Learning Objectives:
1. Recognize the clinical signs of infective endocarditis including retinal Roth spots, petechiae, fever, abnormal heart sounds, subungual splinter hemorrhages, and splenomegaly.
2. Explain how the mechanisms of action of penicillins, cephalosporins, and vancomycin predict synergistic action with gentamicin.
3. Identify the adverse effects of penicillins, cephalosporins, gentamicin, and vancomycin.
4. Explain the mechanisms involved in Type I hypersensitivity.
5. Describe a wheal and flare reaction on the skin.
6. Recognize various microorganisms that commonly cause IE such as Staphylococci, Streptococci, Gram-positive rods, Gram-negative rods based on features observed in Gram stain, biochemical test, and differential media such as blood agar.
7. List the most common causes of native valve endocarditis, prosthetic valve endocarditis, and endocarditis involving previously-damaged heart valves and endocarditis associated with intravenous drug use.
8. Recognize the risk factors for infective endocarditis of prosthetic heart valve implants, rheumatic heart disease, intravenous drug use, dental procedures, mitral valve prolapse, and abdominal surgery involving the colon.
9. Describe the pathogenesis of infective endocarditis.
10. Describe the investigations and criteria used for diagnosis of infective endocarditis.

Endocarditis is an infection of the endocardial surface of the heart, and is characterized by vegetations that develop on heart valves or other endocardial surfaces. The valve most commonly affected is the mitral, followed by the aortic, the tricuspid, and the pulmonary valves. The term infective endocarditis (IE) is now considered preferable to the old term, bacterial endocarditis, because in addition to bacteria, fungi and perhaps even viruses may be responsible for the syndrome. Traditionally, IE is divided into two types: subacute and acute. **Subacute endocarditis** is more common and symptoms develop over a longer period of time; it is classically caused by the viridans Streptococci. **Acute endocarditis** progresses very rapidly with more severe symptoms. This presentation was historically associated with infection caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae* or *Neisseria gonorrhoeae*; however, the latter two are now much less common. Acute endocarditis is common in intravenous (IV) drug users. Furthermore, the acute/subacute classification of IE ignores the nonbacterial forms of the syndrome and there is overlap between the manifestations that occur in acute and subacute IE, thus we are heading towards classification based on etiology.

The current most common etiologies of infective endocarditis:

There is a wide variety of microorganisms known to cause endocarditis and a select few that are more commonly isolated (Table 1). The etiology depends on the condition of the valves, the medical history of the patient, the presence of injection drug use, the presence of a prosthetic heart valve and the length of time the valve has been in place before an infection resulted in symptoms. However, even normal native valves can be attacked. Overall, *Streptococci* and *Staphylococci* account for 80% to 90% of the cases when a pathogen is identified.
The viridans Streptococci are responsible for about 60% of IE cases caused by Streptococci. They were previously the most common cause of endocarditis worldwide and remain the predominant etiology in the developing world. The majority of infections occur on valves with previous damage; historically this was overwhelmingly due to rheumatic heart disease, but more contemporary risk factors include mitral valve prolapse, bicuspid aortic valve, calcific valvular stenosis and prosthetic heart valves. The viridans group of Streptococci is a collection of α- or γ- hemolytic Streptococci, which have minimal or no lysis (clearing) of red-blood cells when grown on blood agar. Recall that the Streptococci are Gram-positive (purple) and spherical in shape (coccI), which are arranged in pairs and/or chains. The name viridans comes from the Latin word for green, viridis, and reflects the fact that many representatives of this family appear green when grown on blood agar. Unlike most of the Streptococcus genus, viridans Streptococci cannot be typed by the Lancefield system; however, they can be differentiated from other common Streptococci by their resistance to the antimicrobial compound Optochin. The classification of the viridans Streptococci is confusing and ever-changing but the current names for the viridans Streptococci that commonly cause IE are S. mitis, S. sanguinis, S. mutans, S. salivarius, and the S. intermedius group (including S. anginosus, S. intermedius, and S. constellatus). The viridans Streptococci are the most prevalent members of the normal flora of the upper respiratory tract and oral cavity and are important for the healthy state of the mucous membranes there. However, the viridans Streptococci are considered the most common isolates among children with IE and from IE patients with mitral valve prolapse. In these cases, the disease usually is subacute with nonspecific symptoms; cure rates are generally >90%. The S. intermedius group organisms are a notable exception due to their predilection for abscess formation and often present more like an acute infection such as that due to S. aureus.

