I. Classification of microorganisms

I.1 Taxonomy

Taxonomy refers to the classification and grouping of organisms. It is based on genotypic (genetic) and phenotypic (observable) similarities and differences. The formal levels of bacterial classification, in successively smaller subsets, are *kingdom, division, class, order, family, tribe, genus, and species.* Bacteria have been placed in a kingdom separate from the animal and plant kingdoms, called Prokaryotae. The kingdom Prokaryotae includes unicellular organisms such as bacteria, fungi, protozoa, and algae. Diagnostic microbiologists traditionally emphasize placement of bacterial species into three categories: the *family* (similar to a human "clan"), a *genus* (equivalent to a human last name), and a *species* epithet (equivalent to a human first name). For example, *Staphylococcus* (genus) *aureus* (species epithet) belongs to the Micrococcaceae family.

I.2 Nomenclature

Nomenclature provides naming assignments for each organism. The following standard rules for denoting bacterial names are used. The family name is capitalized and has an *–aceae* ending (e.g., Micrococcaceae). The genus name is capitalized and is followed by the species name, which begins with a lowercase letter; both the genus and species should be *italicized* (e.g., *Staphylococcus aureus*). Often the genus name is abbreviated by using the first letter of the genus followed by a period and the species epithet (name) (e.g., *S. aureus*). The genus name followed by the word *species* (e.g., *Staphylococcus* species) may be used to refer to the genus as a whole. Species abbreviated *sp* (singular) or *spp* (plural) is used when the species is not specified. When bacteria are referred as a group, their names are neither capitalized nor underlined (e.g., staphylococci). The plural of *genus* is *genera* (e.g., there are many genera within the Enterobacteriaceae family).

II. STAPHYLOCOCCUS

The family *Micrococcaceae* consists of four genera: *Planococcus*, *Stomatococcus*, *Micrococcus*, and *Staphylococcus*. *Planococcus*, a genus of motile, gram-positive cocci, has not been found in humans, and *Micrococcus* is usually recovered as a laboratory contaminant. *Staphylococcus* is a significant human pathogen, causing a wide spectrum of diseases ranging from superficial cutaneous infections to life-threatening systemic maladies.

The name *Staphylococcus* is derived from the Greek term for grapelike cocci. This name is appropriate because the cellular arrangement of these gram-positive cocci resembles a cluster of grapes, although this is most characteristic for staphylococci grown on agar media. Organisms in clinical material are seen as single cells, pairs, or short chains.

Staphylococci are gram-positive cocci, 0.5 to 1.5 μm in diameter, nonmotile, facultatively anaerobic, catalase positive, and able to grow in a medium containing 10% sodium chloride and in a temperature range from 18° C to 40° C. The organisms normally grow on the skin and mucous membranes of humans, as well as that of other mammals and birds. A total of 36 species and seven subspecies are currently recognized in the genus, with 14 species and 2 subspecies found on humans. The species most commonly associated with human infections are *S. aureus* (the most virulent and best-known member of the genus), *S. epidermidis*, *S. haemolyticus*, *S. lugdunensis*, *S. saprophyticus*, and *S. schleiferi*. *S. aureus* is the only species found in humans that produces the enzyme coagulase; thus all other species are commonly referred to as "coagulase-negative staphylococci."(CNS)

II.1 Physiology and Structure

Capsule A loose-fitting, polysaccharide layer is oniy occasionally found on staphylococci cultured in vitro but is believed to be more commonly present in vivo. This capsule protects the bacteria by inhibiting chemotaxis and phagocytosis by polymorphonuclear leukocytes and proli-feration of mononuclear cells following mitogen exposure. It also facilitates adherence of bacteria to catheters and other synthetic material (e.g., graft, prosthetic valves and joints, and shunts). This property is particularly important for the relatively avirulent coagulase-negative staphylococci.

Peptidoglycan The peptidoglycan layer, composed of peptide crosslinked glycan chains, is the major structural component of he staphylococcal cell wall. This layer has endotoxin-like activity, can attract polymorphonuclear leukocytes (abscess formation), and can activate complement. Lysozyme (muramidase) present in tears, saliva, and human leukocytes, monocytes, and macrophages can hydrolyze the linkage between the glycan subunits and thus form a natural barrier to staphylococcal infections.

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Protein A The surface of most *S. aureus* strains (but not the CNS) is uniformly coated with protein A. This protein is covalently linked to the peptidoglycan layer and has the unique affinity for

binding the Fc receptor of immunoglobulins IgG1, IgG2, and IgG4, thus effectively preventing the antibody-mediated immune clearance of the organism.

Teichoic Acid Teichoic acids are complex, phosphate-containing polysaccharides bound to both the peptidoglycan layer and cytoplasmic membrane. These polysaccharides are species specific. Attachment of staphylococci to mucosal surfaces is mediated by the cell wall teichoic acids through their specific binding to fibronectin. Although the teichoic acids are poor immunogens, a specific antibody response is stimulated when they are bound to peptidoglycan. The monitoring of this antibody response has been used to detect systemic staphylococcal disease.

Clumping Factor The outer surface of most strains of *S. aureus* contains clumping factor or bound coagulase. This protein binds fibrinogen and can cause the staphylococci to clump or aggregate.

Cytoplasmic Membrane The cytoplasmic membrane is a complex of protein, lipids, and a small amount of carbohydrates that forms an osmotic barrier for the cell and provides an anchor site for the cellular biosynthetic and respiratory enzymes.

II.2 Pathogenesis and Immunity

Staphylococcal Toxins
S. aureus produces a large number of virulence factors including at least **five cytolytic, or membrane-damaging toxins** (alpha, beta, delta, gamma, and leukocidin), as well as exfoliative toxin, toxic shock syndrome toxin-1, and five enterotoxins. The cytolytic toxins have also been described as hemolysins, but the activities of the first four toxins are not restricted to red blood cells and leukocidin is unable to lyse erythrocytes. The cytotoxins are capable of lysing neutrophils, with the release of the lysosomal enzymes that subsequently damage the surrounding tissues.

Alpha Toxin This toxin is cytotoxic for a number of cells, including erythrocytes, leukocytes, hepatocytes, platelets, human diploid fibroblasts, HeLa cells, and Ehrlich ascites carcinoma cells. The toxin also disrupts the smooth muscle in blood vessels. The alpha toxin is believed to be an important mediator of tissue damage in Staphylococcal disease and causes necrosis when injected subcutaneously.

Beta Toxin This toxin, also called sphingomyelinase C, is a heat-labile protein that is toxic for a variety of cells, including erythrocytes, leukocytes, macrophages, and fibroblasts. This enzyme catalyzes the hydrolysis of membrane phospholipids in susceptible cells. Beta toxin, together with alpha toxin, is believed to be responsible for the tissue destruction and abscess formation characteristic of Staphylococcal diseases and the ability of *S. aureus* to proliferate in the presence of a vigorous inflammatory response.

Delta Toxin This is a thermostable, large, heterogeneous protein. The toxin has a wide spectrum of cytolytic activity, which is consistent with the belief that delta toxin disrupts cellular membranes by a detergent-like action.

Gamma Toxin This toxin is able to lyse a variety of species of erythrocytes, including human, sheep, and rabbit, as well as human lymphoblastic cells.

Leukocidin This toxin has an F component and an S component. Neither component alone has appreciable activity against the leukocyte membrane. However, the combination of the two molecules facilitates structural changes in the cell membrane, pore formation, and increased permeability. Bacteria producing leukocidin have increased resistance to phagocytosis.

Exfoliative Toxin Staphylococcal scalded skin syndrome (SSSS), a spectrum of diseases characterized by exfoliative dermatitis, is mediated by the action of exfoliative toxin, also known as exfoliatin or epidermolytic toxin. Two distinct forms of exfoliative toxin (A and B) have been identified.
Ultrastructural studies have demonstrated that exposure to the toxin is followed by the splitting of the intercellular bridges in the stratum granulosum layer of the outer epidermis. The toxins are not associated with cytolysis or inflammation. Following exposure to the toxin, protective neutralizing antibodies develop, leading to resolution of the toxic process. SSSS is seen only, in young children and only rarely develops in older children or adults, which may be due to the presence of protective antibodies or an insensitivity of the adult epidermis to the toxin.

Toxic Shock Syndrome Toxin-1 Toxic shock syndrome, characterized by fever, hypotension, rash followed by desquamation, and involvement of multiple organ systems, is toxin mediated. Toxic shock syndrome toxin-1 (TSST-1) is an exotoxin secreted during growth of some strains of *S. aureus* and can reproduce most of the clinical manifestations of toxic shock syndrome in an experimental rabbit model. It is now clear that CNS and group A streptococci can cause toxic shock syndrome. TSST-1 is an exotoxin secreted during growth of some strains of S. aureus and can reproduce most of the clinical manifestations of toxic shock syndrome (fever, hypotension, rash followed by desquamation, and involvement of multiple organ systems).

Enterotoxins Five serologically distinct staphylococcal enterotoxins (A through E) have been described. The enterotoxins are resistant to hydrolysis by gastric and jejunal enzymes and are stable to heating at 100° C for 30 minutes. Thus once enterotoxin-producing staphylococci have contaminated a food product and produced their toxins, reheating the food will not be protective.
These toxins are found in both *S. aureus* and *S. epidermidis*, with 30% to 50% of all *S. aureus* strains producing an enterotoxin. Enterotoxin A is most commonly associated with disease. Enterotoxins C and D are associated with contaminated milk products, and enterotoxin B is associated with staphylococcal pseudomembranous enterocolitis. The enterotoxins also stimulate intestinal peristalsis and have a central nervous system effect, as manifested by the intense vomiting associated with this gastrointestinal disease.

Staphylococcal Enzymes

Coagulase *S. aureus* strains possess two forms of coagulase: bound (also called clumping factor) and free. Coagulase bound to the staphylococcal cell wall can directly convert fibrinogen to insoluble fibrin and cause the staphylococci to clump together. The cell-free coagulase accomplishes the same result by reacting with a globulin plasma factor (coagulase-reacting factor [CRF]) to form a thrombin-like factor, staphylothrombin. This factor catalyzes the conversion of

fibrinogen to insoluble fibrin. Coagulase is used as a marker for virulence for *S. aureus*. Coagulase may cause the formation of a fibrin layer around a staphylococcal abscess, thus localizing the infection and protecting the organisms from phagocytosis.

