicillin and nafcillin**, by virtue of **changes in the penicillin-binding protein (PBP)** in their **cell membrane**. Genes on the **bacterial chromosome** called ***mecA*** genes encode these **altered PBPs**.These strains are commonly known as **methicillin-resistant *Sta. aureus* (MRSA)** or **nafcillin-resistant *Sta. aureus* (NRSA).** Strains of *Sta. aureus* with **intermediate resistance to vancomycin (VISA)** and with **full resistance to vancomycin (VRSA)** have also been detected. The **cassette of genes that encodes vancomycin resistance** **are located in a transposon** on a **plasmid and encode the enzymes that substitute D-lactate** for **D-alanine in the peptidoglycan.**  **Prevention**  There is **no vaccine** . **Cleanliness, frequent handwashing**, and **aseptic management of lesions help to control spread of *Sta. aureus****.* Persistent colonization of the nose by *Sta. aureus* can be reduced by **intranasal mupirocin or by oral antibiotics, such as ciprofloxacin or trimethoprim-sulfamethoxazole**. **Shedders m**ay have to be **removed from high-risk areas,** e.g., **operating rooms and** **newborn nurseries.** **Cefazolin** is often used **perioperatively to prevent staphylococcal surgical-wound infections.** |