The viridans Streptococci Streptococcus mutans is a normal inhabitant of the mouth. It is Gram-positive, γ- hemolytic (non-hemolytic), microaerophilic, pleomorphic, and fastidious making it difficult to
isolate. It is very well known for its role in creating dental caries, and S. mutans dental infections have been reported to cause IE. However, the most common Streptococci isolated from IE cases are the viridans group member S. sanguinis and the Group D Streptococci S. bovis (now called S. gallolyticus).

S. pneumoniae is a member of the viridans streptococci group, as it is usually α-hemolytic, but it is usually considered separately due to the severity of its associated diseases. It can be differentiated from other viridans Streptococci by the fact that it is susceptible to growth inhibition by Optochin. In the past, it was responsible for 10% of the IE cases, but more recently this rate has decreased to 1-3%. Alcohol abuse is a notable risk factor. 70% of cases also manifest with meningitis. The mortality rate is very high (50%) and significant valvular destruction generally occurs.

Recall that most Streptococci are classified by Lancefield antigen types as well as by their degree of hemolytic activity (α, β, or γ), but viridans Streptococci do not carry Lancefield antigens. Group D streptococci are sometimes α-hemolytic but are not included among the viridans Streptococci. For example, S. bovis, which is a common inhabitant of the gastrointestinal tract and one of the most common causes of IE, is unique in that it carries the Lancefield group D antigen. Notably, there is a significant association of bacteremia due to S. bovis with carcinoma of the colon such that colonoscopy should be performed if this organism is isolated from blood cultures. Members of group D all share the ability to hydrolyze bile–esculin, but S. bovis can be differentiated from the Enterococci by the fact that S. bovis is salt-sensitive (does not grow in 6.5% salt) while the Enterococci are salt tolerant (can grow in 6.5% salt). The Enterococci are normal inhabitants of the gastrointestinal tract and the urogenital tract. Like all Streptococci, the Enterococci are catalase-negative and nonmotile and may exhibit α, β or γ-hemolysis depending on the species. The Enterococcus group is responsible for approximately 10% of the cases of IE, a number that is increasing. Furthermore, cure of IE caused by Enterococci is difficult because of intrinsic resistance of the Enterococci to many antimicrobials.

Streptococci other than the viridans group and group D are responsible for 5% of the IE cases. The β- hemolytic Group A Streptococcus or S. pyogenes, well known for causing strep throat (pharyngitis), is a rare cause of IE but is associated with high complication rates in adults and children. Recall that Group A Streptococcus is highly pathogenic and can cause serious systemic infections due to the presence of a wide variety of virulence factors. Further, Group A Streptococcus is associated with rheumatic fever which is characterized by inflammation of the heart, joints, and blood vessels, and places the patient at increased risk for endocarditis. Another member of the β-hemolytic Streptococci is Group B Streptococcus (Streptococcus agalactiae), which is a common inhabitant of the mouth, the vagina, and the urogenital tract. Group B Streptococcus can cause serious disease in adults secondary to bacteremia including endocarditis. Risk factors for Group B Streptococcus IE include diabetes mellitus, malignancy, alcohol abuse, hepatic failure, elective abortion, and IV drug use.