Catalase All staphylococci produce catalase, a protective enzyme that catalyzes the conversion of toxic hydrogen peroxide, which accumulates during bacterial metabolism or is released following phagocytosis, to water and oxygen.

Hyaluronidase This enzyme hydrolyzes hyaluronic acids, the acidic mucopolysaccharides present in the acellular matrix of connective tissue. Hyaluronidase facilitates the spread of *S. aureus* in tissues. More than 90% of *S. aureus* strains produce this enzyme.

Fibrinolysin This enzyme, also called staphylokinase, is produced by virtually all *S. aureus* strains and can dissolve fibrin clots. Staphylokinase is distinct from the fibrinolytic enzymes produced by streptococci.

Lipases All *S. aureus* and more than 30% of CNS produce several different lipases. As their name implies, these enzymes hydrolyze lipids, which is essential for the survival of staphylococci in the sebaceous areas of the body. It is believed that these enzymes are required for invasion of staphylococci into cutaneous and subcutaneous tissues and the formation of superficial skin infections (e.g., furuncles [boils], carbuncles).

Penicillinase When penicillin was introduced, more than 90% of staphylococcal isolates were susceptible. However, resistance quickly developed and was primarily mediated by the production of penicillinase (β - lactamase). The widespread distribution of this enzyme is ensured by its presence on transmissible plasmids.

II.3 Epidemiology

Staphylococci are ubiquitous. Virtually all persons have CNS on their skin surface, and transient colonization of moist skin folds is common with *S. aureus*. *S. aureus* and CNS are also found in the oropharynx, gastro-intestinal tract, and urogenital tract. Colonization of neonates with *S. aureus* is common on the umbilical stump, skin surface, and perineal area. Short-term or persistent carriage in older children and adults is more common in the anterior nasopharyrinx.

Adherence to the mucosal epithelium is regulated by receptors for staphylococcal teichoic acids. Approximately 15% of normal healthy adults are persistent nasopharyngeal carriers of *S. aureus*, with a higher incidence of carriage reported in hospitalized patients, medical personnel, individuals with eczematous skin diseases, and in individuals who regularly use needles illicitly (drug abusers) or for medical reasons (e.g., insulin-dependent diabetics, patients receiving allergy injections, or those undergoing hemodialysis).

Because staphylococci are carried on the skin surface and in the nasopharynx, **shedding of the bacteria is common and is responsible for many hospital-acquired infections.**

Staphylococci are susceptible to high temperature, as well as to disinfectants and antiseptic solutions. However, the organisms are capable of survival on dry surfaces for long periods. Transfer of the organisms to a susceptible individual can be either by **direct contact** or **by means of fomites** (e.g., contaminated clothing or bed linens). Therefore medical personnel must use

proper handwashing techniques to prevent transfer of staphylococci from themselves to patients or between patients.

II.4 Clinical syndromes

Staphylococcus aureus

S. aureus causes disease **by either production of toxin or direct invasion and destruction of tissue.**

1. The clinical manifestations of some staphylococcal diseases are almost exclusively due to toxin activity (e.g., staphylococcal scalded skin syndrome, toxic shock syndrome, and staphylococcal food poisoning), whereas other diseases involve proliferation of the organisms with abscess formation and tissue destruction.

Staphylococcal Scalded Skin Syndrome

In 1878 Gottfried Ritter von Rittershain described 297 infants younger than 1 month of age who had bullous exfoliative dermatitis. The disease, now called Ritter's disease or staphylococcal scalded skin syndrome (SSSS), was characterized by an abrupt onset with localized perioral erythema (redness and inflammation around the mouth) that spread to cover the entire body within 2 days. Soon afterward large bullae or cutaneous blisters formed, followed by desquamation of the epithelium. The blisters contained clear fluid with no organisms or leukocytes present consistent with the fact the pathogenesis is due to the bacterial toxin rather than enzymatic activity of growing bacteria. Recovery of intact epithelium occurred within 7 to 10 days when protective antibodies appear.

A localized form of SSSS is ***bullous impetigo***. Specific strains of toxin-producing *S. aureus* are associated with superficial skin blisters. In contrast with the disseminated manifestations of SSSS, bullous impetigo is seen with localized blisters that are culture positive. Erythema does not extend beyond the borders of the blister. The disease is primarily restricted to infants and young children and is highly communicable.

Toxic Shock Syndrome (TSS)

TSS was initially described in children in 1978, although it is now primarily a disease in menstruating women and other adults with localized staphylococcal infections. When the pathogenesis of this disease was first recognized, 80% to 90% of patients with TSS were menstruating women. However, this proportion has gradually decreased with the recognition that use of hyperabsorbent tampons represented a significant risk factor.

The disease starts with an abrupt onset of fever, hypotension, and a diffuse macular erythematous rash, as well as involvement of multiple organ systems (gastrointestinal, musculature, renal, hepatic, hematologic, central nervous system). The rash is followed by desquamation involving the entire skin surface including the palms and soles. The initial fatality rate of 5% to 10% has been decreased with a better understanding of the etiology and epidemiology of this disease.

Vaginal carriage of toxin-producing strains has been reported in virtually all women with TSS but in less than 10% of healthy women. In the presence of hyperabsorbent tampons these organisms can multiply rapidly and release toxin for systemic distribution. Toxin production has also been associated with staphylococcal strains isolated in wounds in patients with TSS.

Staphylococcal Food Poisoning

Staphylococcal food poisoning, one of the most common food-borne illnesses, is an intoxication rather than infection. Disease is due to ingestion of toxin-contaminated food rather than the organisms. The foods most commonly implicated are processed meats such as ham and salted pork, custard-filled pastries, potato salad, and ice cream. Growth of *S. aureus* in salted meats is consistent with the ability of this organism to replicate selectively in nutrient media supplemented with as much as 15% sodium chloride. In contrast with many other forms of food poisoning in which an animal reservoir is important, staphylococcal food poisoning is the result of contamination of the food by a **human carrier**. Although contamination can be avoided by excluding individuals with an obvious staphylococcal skin infection from preparing food, approximately half of the carriers are asymptomatic, with colonization most commonly occurring in the nasopharynx.

After the staphylococci have been introduced into the food, the food must remain at room temperature or warmer to permit the growth of the organisms and release of the toxin. Subsequent heating of the food will kill the bacteria but not inactivate the heat-stable toxin. Furthermore, the contaminated food will not appear or taste tainted.

Following ingestion of the food, the onset of disease is abrupt and rapid with a mean incubation period of 4 hours, consistent with a disease mediated by preformed toxin. Further production of toxin by ingested staphylococci does not occur, so the course of disease is rapid, with symptoms lasting generally less than 24 hours. Staphylococcal food poisoning is characterized by severe vomiting, diarrhea, and abdominal pain or nausea. Sweating and headache may occur, but an elevated fever is not seen. Diarrhea is watery and nonbloody, and dehydration may result from significant fluid loss.

Treatment is symptomatic for relief of the abdominal cramping and diarrhea and replacement of fluids. Antibiotic therapy is not indicated because disease is not mediated by in situ production of toxin. Neutralizing antibodies to the toxin can develop and can be protective.

Certain strains of *S. aureus* can also cause **enterocolitis**, manifested clinically by profuse watery diarrhea, fever, and dehydration. This is primarily observed in patients who have received broad-spectrum antibiotics, which suppress the normal colonic flora and permit the growth of *S. aureus*. The diagnosis of staphylococcal enterocolitis can be confirmed only after other infectious causes have been excluded (e.g., *Clostridium difficile* colitis). Abundant staphylococci are present, and the normal gram-negative flora are absent by Gram stain and culture of stool specimens. Fecal leukocytes are observed, and white plaques on the colonic mucosa with ulceration will be seen.

2. **Staphylococcal diseases after direct invasion and destruction of tissue.**

Cutaneous Infections

Localized pyogenic staphylococcal infections include impetigo, folliculitis, furuncles, and carbuncles.

Impetigo is a superficial infection affecting mostly young children and is manifested primarily on the face and limbs. The initial presentation is a small macule (flattened red spot) hat develops into a pus-filled vesicle (pustule) on an erythematous base. After the pustule ruptures, crusting will occur. Multiple vesicles at different stages of devel-opment are common. Impetigo is usually caused by group A *Streptococcus*, alone or in combination with *S. aureus*, with group A *Streptococcus* responsible for 20% of the cases.

Folliculitis is a pyogenic infection localized to the hair follicle. The base of the follicle is raised and reddened, with a small collection of pus beneath the epidermal surface. If this occurs at the base of the eyelid, it is called **stye**.

Furuncles, or boils, are an extension of folliculitis. Large, painful, raised nodules with an underlying collection of dead and necrotic tissue are characteristic. These in drain spontaneously or with a surgical incision.

Carbuncles result from the coalescence of furuncles and extend to the deeper subcutaneous tissue. Multiple sinus tracts are usually present. In contrast with folliculitis and furuncles, chills and fevers are associated with carbuncles and indicate systemic spread of the staphylocci. Bacteremia with secondary spread to other tissues is common with carbuncles.

Mastitis: infection of the mammary gland, in 1-3 % of breastfeeding women, with erythematous nodule and canalicular abscess formation.

Hidrosadenitis: sweat gland infection localized at axillary, perineal, or genital areas

Staphylococcal wound infections can also occur following surgery or a traumatic injury, with the introduction into the wound of organisms colonizing the skin. In an immunocompetent individual the staphylococci are it able to establish an infection unless a foreign body is present in the wound (e.g., stitches, splinter, dirt). Infections are characterized by edema, erythema, pain, and an accumulation of purulent material. If the wound reopened and the foreign matter removed with drainage of the purulence, the infection can be easily managed. If signs such as fever and malaise are observed, if the wound does not clear with localized management, then antibiotic therapy directed against *S. aureus* is indicated.