Staphylococci are now found to be the most common cause of IE in the industrialized world and 80 to 90% of the staphylococcal cases are due to coagulase-positive S. aureus. Further, the percentage of S. aureus isolates from IE cases appears to be increasing. Recall that Staphylococci are catalase-positive, Gram-positive cocci that grow in clusters. Also, catalase activity helps to differentiate Staphylococci from
Streptococci. For the most part, pathogenic Staphylococci, primarily S. aureus, can be identified based on coagulase production. S. aureus may attack normal native heart valves in a third of cases, and the course of staphylococcal IE is severe and rapid. The mortality rate still approximates 40%. It tends to infect the mitral or aortic valve with wide spread systemic infection including abscess formation in both cardiac and extracardiac tissue. In nearly half of the IE cases caused by S. aureus, the infection is acquired through a nosocomial mechanism and is often caused by methicillin resistant S. aureus (MRSA). IE in intravenous drug users is primarily due to S. aureus, but the disease has a history of being less severe, likely due to tricuspid involvement rather than the left-sided heart valves; this syndrome usually responds to antimicrobial therapy. Paradoxically, the coagulase-negative Staphylococcus epidermidis, which is normally a benign inhabitant of the skin, is an important agent frequently responsible for IE in patients with prosthetic heart valves although it is being identified more frequently in native valve endocarditis as well.

Gram-positive rods rarely cause IE. However, there have been several reports of various species of the Corynebacteria (diphtheroids) causing IE. Corynebacterium diphtheriae has been found in IE patients that are IV drug users, and Corynebacterium has been found responsible for IE in persons who have damaged or prosthetic valves. Other Gram-positive rods isolated from patients with IE include Listeria monocytogenes, Lactobacilli, Erysipelothrix rhusiopathiae, Bacillus species, and Rothia dentocariosa.

Gram-Negative Bacilli (rods) have been reported to cause about 2% of the cases of IE. Those who are most at risk are those with healthcare contact, IV drug users, prosthetic valve recipients, and patients with cirrhosis. Among the members of the Enterobacteriaceae, Salmonella were the most commonly reported species in IE cases. Besides being a Gram-negative rod, Salmonella are facultative, anaerobic fermenters and are oxidase negative. Salmonella can survive in macrophages and thus can be spread from the intestine to other body sites. Salmonella have an affinity for abnormal cardiac valves, usually on the left side of the heart. Salmonella species can also frequently result in mycotic aneurysms. Today, E. coli strains are the most common isolates in gram negative endocarditis cases. IV drug users have a high risk of IE caused by Pseudomonas, although healthcare contact is the more common risk factor for this organism. Prognosis is often extremely poor, especially when found on the left side. Early surgery is often performed due to a very rapid course and a high mortality. The Pseudomonas species are usually motile, straight or slightly curved Gram-negative rods typically arranged in pairs. They can be differentiated from the Enterobacteriaceae by the presence of cytochrome oxidase. But remember, S. aureus is still currently the most common etiological agent responsible for IE in drug users.

The HACEK organisms are a group of unusual Gram-negative bacilli that have been associated with approximately 1% of all IE cases. They tend to cause subacute endocarditis with slowly developing symptoms and clinical signs. The HACEK organisms include Haemophilus, Aggregatibacter (formerly Actinobacillus), Cardiobacterium, Eikenella, and Kingella. All are very hard to grow, potentially taking 2-3 weeks to culture. However, with new automated blood culture systems, incubation periods are much shortened and reliable identification is the norm. Remember, Eikenella corrodens is a common inhabitant of the oropharynx and is often found as the agent involved in endocarditis of IV drug users who lick their needles to clean them (“needle-licker” IE), but can also be involved in disease following dental
Clinical procedures.

**Fungal** IE is rare. However, the *Candida* genus of yeast has been associated with a small number of cases. Interestingly, IV drug use is a risk factor for IE due to the non-albicans species of *Candida*, while in health-care associated fungal IE, *Candida albicans* and *Aspergillus* species tend to predominate. It is important to note that the cure rate in cases of fungal IE is poor and almost all require surgery for any attempt at cure.

Culture negative endocarditis most commonly occurs due to antibiotic exposure prior to obtaining blood cultures. In cases in which another etiology is identified, Bartonella infections are the most common cause in the United States. Many of these etiologies require special testing with serologic or PCR (polymerase chain reaction) studies.

**Clinical Manifestations associated with IE:**

In endocarditis, vegetations develop on the surface of the valves that can dislodge. The dislodged vegetations are then transported by the blood stream where they lodge in small vessels to cause a variety of lesions typically associated with the disease. For this reason, infection of the heart valve can lead to petechiae, splinter hemorrhages, Janeway lesions, and Osler nodes which are all signs of endocarditis.

Petechiae from IE occur in crops or batches, especially in the conjunctiva, buccal mucosa or palate, upper chest, and extremities. **Splinter hemorrhages** are linear red to brown streaks that appear under the fingernails and toenails. **Janeway lesions** are small erythematous nodules observed on the palms and soles. **Osler nodes** are erythematous wheal-like tender nodules 2-15 mm in diameter and are usually located on the pads of fingers and toes. The cause of Osler nodes may be related to immune complexes but are probably initiated by microemboli.

The diagnosis of endocarditis is difficult because most symptoms are non-specific including fever, fatigue, anorexia, weakness, myalgias, arthralgia and malaise. Other key signs include valvular insufficiency, a change in a pre-existing murmur or a new cardiac valvular murmur, and tachycardia in addition to the skin lesions mentioned previously and occasionally round or oval retinal hemorrhages with pale centers (**Roth spots**). It is important to note that while fever is present in 90% of IE patients and murmur in 85% of IE patients, the peripheral signs mentioned above are encountered far less frequently: Osler nodes (10-23%), splinter hemorrhages (15%), petechiae (20-40%), Janeway lesions (<10%), Roth spots in the retina (2-10%).

In **subacute endocarditis**, the interval between the time of bacterial colonization of the endocardium and the onset of symptoms is usually less than 2 weeks. However, because the symptoms are usually nonspecific, there is often a delay of 5 weeks between onset of symptoms and diagnosis. Death might occur in 6 weeks to 3 months in the subacute endocarditis, while with the chronic form death occurs later than 3 months. The most common symptom is a low-grade fever, which is usually accompanied by chills and sometimes by night sweats. Fatigue, anorexia, weakness, myalgias, arthralgias and malaise are common. Debilitating lower back pain is a prominent complaint in a small
percentage of patients. Acute endocarditis has a rapid onset (2-5 days). The patient has a high fever, rigors, systemic toxicity and leukocytosis and appears very ill. The likelihood of extravascular complications is high. Death occurs in days to less than 6 weeks in acute endocarditis.

Sequelae associated with IE include splenomegaly (20-57%), musculoskeletal aches and pains (15%), neurologic symptoms or stroke (20%), renal failure (10-25%), local abscess formation, and metastatic infection including systemic abscesses and mycotic aneurysms.

**Micro-Pathogenesis of endocarditis**

As mentioned previously, endocarditis is usually preceded by damage to the endothelium inside the heart and or the heart valve; this was historically often due to rheumatic heart disease. As a result of the tissue damage there is an accumulation of platelets and fibrin, producing a *nonbacterial thrombotic endocarditis (NBTE)*. IE results when the lesion serves as a site for microorganisms from the blood stream to attach. The microbial infection grows on the surface of the valves and forms vegetations containing bacteria, white blood cells, platelets and fibrin. As a result of the vegetations, there may be destruction of the underlying valve or there may be a variety of extravascular damage due to emboli in the central nervous system, lung, skin (petechiae, Janeway lesions as discussed above), and the eye (Roth spots). This occurs when the vegetations dislodge.

Whenever a mucosal surface that is heavily colonized with bacteria is traumatized, transient bacteremia can occur and in the context of a preexisting NBTE, this may result in the colonization of these lesions and may lead to the development of IE. Dental extractions and other dental procedures, gastrointestinal, urological, and gynecologic procedures are all possible causes of transient bacteremia. Therefore, patients known to have a pre-existing heart valve condition are sometimes given antibiotics prior to any such procedures.