Bacteremia and Endocarditis

S. aureus is a common cause of bacteremia. Whereas bacteremias with most other organisms originate from an identifiable focus such as an infection of the lungs, urinary tract, or gastrointestinal tract, the initial focus of infection approximately one third of *S. aureus* bacteremias is not known. Most likely the infection spreads to the blood-stream from an innocuous-appearing skin infection. More in half of *S. aureus* bacteremias are **acquired in the hospital** following a surgical procedure or result from continued use of a contaminated intravascular catheter. *S. aureus* bacteremias, particularly long-dwelling episodes, are associated with dissemination to other body sites, including the heart.

Acute endocarditis caused by *S. aureus* is a serious disease, with a mortality rate approaching 50%. *S. aureus* endocarditis may initially be seen with nonspecific flu-like symptoms; however, the patient's condition deteriorates rapidly with disruption of cardiac output and peripheral evidence of septic embolization. Unless appropriate medical and surgical intervention is immediate, the patient's prognosis is poor. An exception to this rule is *S. aureus* endocarditis in parenteral drug abusers, whose disease normally involves the right side of the heart (tricuspid valve) rather than the left side. The initial symptoms may be mild, although fever, chills, and pleuritic chest pain caused by pulmonary emboli are generally present. Clinical cure of the endocarditis is the rule, although complications from secondary spread to other organs are common.

Pneumonia and Empyema

S. aureus respiratory disease can develop following **aspiration of oral secretions** or hematogenous spread of the organism from a distant site. Aspiration pneumonia is primarily seen in the very young and the aged and in patients with cystic fibrosis, influenza, chronic obstructive pulmonary disease (COPD), or bronchiectasis. The clinical and radiologic presentations are not unique for this organism. Radiographic examination will reveal patchy infiltrates with

consolidation or abscess formation, consistent with the ability of the organism to form localized abscesses. **Hematogenous pneumonias** are common in patients with endocarditis and in patients with bacteremias from contamination of either intravascular catheters or access sites for hemodialysis.

Empyema will occur in 10% of patients with pneumonia, and *S. aureus* is responsible for one third of all cases of empyema. Because the organism is able to form walled-off areas of consolidation (loculation), drainage of the purulent material is sometimes difficult.

Osteomyelitis and Septic Arthritis

S. aureus osteomyelitis can be a result of hematogenous infection or secondary infection resulting from trauma or an overlying staphylococcal infection. Hematogenous spread in **children**, generally from a cutaneous staphylococcal infection, usually involves the **metaphyseal area of long bones,** a highly vascularized area of bony growth. Hematogenous osteomyelitis in children is characterized by sudden onset of localized pain over the involved bone and high fever. Positive blood cultures are documented in about half of all infections. Hematogenous osteomyelitis in adults commonly occurs as **vertebral osteomyelitis** but rarely as an infection of the long bones. Intense back pain with fever is the initial symptom. Radiographic evidence of osteomyelitis is not seen until 2 to 3 weeks after initial signs (in both children and adults). ***Brodie's abscess*** is a sequestered focus of staphylococcal osteomyelitis of the metaphyseal area of a long bone in adults. Staphylococcal osteomyelitis following trauma or surgery is generally accompanied with evidence of inflammation and purulent drainage from the wound or sinus tract overlying the infected bone. With appropriate antibiotic therapy, and surgery when indicated, the cure rate for staphylococcal osteomyelitis is excellent.

S. aureus is the primary cause of **septic arthritis** in young children and in adults receiving intraarticular injections or with mechanically abnormal joints. Staphylococcal arthritis is characterized by a painful, erythematous joint with purulence on aspiration. Infection is usually demonstrated in the large joints (e.g., shoulder, knee, hip, elbow). The prognosis is excellent in children, although in adults it is influenced by the underlying disease and the occurrence of secondary infectious complications.

II.5 Staphylococcus epidermidis and Other CNS

Endocarditis

S. epidermidis and the related CNS can infect native and prosthetic heart valves. Infections of native valves are believed to be due to the inoculation of organisms onto a damaged heart valve (e.g., congenital malformation, secondary to rheumatic heart disease). This form of staphylococcal endocarditis is relatively rare and more commonly associated with streptococci. In contrast, staphylococci are a major cause of artificial valve endocarditis. The organisms are introduced at the time of heart surgery, and the infection characteristically has an indolent course with clinical signs and symptoms not developing for as long as 1 year after surgery. Although infection can involve the heart valve, the more common occurrence is infection at the site where the valve is sewn to the heart tissue. Thus infection with abscess formation can lead to separation of the valve at the suture line, with mechanical heart failure. Prognosis is guarded for this infection, and prompt medical and surgical management is critical.

Catheter and Shunt Infections

From 20% to 65% of all infections of prosthetic devices, catheters, and shunts are caused by CNS. This has become a major medical problem with the introduction of long-dwelling

catheters for feeding and medical management of critically ill patients. The CNS are particularly well suited for these infections by their ability to produce a polysaccharide slime that can bond them to catheters and shunts and protect them from antibiotics and inflammatory cells. Infections of cerebrospinal fluid shunts can lead to meningitis. Persistent bacteremia is generally observed because the organisms have continual access to the bloodstream. Immune complex-mediated glomerulonephritis occurs on patients with long-standing disease.

Prosthetic Joint Infections

Infections of artificial joints, particularly the hip, can be caused by CNS. Clinical manifestations are usually limited to localized pain and mechanical failure of the joint. Systemic signs such as fever and leukocytosis are not prominent, and blood cultures are usually noncontributory. Surgical replacement of the joint, together with antimicrobial therapy, is required. The risk of reinfection of the new joint is significantly increased.

Staphylococcus saprophyticus

S. saprophyticus has a predilection for causing urinary tract infections in young, sexually active women. The organism appears to be restricted to this population and is only infrequently found as an asymptomatic colonizer of the urinary tract. Infected women usually have dysuria (pain on urination), pyuria (pus in urine), and large numbers of organisms in their urine. Rapid response to appropriate antibiotics and the absence of reinfections are common.

II.6 Host defense and immunity

Opsonization is made through IgG, C3b, or IgM + C3b, then phagocytosis by PMNs. CD4+ T-cells release cytokines. No immunity is gained by infection.

Table 1; LAB TESTS

	S. aureus	***S. epidermidis***	***S. saprophyticus***
Catalase	Pos.	Pos.	Pos.
Coagulase	Pos.	Neg.	Neg.
Dnase	Pos.	Neg.	Neg.
Mannitol	Pos.	Neg.	Neg.
Hemolysis	Beta	None	None
6,5% NaCl	Growth		
Novobiocin		Susceptible	Resistant

II.7 Treatment, prevetion, control

Resistance quickly developed in staphylococci after penicillin was introduced, and today fewer than 10% of the strains are susceptible to this antibiotic. Resistance is mediated by production of penicillinase (β - lactamase), which hydrolyzes the β - lactam ring of penicillin. The genetic information encoding production of this enzyme is carried on transmissible plasmids, which facilitate the rapid dissemination of resistance among staphylococci.

With the problems with **penicillin-resistant staphylococci**, semisynthetic penicillins resistant to β - lactamase hydrolysis (e.g., methicillin, nafcillin, oxacillin, dicloxacillin) were developed. Unfortunately, resistance to these antibiotics also followed, first in Europe,

Scandinavia, and Japan and then more recently in the United States. Although the majority of patients with serious staphylococcal infections can be treated with these penicillins, approximately 10% to 25% of *S. aureus* strains and as many as 40% of CNS are resistant to these penicillins (**methicillin resistent *S.aureus* (MRSA)**. This is a particularly serious problem in large academic medical centers where resistant *S. aureus* have become well established. The mechanism of this resistance is due to alterations in the antibiotic target sites (i.e., penicillin-binding proteins [PBPs]) in the cell wall, which prevents binding of the antibiotics to the bacteria. This phenomenon appears to be chromosomally mediated. Some strains of staphylococci also produce large quantities of β - lactamases that, when present in sufficient amounts, can hydrolyze these antibiotics. Resistance to these semisynthetic penicillins is also **frequently associated with resistance to other classes of antibiotics,** including clindamycin, erythromycin, and the aminoglycosides. The detection of resistance to the semisynthetic penicillins is sometimes difficult because resistance is preferentially expressed in vitro at low temperatures (30° C).

Despite the propensity for staphylococci to develop resistance to antibiotics, virtually all strains are uniformly susceptible to **vancomycin. This is the antibiotic of choice in treatment** of disease caused by staphylococci resistant to β - lactam antibiotics.

Staphylococci are ubiquitous organisms present on the skin and mucous membranes. Introduction through breaks in the skin is frequently unavoidable. However, the number of organisms required to establish an infection (infectious dose) is generally large unless a foreign body is present in the wound (e.g., dirt, splinter, stitch). Proper cleansing of the wound and application of an appropriate disinfectant (e.g., germicidal soap, iodine solution, hexachlorophene) will prevent most infections in healthy individuals.

The spread of staphylococci from person to person is more difficult to manage. Surgical infections with organisms contaminating the operative site can be established by relatively few organisms because foreign bodies and devitalized tissue are present. Although it is unrealistic to sterilize the operating room personnel and environment, proper handwashing and the covering of exposed skin surfaces should minimize the risk of contamination during the operative procedure. The spread of MRSA can also be difficult to control because asymptomatic nasopharyngeal carriage is the most frequent source of these organisms. Some success has been seen with chemoprophylaxis with the combination of vancomycin and rifampin.

Community acquired MRSA (CA-MRSA)

Were documented in the mid-1990, occurring in individuals who have no previous risk factors for MRSA infections (exposure to hospitals). The most commun clinical manifestations of CA-MRSA are skin and soft tissues infections (cellulites and abcesses). CA-MRSA is sensitive to many antibiotics which do not show much activity against hospital acquired MRSA (HO- MRSA): ciprofloxacin, clindamycin, or even to erythromycin, gentamicin, rifampin, tetracycline.

Vancomycin resistance

Until 1997, despite the propensity for staphylococci to develop resistance to antibiotics, virtually all strains were uniformly susceptible to vancomycin. This was the antibiotic of choice in treatment of disease caused by staphylococci resistant to β - lactam antibiotics, even MRSA.