Organisms commonly associated with IE have been shown to adhere more avidly to normal heart valves than those organisms rarely associated with this disease. The adherence of oral *Streptococci* to NBTE has been reported to be dependent on the production of the extracellular polysaccharide, Dextran, which is essential for the pathogenesis of dental caries. Fim A, a surface adhesin gene widely distributed among strains of *viridans Streptococci* has also been shown to mediate adherence. Fibronectins, Laminin, and type-4 collagen, all normal components of damaged endothelium or NBTE, serve as binding sites for circulating bacteria. The exact attachment molecule depends on the infecting organism.

**Epidemiology**

The incidence of endocarditis is hard to determine due to the vague symptoms and variations in the criteria for diagnosis. It is estimated that there are approximately 5 to 7 cases per 100,000 persons per year in the United States. Infections of native or prosthetic heart valves can occur following asymptomatic bacteremias from infected gingivae, the genitourinary tract, or the gastrointestinal tract. Endocarditis usually occurs in patients with prior damage to the surface of the heart valve. Also, it is more common in IV drug users and in patients who have a prosthetic heart valve.
In a recent report of more than 2700 patients from 25 countries with definite IE by the modified Duke criteria, the median age of IE patients is about 58 years old. In children it is uncommon, however in children who do have IE, it is associated primarily with underlying structural defects, surgical repair of heart defects, or nosocomial cathether-related bacteremia particularly in infants. Almost any type of structural heart disease may predispose to IE but risk appears to be higher in patients with mitral valve prolapse. IE occurs more frequently among patients with extensive contact with the health care system due to the introduction of invasive therapeutics (IV lines, catheters, pacemaker, shunts etc). This corresponds to a recent shift from viridans *Streptococci* as the most common cause of IE to *S. aureus* IE, especially associated with intravascular devices.

**Diagnosis:**

As mentioned above, diagnosis of IE is difficult due to the non-specific symptoms. For this reason, a specific set of criteria (based on the Modified Duke Criteria) is used for diagnosis of endocarditis. If IE is suspected (fever with a murmur), there are two major laboratory studies that are essential in confirming the diagnosis, blood cultures and echocardiography. Transesophageal echocardiography (TEE) is the most sensitive study for detecting valvular vegetations. In fact, transesophageal echocardiography has a sensitivity of detecting endocarditis of greater than 90% whereas transthoracic echocardiography (TTE) has a sensitivity of approximately 65%. However, blood cultures are critical in determining the diagnosis of IE and should be performed first. It is important to note that bacteremia is constant and low level. Therefore, three sets (anaerobic and aerobic) of blood samples obtained from separate “sticks” over a 24-hour period are recommended. If there is good bacterial growth from more than one of the blood samples (major criteria 1) and if damage to heart valves is detected by echocardiography (major criteria 2) then IE is confirmed. Some use a third major criterion for IE diagnosis, which is a single blood culture positive for *Coxiella burnetii* (Q fever) or increased antibody titers for *C. burnetii*. Subacute endocarditis is the most common presentation for *C. burnetii*, which was originally classified with *Rickettsia* because it is a small, intracellular bacterium that stains poorly with Gram-stain and best with Giemsa. However, these are not considered common isolates from IE cases.

If it is not possible to confirm the diagnosis by the observation of two major criteria, then three of five minor criteria (below) plus one of the major criteria is sufficient for definitive diagnosis. If all five of the minor criteria (listed below) are observed, then a definitive diagnosis of IE is established.

**The minor criteria include:**

- Predisposing heart disease or intravenous drug use
- High body temperature
- Evidence of vascular phenomena
- Immunological phenomena including glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
- Microbiologic evidence: defined as a single positive blood culture that does not meet the third major criterion, or serologic evidence of an active infection with an organism consistent with IE.

Definite endocarditis can also be diagnosed on pathologic grounds including microorganisms seen on culture or histologic exam of a vegetation or intracardiac abscess or a consistent histologic appearance of the same lesions.
Treatment and Pharmacology

Antimicrobial therapy is dependent on the type of organism involved. Furthermore, combination antimicrobial therapy is often used. Therapy must be continued for several weeks even when symptoms disappear. The reasons prolonged therapy is required are twofold: 1. the infection is in an area of impaired host defense and is encased tightly in a protective fibrin meshwork; and 2. the bacteria in the vegetations reach tremendous population densities.

The mechanisms of action of penicillins, cephalosporins, gentamicin, and vancomycin and the synergistic action between agents

Penicillins vary in spectrum from narrow to broad depending on structure. Penicillin G (benzylpenicillin) has a relatively narrow spectrum in that it is most active against some Gram-positive organisms but has activity against very few Gram-negative organisms. Penicillins act to block cell wall synthesis by competitively inhibiting the cross-linkage between peptidoglycan polymer chains (termed the transpeptidation step) which is in the final stages of and is required for effective cell wall synthesis. Penicillin-treated bacteria eventually lyse due to the activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested. Penicillins are generally bactericidal. In combination with gentamicin, because the 2 agents act through different sites/mechanisms of action, organisms normally not killed but only inhibited (bacteriostatic) by either agent are killed (bactericidal).

Cephalosporins generally are broad spectrum agents. Like penicillins, cephalosporins are beta-lactams and inhibit bacterial cell wall synthesis by inhibiting the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Cephalosporins are generally less susceptible to beta-lactamases and therefore generally have a broader spectrum than penicillins. Cephalosporins are generally bactericidal. Similar to penicillins, the combination of cephalosporins with gentamicin can be bactericidal against organisms to which either drug alone is bacteriostatic.

Vancomycin is active against most Gram-positive organisms and thus generally considered a broad-spectrum agent. The mechanism of action is similar to beta-lactams in that transpeptidation of peptidoglycan polymers is blocked but this occurs by vancomycin binding tightly to the D-alanine terminal region of the peptide precursor. By blocking this final stage of cell wall synthesis, as with beta lactams, vancomycin disrupts the balance between cell wall synthesis and autolysis and thus compromises the cell wall integrity of the organism. Vancomycin is bactericidal against many organisms but bacteriostatic against some. The combination of vancomycin and gentamicin, because they act via separate mechanisms of action, increases the spectrum of organisms covered and bactericidal activity is seen.
Aminoglycosides (prototype gentamicin) are active against aerobic Gram-negative organisms generally. The mechanism of action is inhibition of bacterial protein synthesis. The drug must enter the organism to be effective. This entry into the bacterium is by energy dependent active transport which is blocked in the absence of oxygen, thus these drugs are most effective on aerobes. Aminoglycosides are considered bactericidal. Cell wall synthesis inhibitors such as beta lactam antimicrobials and vancomycin may enhance the active transport of aminoglycosides into the bacterium. This may be the basis or partial basis of the synergy seen between these drug classes.

The adverse effects of penicillins, cephalosporins, gentamicin, and vancomycin

Penicillin (Penicillin G): Penicillin (including penicillin G) hypersensitivity is the most common (estimated at 4 to 10% of population) and potentially a severe adverse effect. Reaction to penicillins can occur even if the person has no known exposure to penicillins (potentially being exposed through food sources). Most allergic reactions to penicillin are T cell-dependent responses mediated by IgE and the ultimate release of histamine (Type I Hypersensitivity). Unconjugated penicillin is not a protein and is incapable of eliciting a T cell-dependent response. However, when penicillin or its metabolites become conjugated to proteins (the protein is called the carrier) these complexes are immunogenic. Penicillin-protein complexes are broken up into peptides that bind to MHC class II molecules, which are then bound by TCRs (T Cell Receptors) on T cells. The penicillin moiety, acting as a hapten, is bound by BCRs (B Cell Receptors) on B cells. Each penicillin-specific IgE that is produced becomes coupled via its epsilon heavy chain (Fc region) to a high affinity Fc receptor for IgE (FcεRI) on mast cells. When penicillin binds to the antigen-binding site on the IgE antibody molecules, it cross-links the FcεRIs on the mast cell. Remember that cross-linking of FcεRIs leads to immediate release of granules from the mast cells that contain histamine and to the synthesis of leukotrienes by the mast cells that are released secondarily. Type I hypersensitivity is called immediate hypersensitivity because many of its symptoms are caused by the immediate release of pre-formed histamine from the mast cells. Immediate hypersensitivity to penicillins may occur as a systemic or a local reaction. Systemic reactions can result in a fatal state of shock. Local reactions can take the form of cutaneous swellings (hives). This “wheat and flare” type of skin reaction is a papule filled with edematous fluid (raised and circumscribed) caused by the release of histamine from mast cells. Surrounding this papule (the wheat) is an area of redness (the flare). Cephalosporins are generally well tolerated in adults. However, superinfection with nonsusceptible organisms can result. The most frequent adverse effect in adults is diarrhea (about 7% for cefpodoxime). Diarrhea in infants and toddlers (up to 2 years) is seen in about 15% of the population with cefpodoxime.