Unfortunately, in 1997, several isolated MRSAs had also acquired **low-level vancomycin resistance.** The incidence of vancomycin resistance has increased, prompting the use of **linezolid, daptomycin, dalfopristin.**

III. *STREPTOCOCCUS* AND RELATED GRAM-POSITIVE BACTERIA

In recent years the classification of gram-positive cocci has become increasingly complex. Currently, seven genera of catalase-negative, gram-positive cocci are recognized as human pathogens. Although *Streptococcus* and *Enterococcus* are the best known and most frequently isolated genera, *Aerococcus*, *Gemella*, *Lactococcus*, *Leuconostoc*, and *Pediococcus* cause significant albeit rare human disease. Differentiation of these bacteria is important for the therapeutic management of infected patients and understanding the epidemiology and pathogenesis of their infections.

Streptococcus

The genus *Streptococcus* encompasses a diverse collection of species of gram-positive cocci that are commonly arranged in pairs or chains. Most species are facultative anaerobes, although atmospheric requirements may range from strictly anaerobic to capnophilic (growth dependent on carbon dioxide). The nutritional requirements are complex, necessitating the use of blood or serum-enriched medium for their isolation. Carbohydrates are fermented with the production of lactic acid and, unlike *Staphylococcus* species, the organisms are **catalase negative.**

The role of streptococci in human disease was appreciated very early. However, the differentiation of species within the genus is complicated because at least four **different schemes for classifying** these organisms are used:

- **clinical presentation** (pyogenic, oral, enteric streptococci);
- **serological properties** (Lancefield groupings A through H, K through V);
- **hemolytic patterns** (complete [β] hemolysis, incomplete [α] hemolysis, and no [γ] hemolysis);
- **biochemical** (physiological) properties.

The serological classification scheme was developed by Lancefield in 1933 for differentiating pathogenic β-hemolytic strains. (Lancefield group-ings A through H, K through V). Most β-hemolytic strains and some α- and nonhemolytic strains possess group-specific antigens, which are either cell wall carbohydrates or teichoic acids. These antigens can be readily detected by immunological probes and have been useful for rapid identification of the most common streptococcal pathogens.

Not all streptococci possess these group-specific cell wall antigens. Thus organisms such as *S. pneumoniae* and the numerous species of α- and nonhemolytic streptococci (collectively termed the viridans group of streptococci) must be identified by their physiological properties. Unfortunately the classification schemes are not mutually exclusive. For example, *S. anginosus* strains may be nontypeable (viridans group) or react with the antisera for groups C, F, and G. Likewise, *S. agalactiae* (group B) is usually β-hemolytic but may also be α-hemolytic or nonhemolytic.

III.1 Group A *Streptococcus*

Group A *Streptococcus*, also called *Streptococcus pyogenes*, is an important cause of pharyngitis, scarlet fever, streptococcal toxic shock syndrome, erysipelas, and pyoderma. In

addition, the organism is responsible for nonsuppurative sequelae – acute rheumatic fever and glomerulonephritis.

III.1.1 Physiology and Structure

Group A streptococci are 0.5 to 1.0 μm spherical cocci that form short chains in clinical specimens and longer chains when grown in liquid media. Growth is optimal on enriched blood agar media but is inhibited if the medium contains a high concentration of glucose. After 24 hours of incubation, 1 to 2 mm white colonies with a large zone of β-hemolysis are observed. Encapsulated strains will appear mucoid on freshly prepared media, but on dry media they appear wrinkled (matt appearance). Nonencapsulated colonies are smaller and glossy.

The antigenic structure of group A streptococci is well defined. The outermost layer of the cell is the capsule, which is composed of hyaluronic acid, identical to that found in connective tissue. For this reason the capsule is nonimmunogenic. Although the capsule is present in actively growing cells, it rapidly diffuses into the extracellular space in nondividing cells.

The basic structural framework of the cell wall is the **peptidoglycan layer**, similar in composition to that found in other gram-positive bacteria. Within the cell wall are the group- and type-specific antigens of group A streptococci. Three type-specific protein antigens have also been identified. The **M protein** is a major antigen associated with virulent streptococci. In the absence of the M protein the strains are not infectious. This protein is located on the end of the hairlike fimbriae that are anchored in the cell wall and extend through the capsule. Thus the M protein is exposed in encapsulated strains. **The M protein and a second type-specific protein, T or trypsin-resistant protein, are important epidemiological markers** of group A strains. The third type-specific protein in the cell wall is the **R protein**. Finally, two other cell surface antigens have been described: the F protein or fibronectin-binding protein and lipoteichoic acid, which is associated with fimbriae.

III.1.2 Pathogenesis and Immunity

The virulence of group A streptococci is determined by a variety of structural molecules and elaborated toxins and enzymes.

***Capsule*.** The hyaluronic acid capsule of group A streptococci is nonimmunogenic and protects the cells against phagocytosis. However, the major antiphagocytic structural component is the M protein.

M Protein. In the absence of specific antibodies against the M protein, the cells are protected against phagocytosis. The M protein also prevents interaction with complement. M serotypes 1, 3, and 18 are associated with serious, invasive streptococcal disease and serotypes M3 and Ml 8 with rheumatic fever.

F Protein. This protein has a receptor for fibronectin, a matrix protein on eukaryotic cells, and may be the major adhesin for bacterial attachment to the epithelial cells of the pharynx and skin.

Lipoteichoic acid. The lipid moiety of lipoteichoic acid has been implicated in binding to fibronectin. However, because this molecule is normally imbedded in the streptococcal cell membrane, what role this plays in binding to epithelial cells is unclear.

Pyrogenic exotoxins. These toxins, also called **erythrogenic toxins,** are produced by lysogenic strains of streptococci, similar to the toxin produced in *Corynebacterium diphtheriae*. Three immunologically distinct, heat-labile toxins (A, B, and C) have been described in group A streptococci and in rare strains of groups C and G streptococci. These toxins have a variety of important effects, including enhancement of delayed hypersensitivity and susceptibility to endotoxin, cytotoxicity, nonspecific mitogenicity for T lymphocytes, and immunosuppression of B-lymphocyte function. The toxins are also responsible for the rash observed in scarlet fever,

Streptolysins S and O. Streptolysin S is an oxygen-stable, nonimmunogenic cell-bound hemolysin capable of lysing erythrocytes, as well as leukocytes and platelets, following direct cell contact. Streptolysin S can also stimulate release of lysosomal contents after engulfment, with subsequent death of the phagocytic cell. Streptolysin O is inactivated reversibly by oxygen and irreversibly by cholesterol. Unlike Streptolysin S, antibodies are readily formed against Streptolysin O and are useful for documenting a recent infection (**ASO test**).

Streptokinases. At least two forms (A and B) have been described. These enzymes are capable of lysing blood clots and may be responsible for the rapid spread of group A streptococci in infected tissues.

DNase. Four immunologically distinct deoxyribonucleases (A through D) have been identified. These enzymes are not cytolytic but are capable of depolymerizing free DNA present in pus. This reduces the viscosity of the abscess material and facilitates spread of the organisms. Antibodies developed against DNase B are an important marker of cutaneous group A streptococcal infections.

Other enzymes. Other enzymes have been described, including hyaluronidase ("spreading factor") and diphosphopyridine nucleotidase (DPNase). Their role in pathogenesis is unknown.

III.1.3 Epidemiology

Group A streptococci commonly colonize the oropharynx of healthy children and young adults. Although the incidence of carriage is reported to be 15% to 20%, these figures are misleading. Highly selective culture techniques are required to detect small numbers of organisms in oropharyngeal secretions. Colonization with group A streptococci is transient, regulated by the individual's ability to mount specific immunity to the M protein of the colonizing strain and the presence of competitive organisms in the oropharynx. Bacteria such as the α- and nonhemolytic streptococci are able to produce antibiotic-like substances called bacteriocins, which suppress the growth of group A streptococci. In general, group A streptococcal disease is caused by recently acquired strains that are able to establish an infection of the pharynx or skin before specific antibodies are produced or competitive organisms are able to proliferate.

III.1.4 Clinical Syndromes

1. Suppurative Streptococcal Disease

PHARYNGITIS. Group A *Streptococcus* is the major cause of bacterial pharyngitis, with group C and G occasionally involved. This is primarily a disease of children between the ages of 5 to 15 years, but infants and adults are also susceptible. The pathogen is spread by person-to-person contact via respiratory droplets. Crowding, such as in classrooms and with play activities for children, increases the opportunity for spread of the organism.

Infection generally develops 2 to 4 days after exposure, with an abrupt onset of sore throat, fever, malaise, and headache. The posterior pharynx can appear erythematous with an exudate, and cervical lymphadenopathy can be prominent. Despite these clinical signs and symptoms, differentiating streptococcal pharyngitis from viral pharyngitis is difficult. For example, only about 50% of patients with "strep throat" will have pharyngeal or tonsillar exudates. Likewise, most young children with exudative pharyngitis will have viral disease. The specific diagnosis can be made only by bacteriological or serological tests.

Scarlet fever is a complication of streptococcal pharyngitis seen when the infecting strain is lysogenized by a temperate bacteriophage that stimulates production of a pyrogenic exotoxin. Within 1 to 2 days after the initial clinical symptoms of pharyngitis, a diffuse erythematous rash will initially appear on the upper chest and then spread to the extremities. The area around the mouth is generally spared (circumoral pallor), as are the palms and soles. The tongue will initially be covered with a yellowish-white coating that later will be shed, revealing a red, raw surface ("strawberry tongue"). The rash, which blanches upon pressure, is best seen on the abdomen and in skin folds (Pastia's lines). The rash will disappear over the next 5 to 7 days and is followed by desquamation.

Suppurative complications of streptococcal pharyngitis rarely occur with the advent of antimicrobial therapy. However, **abscesses of the peritonsillar and retropharyngeal areas** can be observed, as well as disseminated infections to the brain, heart, bones, and joints.

STREPTOCOCCAL TOXIC SHOCK SYNDROME (also Called toxic shock-like syndrome). in the late 1980s when severe streptococcal soft tissue infections (e.g., cellulitis, necrotizing fasciitis) associated with multisystem toxicity were reported. Most affected patients had hypotension, diffuse erythroderma, hypoalbuminemia, hypocalcemia, and multiorgan failure (e.g., kidney, lungs, liver, heart) – features similar to staphylococcal toxic shock syndrome. These patients were bacteremic and had extensive soft tissue infections, in contrast with those with staphylococcal infections. Most patients were younger than 50 years of age and were not immunocompromised. The group A streptococci responsible for this syndrome differ from the strains causing pharyngitis in that most are serotypes **Ml, M3, or M18,** and some have prominent hyaluronic acid capsules (mucoid strains). Production of pyrogenic exotoxins, particularly **exotoxin A,** is also a prominent feature of these organisms, which may explain the severe systemic toxicity.

ERYSIPELAS. This is an acute superficial cellulitis of the skin with prominent lymphatic involvement. Erysipelas occurs most commonly in young children or older adults, involves the face and less frequently the trunk or extremities, and usually is preceded by either respiratory or

skin infections with group A *Streptococcus* (less frequently with groups C or G streptococci). The cutaneous manifestations are accompanied by chills, fever, and systemic toxicity.

PYODERMA. Streptococcal skin infections most commonly occur in warm, moist environments during the summer months. Pyoderma is seen primarily in young children (2 to 5 years of age) with poor personal hygiene. Clinical disease is preceded by initial colonization of the skin with group A streptococci via direct contact with another infected child or fomite, or transfer by an arthropod vector. Introduction into the subcutaneous tissues is by minor break in the skin integrity (e.g., scratch or insect bite). Group A streptococci are responsible for the majority of streptococcal skin infections, although groups C and G have also been implicated. The strains of streptococci that cause skin infections are different from those that cause pharyngitis, although pyoderma serotypes can colonize the pharynx and establish a persistent carriage state.

OTHER SUPPURATIVE DISEASES. Group A streptococci have been associated with a variety of other suppurative infections, including puerperal sepsis, lymphangitis, pneumonia, and others. Although these infections can be seen occasionally, they have become exceedingly rare with the introduction of antibiotic therapy.

2. Nonsuppurative Streptococcal Disease

RHEUMATIC FEVER. Rheumatic fever is a nonsuppurative complication of group A streptococcal disease. It is characterized by inflammatory changes of the heart, joints, blood vessels, and subcutaneous tissues. Chronic, progressive damage to the heart valves may occur, although the specific mechanisms of tissue damage are unknown. A number of theories have been proposed, including (1) direct destruction of the tissue by the organism or a streptococcal enzyme (e.g., streptolysin), (2) serum sickness – like reaction mediated by complexes of antibodies and antigens, and (3) an autoimmune reaction. This latter explanation is currently favored because antibodies directed against heart tissue have been identified in patients with uncomplicated streptococcal disease and rheumatic heart disease. These antibodies can bind to cardiac and skeletal muscles, as well as to the smooth muscles in blood vessels.

Disease is associated with specific serotypes of group A *Streptococcus* (e.g., **M18 and M3,** and to a lesser extent **M5**). As discussed previously, disease caused by serotype M18 has become more prevalent in recent years**. Rheumatic fever is also associated only with upper respiratory infections.** Cutaneous streptococcal infections do not initiate rheumatic fever. The epidemiology of the disease mimics streptococcal pharyngitis: it most commonly occurs in young school-age children, with no male or female predilection, and it occurs during the fall or winter months. Rheumatic fever usually follows severe streptococcal disease, although as many as one third of the patients will have had an asymptomatic infection with group A *Streptococcus*. Recurrence will occur with subsequent streptococcal infection if antibiotic prophylaxis is not used. The risk for recurrence will decrease with time.

Because no specific diagnostic test is available to identify patients with rheumatic fever, diagnosis is made by clinical parameters. Critical to the diagnosis is documentation of recent group A streptococcal disease by either culture, antigen detection, or serologic testing.

ACUTE GLOMERULONEPHRITIS. The other nonsuppurative complication of strepto-coccal disease is acute glomerulonephritis, which is characterized by acute inflammation

of the renal glomeruli with edema, hypertension, hematuria, and proteinuria. Specific nephritogenic strains of group A streptococci are associated with this disease. The pharyngeal strains and pyodermal strains differ. The epidemiology of the disease is similar to the initial streptococcal infection. The clinical diagnosis is based on the clinical presentation and evidence of a recent group A Streptococcal infection. Progressive, irreversible loss of renal function has been reported in adults.

III.1.5 Host defense and immunity

IgA, IgM, IgG antibodies to M protein offer resistance and type specific immunity. PMNs are also involved in defense.

Autoimmunity develops via cross reaction in post – streptococcal acute rheumatic fever. Immune complexes C3 from complement alternate pathway are deposited at glomerular basal membrane in post – streptococcal acute glomerular nephritis. Elevated titers of ASO in both conditions described above.

III.1.6 Treatment, Prevention, and Control

Group A streptococci are **very sensitive to penicillin**. For patients with a history of penicillin allergy, **erythromycin** can be used. Persistent oropharyngeal carriage of group A streptococci after a complete course of therapy can occur. This may represent poor compliance with the prescribed course of therapy, reinfection with a new strain, or persistent carriage in a sequestered focus. Antibiotic resistance has not been reported; thus an additional course of treatment can be initiated. If carriage persists, retreatment is not indicated because prolonged antibiotic therapy can disrupt the normal protective bacterial flora. Carriers have not been shown to be at increased risk for relapse infections or transmission of their organism to susceptible individuals.

Patients with a history of rheumatic fever require long-term use of antibiotic prophylaxis to prevent recurrent disease. In addition, damage to the heart valve predisposes the patient to subsequent endocarditis. Antibiotic prophylaxis is required before the use of procedures that induce transient bacteremias (e.g., dental procedures). Specific antibiotic therapy will not alter the course of acute glomerulonephritis and is not indicated for prophylaxis because recurrent disease is not observed.

III.2 Group B *Streptococcus*

Group B *Streptococcus*, or *Streptococcus agalactiae*, was initially recognized as a cause of puerperal sepsis. Although the organism is still associated with this disease, it has gained more notoriety as a significant cause of septicemia, pneumonia, and meningitis in newborn children.

III.2.1 Physiology and Structure

Group B streptococci are gram-positive cocci (0.6 to 1.2 μm) that form short chains in clinical specimens and longer chains in culture. The organism grows well on nutritionally enriched

medium as buttery colonies, larger than seen with group A streptococci, and surrounded by a narrow zone of β-hemolysis. Rare strains will be nonhemolytic or α-hemolytic.

Serologic cross-reactions have been observed between some group B and group G streptococci. Six immunologically distinct serotypes have been described. These serotypes are important epidemiological markers.

III.2.2 Pathogenesis and Immunity

Antibodies developed against the type-specific capsular antigens in group B streptococci are protective. This in part explains the predilection of this organism for neonates. In the absence of type-specific maternal antibodies the infant is at increased risk for infection. Bactericidal activity for group B streptococci also requires complement. If the level of complement is low in the neonate, then there is a greater likelihood of systemic spread of the organism in colonized infants.

Group B streptococci produce a number of enzymes, including deoxyribonucleases, hyaluronidase, neuraminidase, proteases, hippurase, and hemolysins. Although these enzymes are useful for identification of the organism, their role in the pathogenesis of infection is unknown.

III.2.3. Epidemiology

Group B streptococci colonize the upper respiratory tract, lower gastrointestinal tract, and vagina. Transient vaginal carriage has been reported in as many as 40% of pregnant women, although this is influenced by the time of sampling during the gestation period and culture techniques employed.

Infection, with subsequent development of disease in the neonate, can occur **in utero, at the time of birth, or during the first few months of life**. Infections at or before birth are called **early-onset disease**. The incidence of neonatal disease is approximately 3 per 1000 live births, with early-onset disease about twice as frequent as late-onset disease. **Late-onset disease** generally occurs in infants from 1 week to 3 months of life.

Early-onset disease is associated with all serotypes of group B *Streptococcus* in a proportion similar to maternal colonization.

III.2.4 Clinical Syndromes

Early-onset neonatal disease. Clinical symptoms of group B streptococcal disease acquired in utero or at the time of delivery generally will develop during the first 5 days of life. Early-onset disease, characterized by bacteremia, pneumonia, or meningitis, will appear indistinguishable from sepsis caused by other organisms. Mortality has been decreased with rapid diagnosis and better supportive care. However, 60% of infected, low birth weight, premature infants will die, and a significant proportion of survivors will have **neurological sequelae including blindness, deafness, and severe mental retardation.**

Late-onset neonatal disease. Disease in older infants is acquired from an exogenous source (e.g., mother, another infant). The predominant manifestation is bacteremia with meningitis, which again resembles disease caused by other bacterial pathogens. Although survival (greater than 80%)

is significantly better than with early-onset disease, neurological complications in children with meningitis are common.

Postpartum sepsis. Postpartum group B streptococcal disease generally is seen as endometritis or a wound infection, with bacteremia frequently documented. Because child-bearing women are generally in good health, the prognosis is excellent when appropriate therapy is initiated. Secondary complications following bacteremia, such as endocarditis, meningitis, or osteomyelitis, have been rarely reported.

III.2.5 Treatment, Prevention, and Control

Group B streptococci are **generally susceptible to penicillin G**, which is the **drug of choice**. However, the minimum inhibitory concentration (MIC) is approximately 10 times greater than with group A streptococci. In addition, tolerance to penicillin (ability to inhibit but not kill the organism) has been reported. For these reasons, a **combination of penicillin plus an aminoglycoside is frequently used** in serious infections. Resistance to erythromycin and tetracycline has also been observed. Thus specific antimicrobial susceptibility tests will have to be performed for isolates from patients allergic to penicillin.

Attempts to prevent neonatal disease have met with limited success. Although early-onset disease occurs in infants of colonized women, the incidence of colonization is high. Only a small proportion of these women will deliver infants who will become colonized and subsequently develop disease, and infants at greatest risk for disease cannot be identified unless maternal antibodies are measured (a procedure rarely done). Intrapartum antibiotic therapy reduces the incidence of neonatal disease, but the routine treatment of all colonized women is not currently recommended.

Passive immunization of high-risk babies by transfusion with blood containing type-specific antibodies has reduced morbidity and mortality associated with group B streptococcal disease. However, most whole blood has inadequate levels of protective antibodies. Future efforts to eliminate this disease will be directed toward the detection and immunization of women of childbearing age without protective antibodies.

III.3 Other β-Hemolytic Streptococci

Although a large variety of other groupable β-hemolytic streptococci have been described, the most commonly isolated strains belong to **groups C, F, and G.** These groups can be subdivided into large colony or "*S. pyogenes*-like" strains and small colony strains. Most small colony strains are *S. anginosus* (also referred to as *S. milleri* group).

The taxonomic classification of **group C streptococci has undergone recent changes**. The two species most commonly associated with human disease, ***S. equisimilis*** **and** ***S. anginosus***, can be part of the normal microbial flora of the pharynx, gastrointestinal tract, and genitourinary tract. Group C streptococci have been implicated in a **variety of infections** including pharyngitis (sometimes complicated by acute glomerulonephritis but never rheumatic fever), epiglottitis, sinusitis, meningitis, soft tissue and bone infections, intraabdominal abscesses, pericarditis, and endocarditis.

All group F streptococci are considered to be *S. anginosus*. These organisms colonize the same body sites as group C streptococci and have been associated with a wide distribution of infections. Abscess formation is a prominent feature of these infections.

Group G streptococci are a heterogeneous collection of organisms sharing reactivity with antibodies directed against the group G carbohydrate. The "small colony" variants have been classified as *S. anginosus* and are associated with the same diseases attributed to the other serogroups of this species. These include respiratory infections (possibly complicated by acute glomerulonephritis), cutaneous infections, bacteremia, endocarditis, meningitis, arthritis, and puerperal sepsis.

III.4 Viridans Streptococci

The viridans group of streptococci are a **heterogeneous collection of α- and nonhemolytic streptococci.** Taxonomic nomenclature for these species is confusing because a consensus between European and American microbiologists has not been reached. Although most isolates of viridans streptococci do not possess a group-specific carbohydrate, reactivity with some groups has been reported (e.g.. A, C, E, F, H, K, M, and O).

Like most other streptococci, these species are nutritionally fastidious, requiring complex media supplemented with blood products and an incubation atmosphere frequently augmented with 5% to 10% carbon dioxide.

The viridans streptococci are the **most common group of organisms in the oropharynx** and can also be isolated from the gastrointestinal and urogenital tracts. Although these organisms can cause a variety of infections, they are most commonly associated with **dental caries, subacute endocarditis, and suppurative intraabdominal infections.** Adherence to tooth enamel or previously damaged heart valves is believed to be due to the production of insoluble dextran from glucose. This is most commonly observed with ***S. mutans*** **and** ***S. sanguis*****.** ***S. anginosus*** is the species most commonly associated with pyogenic infections. The pathogenesis of this abscess formation has not been defined.

Most strains of viridans streptococci are **highly susceptible to penicillin** with MICs ≤ 0.1 μg/ml, although moderately resistant streptococci (penicillin MIC 0.2 to 0.5 μg/ml) have been observed in as many as 10% of some species. Infections with these isolates can generally be treated with a **combination of penicillin and an aminoglycoside**. High-level resistance, because of an alteration of the penicillin-binding proteins, is rare. Tolerance to the killing activity of penicillin has also been reported, but the clinical significance is controversial.

III.5 *Streptococcus pneumoniae*

Streptococcus pneumoniae was initially isolated independently by Pasteur and Steinberg more than 100 years ago. Since that time research with this organism has increased our understanding of molecular genetics, antibiotic resistance, and vaccine-related immunoprophylaxis. Unfortunately, pneumococcal disease is still a leading cause of morbidity and mortality.

III.5.1 Physiology and Structure

The pneumococcus is an encapsulated gram-positive coccus. The cells are 0.5 to 1.2 μm in diameter, oval or lancet-shaped, and arranged in pairs or short chains. Older cultures will decolorize readily and appear gram-negative. Colonial morphology will vary. Encapsulated strains are generally large (1 to 3 mm on blood agar; smaller on chocolatized or heated blood agar), round, mucoid, and unpigmented; nonencapsulated strains are smaller and appear flat. All colonies will undergo autolysis with aging (the central portion of the colony will dissolve, leaving a dimpled colony). Colonies will be α-hemolytic on blood agar when incubated aerobically and may be β-hemolytic when grown anaerobically.

The organism has fastidious nutritional requirements and is capable of growth only on enriched media (e.g., tryptic soy agar or brain heart infusion agar) supplemented with blood products. Like all streptococci the organism lacks catalase. Unless an exogenous source of catalase is provided (e.g., from blood), the accumulation of hydrogen peroxide will inhibit growth of *S. pneumoniae*. The poor growth of isolates on chocolatized blood agar is the result of the heat-denaturation of catalase present in the blood.

Virulent strains of *S. pneumoniae* are covered with a complex polysaccharide capsule. The capsular polysaccharides are antigenically distinct and have been used for serologic classification of strains. At present, **84 serotypes** are recognized. Purified capsular material from the most commonly isolated serotypes are used in a **polyvalent vaccine**. Antibodies directed against the capsules have also been used for diagnostic purposes.

The cell wall peptidoglycan layer of the pneumococcus is typical of gram-positive cocci. The other major component of the cell wall is teichoic acid rich in galactosamine, phosphate, and choline. The presence of **choline** is unique to the cell wall of *S. pneumoniae* and plays an important regulatory role in cell wall hydrolysis. In the absence of choline the pneumococcal autolytic enzyme is unable to function and cell division ceases. Two forms of teichoic acid exist in the pneumococcal cell wall: one exposed on the cell surface and a similar form covalently bound to the plasma membrane lipids. **The exposed teichoic acid (also called C-substance**) is species-specific and unrelated to the group-specific carbohydrates described by Lancefield in β-hemolytic streptococci. The C-substance will precipitate a serum globulin fraction (C-reactive protein [CRP]) in the presence of calcium. CRP is present in low concentrations in healthy individuals but is elevated in patients with acute inflammatory diseases.

III.5.2 Pathogenesis and Immunity

Capsule. The virulence of *S. pneumoniae* is directly associated with the capsule, which inhibits phagocytosis in the absence of specific antibodies. Encapsulated (smooth) strains are able to cause disease in humans and experimental animals, whereas nonencapsulated (rough) strains are avirulent. Antibodies directed against the capsular polysaccharides protect against disease caused by immunologically related strains. The capsular polysaccharides are soluble and have been referred to as specific soluble substance (SSS).

Pneumolysin. This is a temperature- and oxygen-labile hemolysin immunologically related to streptolysin O. Pneumolysin is responsible for the β-hemolysis observed when *S. pneumoniae* is grown anaerobically. The protein is dermatoxic and causes hemolytic anemia in experimental rabbit infections.

Neuraminidase. This enzyme is active against cell glycoproteins and glycolipids and may play a role in the spread of pneumococci through infected tissues.

***Autolysins*.** The pneumococcal autolysin, amidase, hydrolyzes the peptidoglycan layer. If choline is absent from the cell wall teichoic acid, the amidase is inactive. Although its role in cell division is well defined, the importance of the amidase in pathogenesis is not known.

III.5.3 Epidemiology

S. pneumoniae is a common inhabitant of the throat and nasopharynx of healthy individuals. Carriage has been reported to range from 5% to 75%. Colonization is more common in children than in adults, with *S. pneumoniae* initially detected at about 6 months of age. Subsequently, the child is transiently colonized with other serotypes of the organism. Acquisition of new serotypes occurs throughout the year, although carriage and associated disease is highest during the winter and spring months. The strains of pneumococci that cause disease are the same ones associated with carriage.

Pneumococcal disease originates from spread of organisms colonizing the nasopharynx and oropharynx to distal loci: lungs (pneumonia), paranasal sinuses (sinusitis), ears (otitis media), and meninges (meningitis). Bacteremia, with subsequent spread to other body sites, can occur with all of these infections.

S. pneumoniae is the most common cause of **bacterial pneumonia**, as well as **bacterial meningitis**. In addition, the organism is a common cause of **otitis and sinusitis.** The incidence of disease is highest in children and the elderly.

III.5.4 Clinical Syndromes

***Pneumonia*.** Infections are caused by aspiration of the endogenous oral organisms. Although strains can be transferred from one person to another by droplets in a closed population, epidemics are rare.

Disease occurs when the natural defense mechanisms are circumvented, permitting organisms colonizing the oropharynx to gain access into the lower airways. Pneumococcal disease is most commonly **associated with an antecedent viral respiratory disease** such as influenza or measles, **or with other conditions** that interfere with bacterial clearance, such as chronic pulmonary disease, alcoholism, congestive heart failure, diabetes mellitus, and chronic renal disease.

The pathogenesis of pneumococcal pneumonia is due to **bacterial multiplication** in the alveolar spaces. The **clinical manifestations** of pneumococcal pneumonia are abrupt in onset, with a severe shaking chill and sustained fever of 39° C to 41° C. The patient commonly has symptoms of a viral respiratory infection 1 to 3 days before the initial onset. A productive cough with blood-tinged sputum is seen in most patients, and chest pain (pleurisy) is common. Because the disease is associated with aspiration, disease is generally localized in the lower lobes of the lungs (hence the name **lobar pneumonia**). However, a more generalized **bronchopneumonia** can be seen in children or the elderly. Recovery is usually rapid after the initiation of appropriate antimicrobial therapy, with complete radiological resolution in 2 to 3 weeks. The overall mortality is 5%, although this is influenced by the serotype of the organism and the age and underlying disease of the patient. Mortality is significantly increased in disease caused by ***S. pneumoniae* type 3**, as well as in elderly patients or in patients for whom bacteremia is documented. Pleural effusions are seen in about 25% of patients with pneumococcal pneumonia, and empyema (purulent effusion) is a rare complication.

Sinusitis and Otitis Media. *S. pneumoniae* is a common cause of acute infections of the paranasal sinuses and ear. Disease is usually preceded by a viral infection of the upper respiratory tract, leading to infiltration with polymorphonuclear leukocytes and obstruction of the sinuses and ear canal. Middle ear infection (otitis media) is primarily seen in young children; bacterial sinusitis can occur at all ages.

Meningitis. Spread of *S. pneumoniae* into the central nervous system can follow bacteremia, infections of the ear or sinuses, or head trauma with communication between the subarachnoid space and the nasopharynx. Bacterial meningitis can occur at all ages, although it is primarily a pediatric disease. Pneumococcal meningitis is relatively uncommon in neonates; however, about 15 % of meningitis in children and 30% to 50% of adult disease is caused by *S. pneumoniae*.

Bacteremia. Bacteremia will occur in 25% to 30% of patients with pneumococcal pneumonia and more than 80% of patients with meningitis. In contrast, bacteria are generally not present in the bloodstream of patients with sinusitis or otitis media. Endocarditis can occur in patients with normal or previously damaged heart valves. Destruction of the valve tissue is common.

III.5.5 Treatment, Prevention, and Control

Penicillin rapidly became the treatment of choice for pneumococcal disease. For patients allergic to penicillin, alternative effective agents have included the cephalosporins, **erythromycin, and chloramphenicol** (for meningitis). Resistance to penicillin has been reported for as many as one third of isolates (higher in USA, Hungary, Spain, rare in Germany, Austria). Because the pneumococcal capsule is the primary virulence factor associated with this organism, efforts to prevent or control the disease have focused on the development of an effective vaccine (Pneumovax). The effectiveness of the vaccine in patients at risk for pneumococcal disease is less satisfactory.

Because the pneumococcal capsule is the primary virulence factor associated with this organism, efforts to prevent or control the disease have focused on the development of an **effective vaccine**. The current vaccine contains 23 different capsular polysaccharides. Approximately 94% of all strains isolated from infected patients are either included in the vaccine or are serologically related to the vaccine serotypes. The vaccine is immunogenic in normal adults, and the immunity is long lived. However, the effectiveness of the vaccine in patients at risk for pneumococcal disease (e.g., patients with asplenia, sickle cell disease, hematological malignancy, renal transplant, or young children and the elderly) is less satisfactory.

III.6 *Enterococcus*

The enterococci were **previously classified as group D streptococci** because they possess the group D cell wall antigen (glycerol teichoic acid associated with the cytoplasmic membrane). Despite this observation, it was recognized that these organisms were distinct from other group D streptococci (referred to as nonenterococcal group D streptococci, e.g., *S. bovis*). At present, 12 species of enterococci are recognized, although the species most commonly responsible for human infections are ***E. faecalis*** **and** ***E. faecium***.

The enterococci are gram-positive cocci typically arranged in pairs and short chains. The microscopic morphology of these isolates frequently cannot be differentiated from *S. pneumoniae*

when grown in broth culture. They grow readily on blood agar media, producing large white colonies after 24 hours of incubation.

E. faecalis is found in small numbers in the upper respiratory tract and small intestine and in large numbers (e.g., 10^7 org/gm of feces) in the large intestine. *E. faecium* has a similar distribution, although it is found less frequently. **The enterococci are uniquely suited for survival. They are able to grow in the presence of a high concentration of bile and sodium chloride, which is necessary for survival in the bowel and gall bladder.**

Enterococci are a **common cause of urinary tract infections in hospitalized patients**, particularly those patients with an indwelling catheter and receiving broad-spectrum antibiotics with limited activity against these organisms. The etiological role of enterococci in **intraabdominal abscesses and wound infections** is less clear because the infections are generally polymicrobic. Enterococci are also able to cause **bacterial endocarditis**.

Antimicrobial therapy for enterococcal infections is complicated because most antibiotics are not bactericidal at clinically relevant concentrations. Therapy has traditionally consisted of the **synergistic combination of an aminoglycoside and a cell-wall active antibiotic** (e.g., penicillin, ampicillin, vancomycin). However, resistance to aminoglycosides, ampicillin, penicillin, and vancomycin has been reported (**VRE** frecvently reported in ICUs).These strains are particularly troublesome because this resistance is plasmid mediated and can be transferred to other bacteria. At present, no combination of antibiotics has proven bactericidal activity against these organisms.

IV NEISSERIA

The best known *Neisseria* species are *Neisseria meningitidis* and *Neisseria gonorrhoeae. Neisseria meningitidis* can either colonize the upper respiratory tract or cause significant human disease. In contrast, *Neisseria gonorrhoeae* is always considered pathogenic, even in individuals with asymptomatic colonization. The other *Neisseria* species normally colonize mucous membranes and the skin surface and are rare causes of disease.

IV.1 Neisseria meningitidis

The meningococci are encapsulated, gram – negative diplococci that can asymptomatically colonize the nasopharynx of healthy individuals or cause fulminant meningitis, pneumonia, or overwhelming sepsis (meningococcemia), urethritis, arthritis.

Physiology and structure

The meningococci form transparent, nonpigmented, nonhemolytic colonies on chocolate blood agar, with enhanced growth in a **moisture atmosphere with 5 % carbon dioxide**. Isolates with large capsules appear as mucoid colonies. Meningococci are **oxidase positive** and are differentiated from other neisseria by acid production from glucose and maltose but not sucrose or lactose.

Neisseria meningitidis is subdiveded into **serogroups** (the antigenic determinant – polysaccharide capsule) and imunotypes (the antigenic determinant – lipopolysaccharide). Serogroups A, B, C, Y and W135 are most commonly associated with meningococcal disease. All group A meningococci have the same outer membrane protein and belong to a single serotype, whereas multiple serotypes have been described for group B and C. Membrane proteins and serotype classification are shared between the two groups.

Pathogenesis and immunity

Three major factors are responsible for meningococcal disease: **the ability of *Neisseria meningitidis* to colonize the nasopharynx (mediated by pili), systemic spread without antibody – mediated phagocytosis (protection afforded by polysaccharide capsule), and expression of toxic effects (mediated by the lipooligosaccharide endotoxin).** Meningococci attach selectively to specific receptors for menigococcal pili on nonciliated columnar cells of nasopharynx. Meningococci without pili have decreased binding to these cells. The organisms are internalized in phagocytic vacuoles, and after 18 to 24 hours the meningococci are found in the subepithelial space. The antiphagocytic properties of the polysaccharide capsule protect *Neisseria meningitidis* from phagocytic destruction. The diffuse vascular damage associated with meningococcal infections (e.g., endothelial damage, inflammation of vessel walls, thrombosis, disseminated intravascular coagulation) is in large part attributed to the action of the lipopoligosaccharide (LPS) endotoxin.

Immunity

Serum bactericidal antibodies are important for preventing systemic meningococcal disease. Thus infants younger than 1 year of age are more susceptible to disease related to the decline in maternal antibodies. Bactericidal activity also requires complement activity. Individuals

with deficiencies in C5, C6, C7, or C8 in the complement system are at increased risk (6000 – fold) for meningococcal disease. Although immunity is primarly mediated by the humoral immune response, lymphocyte responsiveness to meningococcal antigens is markedly depressed in patients with acute disease.

Iron-scavenging protein scavenges iron from host stores (such as hemoglobin, transferrin, and lactoferrin of PMNs). Iron is needed by *N. meningitidis* for its own metabolic processes.

Epidemiology

Endemic meningococcal disease occurs worldwide, and **epidemics are common in developing countries**. Pandemic outbreaks of disease have been uncommon in developed countries since one swept Europe and North America following World War II. Approximately 90% of meningococcal disease is caused by serogroups **A, B, and C,** with B responsible for most endemic disease in the US and serogroup A the major pathogen in Asia and Africa. Transmission of *Neisseria meningitidis* is by **respiratory droplets** among persons who have prolonged close contact, such as family members living in the same household, and within crowded communities such as the military. Classmates and hospital employees are not considered close contacts and are not at significantly increased risk unless they are in direct contact with respiratory secretions.

Humans are the only natural carriers for *Neisseria meningitidis*, so the bacterium is spread from person to person by aerosolization of respiratory secretions. The oral and nasopharyngeal carriage rates are highest in school – age children and young adults, higher in lower socioeconomic populations (possibly caused by crowding), and do not vary with seasons of the year (even though disease is most common during the dry season). Endemic disease is most common in children younger than 5 years of age, with the highest attack rates in infants from 3 months to 1 year of age. Older individuals, particularly those living in closed populations (e.g., military, prisons) are infected during epidemics.

During the first months of life, maternal bactericidal antibodies are protective. However, as passive immunity wanes and before acquired immunity develops, children are susceptible to infection. Acquired immunity develops in asymptomatically colonized persons, with bactericidal antibodies detectable within 2 weeks of colonization. Cross – reacting antibodies providing immunity to *Neisseria meningitidis* can occur with antigenically related strains of meningococci or with bsacteria of other genera (e.g., *Escherichia coli* serotype K1 cross – react with group B *Neisseria meningitidis*). The majority of meningococcal strains acquired during carriage are typable.

Clinical Syndromes

Meningitis

Disease usually begins abruptly with headache, meningeal signs (neck pain, headache, positive Brudzinski sign and Kernig sign), and fever. However, very young children may have only nonspecific signs such as fever and vomiting. Mortality approaches 100% in untreated patients but is less than 15% when appropiate antibiotics are promptly instituted. The incidence of neurologic sequelae is low, with hearing deficits and arthritis most commonly reported.

Diagnosis is made by **lumbar puncture prior to antibiotic treatment**. CSF has increased number of PMNs, low level of glucose, cloudy appearance.

Meningococcemia

Septicemia (meningococcemia) with or without meningitis is a life – threatening disease with mortality rate of 25% even in patients who are promptly treated. Thrombosis of small blood vessels and multiorgan involvement are characteristic. Small pethecial skin lesions on the trunk and lower extremities are common and may coalesce to form larger hemorrhagic lesions. The disease may progress to overwhelming disseminated intravascular coagulation with shock and includes bilateral destruction of the adrenal glands (Waterhouse – Friderichsen syndrome).

A milder, chronic septicemia has also been described. Bacteremia can persist for days or weeks in these patients, with the only signs of infection being low-grade fever, arthritis, and petechial skin lesions. Response to antibiotic therapy is generally excellent.

Other syndromes

Additional infections associated with *Neisseria meningitidis* include **pneumonia, arthritis, and urethritis**. Meningococcal pneumonia is usually preceded by a respiratory infection. Symptoms include cough, chest pain, rales, fever, and chills. Evidence of pharyngitis is observed in the majority of patients. The prognosis for this infection is good.

Lab tests

Catalase and oxidase are positive, glucose and maltose are used with acid production. **Latex agglutination of CSF may be used for rapid diagnosis**. PCR or LCR tests may be used for identification in cases where culture is not possible.

Treatment, Prevention, and Control

Antibiotic therapy and supportive management of the complications of meningococcal disease have significantly reduced the associated mortality. Although sulfonamides were the basis for the initial therapeutic successes, widespread resistance has negated their effectiveness. **Penicillin is the antibiotic of choice**; however, resistance to penicillin is becoming more common. **High – level resistance** (MIC greater than or equal to 2 μg/ml) mediated by the production of β – lactamase is very rare. However, moderate resistance (MIC 0.1 to 1.0 μg/ml) caused by the antigenic alteration of penicillin – binding proteins (specifically, PBP 2) has been reported. Alternative **antibiotics include chloramphenicol and the broad – spectrum cephalosporins that remain active in vitro.**

Eradication of the pool of healthy carriers is unlikely. Efforts have concentrated instead on the prophylactic treatment of persons who have significant exposure to diseased patients and the enhancement of immunity to serogroups most commonly associated with disease. At the present prophylaxis with a sulfonamide is recommended for persons exposed to sulfonamide – susceptible strains, with rifampin used for sulfonamide – resistant strains.

Vaccines directed against the group – specific capsular polysaccharides have been developed for antibody – mediated immunoprophylaxis. Vaccination can be used to control an outbreak of disease with serogroup present in the vaccine, for travelers to hyperendemic areas, or for individuals at increased risk for disease (e.g., patients with complement deficiency).

IV.2 Neisseria gonorrhoeae

Infection with *Neisseria gonorrhoeae* is one of the most common sexually transmitted disease. Clinical manifestations include **urethritis, cervicitis, salpingitis, proctitis, septicemia, arthritis, conjunctivitis, pharyngitis, pelvic inflammatory disease.**

Physilogy and Structure

Gonococci, like meningococci, are small, gram – negative diplococci. Five morphologically distinct colony types (T1 through T5) have been described, based on such features as color, size, and opacity, with virulence associated with T1 and T2.

The structure of gonococcus is similar to *Neisseria meningitidis.* The outer surface is covered with a loosely associated capsule of unknown composition. Protruding through the surface of the bacteria are filamentous, protein pili, which are present only in the virulent T1 and T2 colony types. Considerable heterogenicity exists in the pilin protein, with antigenic variations exhibited during infection and only limited relatedness observed in pili from different strains. The presence of pili is important for the initial attachment. Piliated strains are also more resistant to phagocytosis. Nonpiliated cells such as those present in colony types T3 and T5 are avirulent. The major protein in the outer membrane is **Protein I (porin).** Sixteen serotypes of Protein I have been described and are useful for the epidemiologic classification of isolates. Protein I can interfere with neutrophil degranulation. Whether this blocks intracellular killing of phagocytosed bacteria is unclear. **Protein II (Opa)** is a minor membrane protein found in avirulent, opaque colonies. The presence of this protein is associated with intercellular adhesiveness, as well as increased adherence of gonococci to cultured mammalian cells. **Protein III (Rmp)** is a highly conserved surface protein closely associated with Protein I. A 37,000 d protein common to all gonococci is responsible for the removal of iron from host – binding proteins (e.g., lactoferrin, transferrin). Iron is essential for the growth and metabolism of gonococci. The endotoxin lipopoligosaccharide (LPS) of *Neisseria gonorrhoeae* resembles that found in *Neisseria meningitidis.* The endotoxin contains lipid A and a core polysaccharide, although the strain – specific O side chains that are present in many gram – negative bacilli are absent. The lipopoligosaccharide is released in an active form into the extracellular space much like with *Neisseria meningitidis.* Other proteins associated with the gonococci are a protease capable of cleaving immmunoglobulin A and β – lactamase that hydrolytically destroys penicillin. The capsule protects against phagocytosis by PMN.

Pathogenesis and Immunity

Similar to infections with *Neisseria meningitidis,* gonococci attach to mucosal cells, penetrate into the cells and multiply, and then pass through the cells into the subepithelial space where infection is established. The presence of pili is important for the initial attachment. Nonpiliated cells such as those present in colony types T3 and T5 are avirulent. In the absence of specific opsonic antibodies and complement, the capsule protects against phagocytosis by polymorphonuclear leukocytes. Piliated strains are also more resistant to phagocytosis than are strains without pili.

Protein I can interfere with neutrophil degranulation. Whether this blocks intracellular killing of phagocytosed bacteria is unclear. The biologic role of Protein II and Protein III are unknown. The gonococcal endotoxin is responsible for tissue destruction in cell culture and is believed to be the major virulence factor in vivo. In persistent infection, chronic inflammation and fibrosis occur, which can lead to sterility, arthritis with joint destruction, or blindness.

Ig G_3 is the predominant Ig G antibody response to gonococcal infection. Whereas the antibody response to Protein I is minimal, serum antibodies to pilin preotein, Protein II, and lipooligosaccharide are readily detected. Antibodies to lipooligosaccharide can activate complement, realising C5a, which is chemotaxic to neutrophils. However, Ig G and secretory Ig

A antibodies directed against Protein III can block this bactericidal antibody response. As observed with *Neisseria meningitidis*, individuals with inherited complement deficiencies are at significantly increased risk for systemic disease.

Epidemiology

Gonorrhea is a disease found only in humans; it has no other known reservoir. The peak incidence of disease is in the 20- to 24-year age-group, with significant increases since 1970 in the incidence of disease in teenage patients.

Transmission of *Neisseria gonorrhoeae* is primarily by sexual contact. The risk of infection for women after a single exposure to an infected man is 50%; the risk for men after exposure to an infected woman is approximately 20%. The incidence of infection increases with multiple sexual encounters. Gonorrhea is more common in homosexual and bisexual men than in heterosexual men.

The major reservoir for the gonococcus is the asymptomatically infected individual. Determining a true incidence of asymptomatic infection is difficult. Disease is more commonly diagnosed in men than in women. **Asymptomatic carriage is more frequent in women** than in men. As many as half of all infected women have mild or asymptomatic infections, whereas most men are initially symptomatic. In untreated disease, however, the symptoms generally clear within a few weeks and asymptomatic carriage may become established. These carriers can transmit disease. Carriage is also influenced by the site of infection; rectal and pharyngeal infections are more commonly asymptomatic than are genital infections.

Clinical Syndromes

Genital infection **in men** is primarily restricted to the urethra. Purulent urethral discharge and dysuria develop after a 2- to 7-day incubation period. Approximately 95% of all infected men have acute symptoms. Although complications are rare, epididymitis, prostatitis, and periurethral abscesses can occur.

The primary site of infection **in women** is the cervix, although gonococci can be isolated in the vagina, urethra, and rectum. Vaginal discharge, dysuria, and abdominal pain are commonly reported in symptomatic patients. Ascending genital infection, including salpingitis, tubo-ovarian, abscesses, and pelvic inflammatory disease are reported in 10% to 20% of women. Disseminated infections with septicemia and infection of skin and joints occurs in 1% to 3% of infections in women and in a much lower percentage of infected men. The increased proportion of disseminated infections in women is caused by the large number of untreated asymptomatic infections in this population. Clinical manifestation of disseminated disease includes fever, migratory arthralgias, suppurative arthritis in the wrists, knees, and ankles, and a pustular rash on an erythematous base over the extremities but sparing the head and trunk. *Neisseria gonorrhoeae* is a leading cause of purulent arthritis in adults.

Other diseases associated with *Neisseria gonorrhoeae* include perihepatitis (Fitz – Hugh – Curtis syndrome), purulent conjunctivitis (particularly in newborns infected during vaginal delivery – ophthalmia neonatorum), anorectal gonorrhea in homosexual males, and pharyngitis.

Lab tests

Catalase and oxidase are positive, only glucose is used with acid production. PCR or LCR tests may by used for identification in cases where culture is not possible.

Treatment, Prevention, and Control

Penicillin historically has been the treatment of choice. However, three changes have been observed. First, the concentration of penicillin required to inhibit growth of *Neisseria*

gonorrhoeae has steadily increased, necessitating significantly higher doses for clinical cures.. Second, penicillin resistance mediated by enzymatic hydrolysis of β-lactam ring was initially reported in Southeast Asia and now has worldwide distribution. The genetic information for this resistance is encoded on a transmissible plasmid. Thus this increase in resistance should continue. Finally, strains of penicillin – resistant *Neisseria gonorrhoeae* that do not produce β - lactamase have been isolated. This chromosomally mediated resistance is not limited to the penicillin antibiotics but also includes resistance to tetracyclines, erithromycin, and aminoglycosides. This resistance appears to be the result of changes on the cell surface that prevent antibiotic penetration into the gonococcal cell. Because the incidence of penicillin resistace is now relatively high, the Centers of Disease Control recommends **ceftriaxone** should be used as initial therapy for uncomplicated gonorrhea, combined **with tetracycline** to manage dual infections with *Chlamydia.*

Immunity to infections with *Neisseria gonorrhoeae* is poorly understood. Antibodies can be detected to pili antigens, as well as to Protein I and lipooligosaccharide. **Multiple infections in sexually promiscuous individuals are common.** This lack of protective immunity is explained in part by the **antigenic diversity of gonococcal strains**. The variable region at the carboxy terminus of the pilin protein is immunodominant portion of the molecule. Antibodies developed against this region protect against reinfection with a homologous strain, but cross – protection against heterologous strains is incomplete. This also explains the ineffectiveness of vaccines developed against pilin proteins.

Chemoprophylaxis is also ineffective, except in protection against gonococcal eye infections in newborns (ophthalmia neonatorum) in which 1% **silver nitrate**, 1**% tetracycline**, or 0.5% **erythromyc in** eye ointments are routinely used. Prophylactic use of penicillin to prevent genital disease has been demonstrated to be ineffective and may select for resistant strains.

It is important to realize that gonorrhea is not an insignificant disease. **Chronic infections can lead to sterility**, and asymptomatic infections perpetuate the reservoir of disease and lead to a higher incidence of disseminated infections.