Aminoglycosides: The most common (>10%) adverse effects for all or many aminoglycosides including gentamicin are ototoxicity (both auditory and vestibular) and nephrotoxicity. Ototoxicity can be and often is irreversible. The aminoglycosides accumulate disproportionally in the inner ear and have slow diffusion out of the inner ear. This disproportionate accumulation is particularly observed when blood levels of the drug are high and the diffusion out of the inner ear is particularly slow until blood levels are low. Persistently elevated blood levels increase the incidence of irreversible ototoxicity.
Irreversible ototoxicity is due to progressive destruction of vestibular and cochlear sensory cells of the inner ear. Gentamicin has more vestibular (vertigo, ataxia, loss of balance) toxicity than auditory (tinnitus and high frequency hearing loss) toxicity. Nephrotoxicity is usually reversible but common (10 to 25%) in patients who receive aminoglycosides for more than several days. Damage begins in brush borders but can progress throughout the nephron if dosing continues. Reversibility is due to the regenerative capacity of the nephron cells. Nephrotoxicity can be detected early by monitoring for increases in trough aminoglycoside levels or for increase in serum creatinine.

A potential mechanism to avoid the serious complications of ototoxicity and nephrotoxicity is by the dosing regimens used. Traditionally 2 or 3 equally divided daily doses of gentamicin are administered (by IM or IV since GI absorption is negligible). When there is known or suspected potential for ototoxicity or nephrotoxicity a once-daily high dose regime can be used. Aminoglycosides have “concentration-dependent killing” (i.e. increasing concentrations kill an increasing proportion of bacteria and at a more rapid rate). They also have significant post antibiotic effect, such that the antibacterial activity persists well beyond the time during which measurable drug is present (several hours in many cases). So, a given total amount of aminoglycoside (such as gentamicin) may have better efficacy when administered as a single large dose than when administered as multiple smaller doses.

Aminoglycoside adverse effects are both time and concentration dependent. Toxicity is unlikely to occur until a certain threshold (blood concentration) is reached, but once that concentration is achieved the time beyond this threshold becomes critical. The threshold is not precisely defined but a trough above 2 micrograms/mL (2 mcg/mL) is predictive of toxicity. Clinically, the total time above this threshold is greater when multiple small doses of drug are used than when a single large dose is used. It should be noted that once-daily, high dose aminoglycoside therapy is not recommended in treatment of enterococcal endocarditis as part of combination therapy. Two or three daily doses are recommended. Vancomycin is generally well tolerated but with GI disturbances (bitter taste sensation, nausea, vomiting) occurring in up to 10% of the population. Infrequently (< 1%) ototoxicity and nephrotoxicity can be seen. There is the potential of additive or synergistic ototoxicity and nephrotoxicity with other agents causing these effects (such as gentamicin) and so there is a relative contraindication of these combinations.

Surgical intervention is necessary in up to half of endocarditis cases. The most common indications for surgical intervention include the development of heart failure, paravalvular abscess, recurrent embolic events, persistent sepsis, and pathogens that are difficult to treat including those with significant resistance and fungal etiologies.

References:


