Basic Bacteriology

Bacteria can be divided into categories primarily by their shape, arrangement and gram staining characteristics. The shape of a bacterium is determined by its rigid cell wall, while orientation and attachment during cell division determine the arrangement of cells. The three basic groups of bacteria are cocci, bacilli and spirochetes that are arranged into pairs, chains, or clusters. The structure of the bacterial cell wall also determines its gram staining characteristics. The gram-positive cell wall has a thick layer of peptidoglycan that may be surrounded by a layer of teichoic acid. The gram-negative cell wall has an inner periplasmic space and a complex outer layer made up of lipopolysaccharide (endotoxin), lipoprotein, and phospholipid. The rest of the cell structure consists of the phospholipid bilayer cell membrane, cytoplasm with ribosomes, granules, and metabolites, and the nucleoid region containing the cells DNA.

Bacteria reproduce by binary fission and exhibit an exponential growth pattern. One parent cell forms two progeny. Thus, after four cell division cycles one bacterium will produce 16 progeny bacteria. There are four phases of the bacterial growth cycle. During the lag phase bacteria demonstrate intense metabolic activity but do not divide. Rapid cell division occurs during the second or log phase. The stationary phase is a steady state in which the number of dividing cells equals the number of dying cells. This occurs secondary to nutrient depletion or accumulation of toxic byproducts. Finally, the death phase is characterized by a decline in the number of viable bacteria.

In the healthy state, it is normal to find a permanent population of bacteria and/or fungi inhabiting various body surfaces. The types of organisms that make up this normal flora vary from one body site to another. This flora has two roles in the maintenance of health—a host defense mechanism and a nutritional function of vitamin production. In the immunocompromised patient these organisms can become pathogenic if growth occurs outside of their normal habitat.

Host defense against infection consists of nonspecific mechanisms and specific natural or acquired immunity. Nonspecific defense mechanisms include barriers such as skin and mucus membranes. These barriers may also produce protective substances such as fatty acids from sebaceous glands, hydrolytic enzymes in saliva, gastric acids and intestinal enzymes. The inflammatory response, characterized by swelling, erythema, pain and warmth, is also a nonspecific protective mechanism. This reaction is produced by polymorphonuclear leukocytes and macrophages in response to local tissue reaction to foreign body and the production of chemical mediators. Specific immunity can be passively or actively acquired. Passive immunization occurs in the case of immunoglobulins passed through the placenta from mother to fetus, or in the case of administration of preformed antibodies. The protection offered by passive immunity is immediately available, however it is short lived. Active immunization occurs after exposure to the pathogen either with subclinical or overt illness or with vaccination. This response is mediated by T cells and specific immunoglobulins and has slower onset but longer duration.
Clinical Microbiology

Gram-Positive Cocci

The gram-positive cocci include Staphylococcal and Streptococcal species that are differentiated by grouping into grape-like clusters, chains, or pairs. Of the Staphylococcal species—S. aureus, S. epidermidis, and S. saprophyticus—S. aureus is the primary pathogen. This organism causes clinical disease by local suppurative inflammation or the production and release of toxins. Toxic shock syndrome is a complex of symptoms caused by a staph produced toxin that has been seen in association with nasal packing and tampon use. It is characterized by fever, hypotension, skin desquamation, shock and, potentially, death. In the head and neck region S. aureus may be associated with sinusitis, tonsillitis, otitis externa or media, tracheitis, and cellulitis. Up to 80% of the S. aureus isolates in the U.S. are resistant to penicillin, primarily due to bacterial production of beta lactamase. There are six medically important Streptococcal species of which three—S. viridans, S. pyogenes, and S. pneumoniae—may be involved in head and neck infections. S. viridans is a normal member of oral flora and may enter the bloodstream after dental procedures. This bacteremia may then lead to seeding of previously damaged or abnormal heart valves, thereby causing infective endocarditis. S. pyogenes, or group A beta-hemolytic strep, is a common cause of bacterial pharyngitis. It is also commonly found on human skin and can cause cellulitis, impetigo or necrotizing fasciitis after skin disruption. The pathogenicity of this organism is related to potential sequelae of infection in addition to the primary infection. Rheumatic fever, characterized by fever, migrating polyarthritis and carditis, has developed after strep pharyngitis. This occurs secondary to immunologic cross reactivity between strep antigens and proteins in joint and heart tissue, leading to an autoimmune attack on these systems. Acute glomerulonephritis may occur after a strep cellultis. Features of this disease include edema, hypertension and hematuria. The pathogenic mechanism is immune response to strep antigen-antibody complexes that are deposited along the glomerular basement membrane. Both of these sequelae may be prevented with early diagnosis and treatment of the primary strep infection. S. pneumoniae is a prominent agent in bacterial otitis media, sinusitis, bronchitis and meningitis. Pneumococci are isolated from the middle ear in 30-40% of acute otitis media in children and from 25-36% of acute sinusitis in all age groups. It is the most common pathogen in community acquired bacterial pneumonia and causes 15% of cases of meningitis in children and 30-50% in adults. Some strains are highly susceptible to penicillin therapy but increasing resistance has been seen recently.

Gram-Negative Cocci

The gram-negative cocci are the Neisseria species, meningitidis and gonorrhoeae, and Moraxella. N. meningitidis is the most common cause of epidemics of bacterial meningitis. This is likely related to airborne transmission, which leads to colonization of the nasal mucosa and a high carrier rate in close living quarters. The symptoms of meningitis are fever, headache, stiff neck, lethargy or mental status changes. Meningococcemia is caused by dissemination of the bacteria in the bloodstream. A life-threatening form of this bacteremia is the Waterhouse-Frederichsen syndrome that is characterized by high fever, shock, purpura, DIC and adrenal insufficiency. M. catarrhalis, formerly known as Branhamella catarrhalis, is a gram-negative coccobacillus that is part of normal nasopharyngeal flora. It is a common pathogen in otitis, mastoiditis, sinusitis, bronchitis and pneumonia. Eighty to ninety percent or more of isolates produce beta lactamase and are penicillin resistant.

Gram-Positive Bacilli

The gram-positive rods can be divided into spore forming and non-spore forming organisms. The spore formers are Bacillus and Clostridium species. Head and neck manifestations caused by these organisms include the grimace, trismus and potential respiratory failure caused by C. tetani infection. Botulism, caused by C. botulinum, is characterized by descending weakness and paralysis. Early signs include diplopia and dysphagia, which may progress to respiratory muscle failure. C. perfringens causes gas gangrene that may progress from any contaminated wound site. The non-spore formers are Corynebacterium, Listeria, Actinomycyes, and Nocardia. C. diptheriae is a rare pathogen in the U.S. due to widespread vaccination with diphtheria toxoid. However, because of the potential morbidity of the illness, it is important to recognize and treat this disease early in its course. Nonspecific signs include fever, pharyngitis, and cervical lymphadenopathy. The pathognomonic sign is the formation of a thick, gray, adherent membrane over the tonsils and oropharynx. Potential sequelae include airway obstruction, recurrent laryngeal nerve palsy, and myocarditis. Treatment is immediate administration of diphtheria

Gram-Negative Bacilli

The gram-negative bacilli include the Pasteurella species. P. multocida is the most common cause of infections in the head and neck region. It is a common pathogen in tularemia. P. pneumotropica is a rare cause of endocarditis. Bacteremia may be prevented with early diagnosis and treatment of the primary strep infection. P. carini is a lung pathogen that causes AIDS. P. spirochaetum is a rare cause of meningitis. P. pseudotuberculosis is a rare cause of meningitis. P. phlei is a rare cause of meningitis. P. variutans is a rare cause of meningitis.
antitoxin followed by appropriate antibiotic therapy. Listeria is a cause of meningitis and sepsis in neonates and immunocompromised hosts. Actinomyces and Nocardia are gram-positive filamentous rods. Actinomyces is part of the normal oral cavity flora. Actinomycosis involves the face and neck in about 50% of infections. It is characterized by a hard, tender swelling that progresses to a collection of pus and sulfur granules with draining sinus tracts. Nocardia is found in the environment and can be differentiated from Actinomyces by the lack of production of sulfur granules. It is a very rare cause of otitis, mastoiditis or sinusitis. Dissemination with CNS involvement may lead to brain abscess formation.

Gram-Negative Bacilli

The gram-negative rods are a large group of bacteria, many of which are part of the normal flora in the intestinal tract. The Enterobacteriaceae is a large group of facultative anaerobes found primarily in the colon, many of these organisms cause intestinal or urinary tract infections. However, Klebsiella, Enterobacter, Proteus and Serratia are associated with nosocomial otitis, sinusitis, and pneumonia. Because they are associated with hospital-acquired infection, resistance patterns are highly variable and treatment is best determined by sensitivity testing. K. rhinoscleromatis is the causative organism in a unique infection characterized by scleroma formation in the upper and lower respiratory mucosa. The disease progresses through three distinct phases, the catarrhal, granulomatous, and cicatricial stages. Signs and symptoms of this illness include fetid nasal drainage, mucosal crusting, granuloma formation and eventual scarring with the development of strictures. Treatment includes combination of antibiotic therapy and surgical debridement. Other important facultative anaerobes that cause upper respiratory tract infection include Haemophilus, Bordetella and Legionella. H. influenzae has six serotypes, of which type b is primarily responsible for uveitis, epiglottitis, meningitis and sepsis. The other serotypes are more commonly associated with otitis, conjunctivitis, sinusitis, or pneumonia. The Hib vaccine, given to children between the ages of 2 and 15 months, has greatly reduced the incidence of severe Haemophilus infections in the pediatric population. From 10-30% of both nontypeable and type b H. influenzae produce beta lactamase and are penicillin resistant. Legionella is a cause of both community acquired and nosocomial atypical pneumonia. Epidemics of legionellosis are typically associated with contaminated environmental water sources. Many of these isolates are also beta lactamase producers. B. pertussis causes whooping cough, an acute tracheobronchitis characterized by paroxysmal coughing spells. Immunization with killed B. pertussis bacteria has reduced the incidence of disease in the U.S. Antibiotic therapy may decrease sequelae of the infection but does not alter disease course due to the preexistent damage caused by bacterial toxins. Zoonotic facultative anaerobic gram-negative rods that may present with infection in the head and neck region include Yersinia, Francisella, and Pasturella. Y. pestis causes the plague, an illness which has been seen in the southwestern U.S., and is associated with flea bites. Fevers, arthralgias, myalgias, and prostration characterize the disease. Head and neck manifestations may include cervical buboes—tender, enlarged, matted lymph nodes. F. tularensis is the cause of tularemia, which may present with sore throat, exudative tonsillipharyngitis, and cervical or occipital lymphadenopathy. Deep neck space abscesses may form from this adenitis. Infection with P. multocida is most often associated with cat or dog bites, which frequently occur on the face. Illness is typified by a rapidly progressive cellulitis spreading from the site of inoculation.

Pseudomonas is a strictly aerobic gram negative rod. P. aeruginosa is primarily an opportunistic pathogen that causes infections in seriously ill, immunocompromised people. It is associated with 10-20% of nosocomial infections. In spite of this fact, many head and neck infections caused by Pseudomonas are community acquired. For example, simple external otitis is caused by P. aeruginosa in 49% of cases and it is a common causative agent in chronic otitis media with otorrhea in children. Malignant external otitis is a potentially morbid infection that occurs in the external auditory canal of elderly diabetic patients. While this infection may be polymicrobial, P. aeruginosa can nearly always be isolated from the ear fluid. Sinusitis caused by Pseudomonas has been seen in intubated ICU patients and AIDS patients. One to five percent of cases of chronic sinusitis are caused by this organism and it is a well recognized pathogen in cystic fibrosis patients. Treatment of nosocomial Pseudomonas infections should be directed by sensitivity testing.

Anaerobes

Anaerobic bacteria of importance in head and neck infection are found as part of the normal flora of the oral cavity and include gram-positive cocci and bacilli as well as gram-negative bacilli. Representative species include Bacteroides, Fusobacterium, Peptostreptococcus, Actinomyces, and Prevotella. These organisms are prevalent in such ENT infections as acute and chronic otitis media or tonsillitis, up to 67% of
chronic sinusitis, all odontogenic infections and many deep neck space infections. They are also frequently associated with wound infection following head and neck surgery. The majority of anaerobic infections are polymicrobial and proper therapy is dictated by susceptibility testing.

**Spirochetes**

The spirochetes—*Treponema* and *Borrelia*—are identified using darkfield microscopy or silver staining. *T. pallidum* is the causative agent of syphilis. Head and neck manifestations occur in the secondary or tertiary stages of disease and may include any of a multitude of signs and symptoms. Mucosal involvement may cause oral ulcers or nasal septal ulcers that may progress to saddle nose deformity, rhinitis, laryngitis or pharyngitis. Cutaneous involvement includes rashes, alopecia or loss of eyelashes. Bony involvement with granulomatous infiltration can effect the mandible or maxilla, or present in the form of osteomyelitis of the temporal bone. Cranial nerve involvement may lead to hoarseness and dysphagia and infection of the labyrinth may lead to sensorineural hearing loss or vertigo. *B. burgdorferi* causes Lyme disease and is transmitted by tick bite. The disease has 3 stages and begins with erythema chronicum migrans and nonspecific flu-like symptoms. The second stage occurs weeks to months later and demonstrates neurologic and cardiac involvement. Stage three occurs after a latent phase and involves progressive large joint arthritis and central nervous system deterioration.

**Mycobacteria**

Mycobacteria are aerobic acid-fast staining rods. The major pathogens include *M. tuberculosis*, *M. leprae*, and the atypical mycobacteria *M. avium-intracellulare*. One third of the world’s population is infected by *M. tuberculosis*, and it is responsible for approximately three million deaths annually. Infection is classified as pulmonary (82%) and extrapulmonary (18%) based upon organ involvement. Primary pulmonary tuberculosis causes a pneumonitis in the middle and lower lobes and hilar adenopathy. Nodules or cavities in the lung apices characterize reactivated pulmonary disease. Associated systemic symptoms include fever, fatigue, weight loss and night sweats. Extrapulmonary disease can effect nearly every organ system in the body and occurs more frequently in immunocompromised hosts. The most common site of extrapulmonary involvement is the cervical and retroperitoneal lymph nodes. Scrofula may eventually lead to sinus tract and fistula formation with chronic drainage. Laryngeal involvement may cause cough, dyspnea, dysphagia, stridor or hemoptysis. Examination reveals mucosal hypertrophy, fibrosis, nodules or ulcers anywhere on the glottis or supraglottis. A painless nonhealing ulcer on the gingiva, tongue, palate or floor of mouth is typical of oral tuberculosis. Painless chronic otorrhrea that is unresponsive to antibiotic therapy characterizes aural TB. The tympanic membrane becomes thickened initially, then this is followed by tubercle formation and multiple coalescent perforations. Pale, polypoid granulation tissue forms and extends into the external auditory canal. If untreated, this disease may progress to hearing loss, facial nerve palsy or intracranial infection. Nasal, pharyngeal or salivary gland involvement are rare manifestations of the disease. Treatment of TB involves multi-drug therapy for prolonged periods of time. *M. leprae* is the causative agent in leprosy. Head and neck manifestations include thickening of the facial skin leading to leonine facies and loss of the lateral eyebrow. Nasal symptoms include chronic congestion, rhinitis and epistaxis with eventual progression to septal erosion and saddle nose deformity. The eyes are involved in 50-90% of cases and may eventually cause blindness. *M. avium-intracellulare* (MAI) complex is an atypical mycobacterium that causes disease in immunocompromised hosts. It produces a pulmonary illness that is essentially identical to pulmonary TB. It also may cause extrapulmonary involvement leading to cervical lymphadenitis, otomastoiditis, or cutaneous lesions.

**Antibiotic Therapy**

Antibiotics are effective because of their property of selective toxicity. They are able to attack bacterial cells without having an adverse effect on host cells. This property is made possible by biochemical differences between the cells of the host and the infecting organism. These drugs can be classified as bacteriostatic or bactericidal. Bacteriostatic antibiotics arrest the growth cycle of bacteria, thereby limiting spread of infection and allowing the host immune system to eliminate remaining organisms. In contrast, bactericidal drugs kill all infecting pathogens. Antibiotics can be further classified by their chemical structure, activity against specific organisms, or mechanism of action. The following paragraphs will discuss antimicrobial agents along the categories of mechanism of action.
**Inhibitors of Cell Wall Synthesis**

The peptidoglycan cell wall is a structure that is unique to bacterial cells, giving these antibiotics their selective toxicity. Because they effect a step of cell synthesis and growth, these drugs are primarily effective against actively dividing cells.

**Beta Lactams**

The beta lactam antibiotics include penicillins, cephalosporins, carbapenems and monobactams. These drugs bind to penicillin binding proteins (PBPs) in the bacterial cell wall and inhibit cross link formation between peptidoglycan chains. The result is disruption of cell wall integrity, making the cell osmotically unstable and susceptible to lysis. Alternatively, drug binding to PBPs may activate autolysins and cause cell wall disruption.

Penicillins are derived from the fungus Penicillium, and modifications made upon the parent compound can alter the drug’s spectrum of action. Penicillins reach therapeutic concentrations in serum, bile, tissues, joint and pleural fluids. Inflammation of the meninges increases the penetration of penicillin into the CSF, but concentration still only reaches 5-10% of serum. Drug excretion occurs through the kidneys and dose should be adjusted as indicated. Adverse reactions include hypersensitivity, nephritis, neurotoxicity, and platelet dysfunction. The natural penicillins—Penicillin G and V—remain the drugs of choice for infections caused by S. pyogenes, Listeria, Enterococcus (except endocarditis), Actinomycetes, Peptococcus, Peptostreptococcus, N. meningitidis, Treponema, Borrelia, and Clostridium. Increasing resistance of S. pneumoniae, 25% or more of isolates, precludes the use of penicillin for empiric treatment of infections caused by this organism. The penicillinase-resistant drugs—methicillin, nafcillin, oxacillin, dicloxacillin—are primarily used for staphylococcal infections. This class of antibiotics is useful against nearly all S. aureus, except of course MRSA, and S. epidermidis. They are less active against many other bacteria than the natural penicillins and are essentially restricted to use in beta lactamase producing staph infections. The aminopenicillins—amoxicillin and ampicillin—are effective against E. coli, Proteus, Salmonella and Shigella. They are generally less active in gram positive and spirochete infections. However, their spectrum of activity can be extended to include these organisms with the addition of a beta lactamase inhibitor—clavulanate and sulbactum. Piperacillin, ticarcillin and carbenicillin are the extended spectrum penicillins. They have the highest level of activity against Enterobacteriaceae and are also effective against Pseudomonas. Clavulanate or tazobactam can be added to these agents to expand their activity.

Cephalosporins are another class of beta lactam antibiotics that are structurally and functionally similar to the penicillins. These drugs achieve therapeutic concentrations in the urine, joint and periocardial fluids, and bile. They are capable of crossing the placenta and the third and fourth generations drugs penetrate the CSF. Most of these drugs are excreted unmetabolized in the urine. All cephalosporins can cause an allergic reaction. Cefamandole and cefoperazone have a disulfiram-like effect if taken with alcohol and have been associated with bleeding problems due to an anti-Vitamin K effect. The first generation cephalosporins—cefazolin, cephalothin, and cephalexin—are generally effective for Streptococcus and have some activity against Staphylococcus, E. coli, and Klebsiella. Commonly they are used for prophylactic coverage of gram-positive skin flora. The second generation cephalosporins—cefuroxime, cefprozil, cefaclor, loracarbef, cefoxitin, and cefotetan—have less gram-positive but more gram-negative activity that the first generation drugs. They are generally active against E. coli, Klebsiella, Proteus, Haemophilus, and Moraxella. Cefoxitin and cefotetan are particularly effective for Bacteroides infection. Cefprozil has the most anti-strep activity while loracarbef is more stable in the presence of beta lactamase. Cefotaxime, cefixime, ceftriaxone, and ceftazidime are third generation cephalosporins. They have improved gram negative coverage while retaining action against susceptible strep and staph species. Cefotaxime and ceftriaxone are considered first line therapy for community acquired meningitis and pneumonia with excellent coverage of S. pneumoniae, H. influenzae, and N. meningitidis. Ceftazidime is used for hospital acquired meningitis and has the best Pseudomonas coverage. The fourth generation cephalosporins include cefpirome, cefepime, cefoselis, cefclidin, cefozopram, and cefluprenam, of which cefpirome and cefepime are available for clinical use. These drugs have the advantage of increased gram-positive cocci activity, especially against S. viridans and penicillin resistant pneumococcus. They are also more effective against Enterobacteriaceae, particularly beta lactamase producing Pseudomonas and Enterobacter.

Aztreonam is the only monobactam used in clinical practice. It is also a beta lactam and binds to PBPs to effect cell wall synthesis. Its role is primarily in gram-negative infections, with good activity against Enterobacteriaceae and Pseudomonas. This drug is a safe and effective option for gram-negative coverage.
in penicillin allergic patients. It may be associated with phlebitis, rash or elevated liver function tests.

Carbapenems include imipenem and meropenem. These drugs rapidly lyse cells after binding to PBPs. Due to their high level of beta lactamase stability, they have a very broad spectrum of activity. Gram-positive or negative, aerobic or anaerobic infections are generally covered by these antibiotics. Carbapenems have the additional feature of variable activity against MRSA. Adverse effects include nausea, vomiting, diarrhea, eosinophilia, neutropenia and lowering of the seizure threshold. Imipenem is metabolized in the kidney to potentially nephrotoxic byproducts. This reaction can be prevented by combining imipenem with cilastin.

Vancomycin
Vancomycin is an antibiotic that works by inhibiting the synthesis of cell wall phospholipids in addition to interfering with peptidoglycan cross-linking. It readily distributes into ascitic, pericardial, pleural, and joint fluids. Variable CSF penetration occurs with inflammation of the meninges. Vancomycin is primarily effective against gram-positive organisms. It is especially useful for infections caused by MRSA or penicillin resistant pneumococcus. Drug elimination occurs through the kidneys and its dosing schedule is dictated by the patient's creatinine clearance. Infusion related adverse reactions include fever, chills, phlebitis, “red man syndrome,” and shock. Vancomycin has been associated with ototoxicity and nephrotoxicity, primarily when the drug is given in combination with an aminoglycoside.

Protein Synthesis Inhibitors
This group of antibiotics includes the tetracyclines, aminoglycosides, macrolides, chloramphenicol and clindamycin. They work by preferentially binding to the bacterial ribosome, which differs from the human ribosome in size. The bacterial ribosome is 70S with 30S and 50S subunits, while the human ribosome is 80S with 40S and 60S subunits. This ribosomal binding prevents subsequent protein translation.

Tetracyclines
The tetracyclines—demeclocycline, doxycycline, minocycline and tetracycline—are bacteriostatic drugs that were isolated from Streptomyces aureofaciens. They have in common a basic four ring structure and work by reversibly binding to the bacteria 30S ribosomal subunit. Tetracyclines penetrate most tissues and reach therapeutic levels in sinus mucosa, saliva, and tears. These drugs have a very broad spectrum of activity and are drugs of choice for Chlamydia, Mycoplasma or Borrelia infections. Additionally, they have good activity against Nocardia species. Because of their broad spectrum of coverage they are a reasonable alternative for many ENT infections, although increasing bacterial resistance somewhat limits their use. Drug concentration and metabolism occurs in the liver and metabolites are excreted in the bile, reabsorbed and eliminated in the urine. Doxycycline is excreted in the feces and is safe for use in renal failure patients. Adverse reactions include gastrointestinal distress, hepatotoxicity, photosensitivity, vertigo, pseudotumor cerebri and deposition in calcified tissues leading to hypoplastic discolored teeth and stunted growth. The use of tetracyclines is contraindicated during pregnancy or breast feeding and for children under 8 years of age.

Aminoglycosides
The aminoglycosides are a bactericidal group of drugs derived from Streptomyces and Micromonospora. Their mechanism of action is irreversible binding to the 30S ribosomal subunit. These antibiotics are actively transported into the bacterial cell by an oxygen requiring transport system. This characteristic makes anaerobes inherently resistant to aminoglycosides. They are primarily used for aerobic gram-negative infections but also have activity against gram-positive aerobes and the facultative bacteria. Tissue and body fluid penetration is variable. Even with meningeal inflammation, CSF penetration is inadequate. Aminoglycosides concentrate in the perilymph, not because of increased penetration, but because of a slower elimination process. Drug elimination occurs in the kidney and essentially correlates with the glomerular filtration rate. Toxic effects of these drugs are dose related and plasma levels must be monitored closely. Nephrotoxicity, ototoxicity and neurotoxicity have all been associated with aminoglycoside administration. Specific uses for the aminoglycosides in ENT include malignant otitis externa, chronic otitis media with otorrhea, and chronic sinusitis in cystic fibrosis patients. Malignant otitis externa is aggressively managed with both topical and systemic aminoglycosides, usually in combination with an extended spectrum penicillin or fluoroquinolone. Ototopical gentamycin is effective for chronic otitis
and otorrhea when the infecting agent is frequently Pseudomonas. Patients with CF will frequently have chronic sinusitis secondary to thickened mucus and incomplete clearance by the mucociliary transport system in the sinonasal mucosa. Routine medical management commonly fails to eradicate infection due to poor drug penetration or the presence of anaerobes or Pseudomonas. Aggressive treatment with parenteral aminoglycosides plus sinus irrigation with aminoglycoside solution may be effective. Additionally, gentamycin or streptomycin, administered transtympanically, can be used for incapacitating Menieres disease.

Macrolides

The macrolides are a large family of antibiotics characterized by a macrocyclic lactone structure. Erythromycin, clarithromycin, and azithromycin are the three most commonly used members of this group. They exert their antibacterial effect by irreversibly binding to the 50S ribosomal subunit. Erythromycin exhibits nearly the same spectrum of activity as penicillin and is very useful in penicillin allergic patients. It remains the drug of choice for pharyngitis due to Chlamydia or Mycoplasma, C. diptheriae infection and carrier state and is highly effective for pertussis. Clarithromycin is similar to erythromycin and additionally demonstrates increased activity against Bacteroides and atypical Mycobacteria. Azithromycin is less effective for staph and strep infections but has increased activity against Hemophilus, Moraxella, Pasteurella and Mycoplasma. All three of these drugs are viable alternatives for the common ENT infections of otitis, sinusitis, and pharyngitis in the penicillin allergic patient. These drugs do not penetrate into CSF but achieve good concentrations in oropharyngeal and respiratory secretions. Concentration within macrophages and neutrophils also occurs. Erythromycin and Clarithromycin are metabolized in the liver and may interfere with other drug metabolism that utilizes the cytochrome P-450 system. Excretion occurs through both the GI and renal systems. Adverse effects include ototoxicity, hepatotoxicity with cholestatic jaundice, and GI distress. Hepatic dysfunction is a contraindication to their use.

Chloramphenicol

Chloramphenicol was originally isolated from Streptomyces and acts by reversibly binding to the 50S ribosomal subunit. It has a broad spectrum of activity against both gram-positive and gram-negative bacteria and is highly effective against anaerobes. It is most commonly bacteriostatic but is bactericidal against H. influenzae, pneumococcus, and N. meningitidis. Indications for its use include life-threatening infections with the above mentioned bacteria and severe anaerobic infections such as brain or deep neck space abscesses. It has good tissue penetration secondary to its lipophilic structure and readily enters the CSF. Chloramphenicol is metabolized in the liver and excreted in the kidney. It has an inhibitory effect on the P-450 enzyme system and can increase serum levels of warfarin and phenytoin. Although it is a highly effective antimicrobial, its use is restricted by its severe toxicity. It has been shown to cause a dose-related reversible anemia, hemolytic anemia in patients with G6PD deficiency and idiosyncratic dose-independent aplastic anemia. Gray baby syndrome occurs when used in neonates and is caused by drug accumulation leading to cyanosis, cardiovascular collapse and eventual death.

Clindamycin

Clindamycin is a semisynthetic antibiotic that binds to bacterial 50S ribosomal subunit. It is highly effective for the treatment of gram-positive and negative anaerobes, has good gram-positive aerobe activity, but is not effective against gram-negative aerobes. It is very useful for polymicrobial infections in the head and neck caused by members of the oropharyngeal flora. Clindamycin is indicated in the treatment of chronic otitis, mastoiditis, or sinusitis, odontogenic infections, head and neck abscesses, and post-operative wound infections. It achieves good tissue concentrations and penetrates saliva, sputum, pleural fluid and bone, but it does not enter the CSF. It is metabolized in the liver, enters the feces, undergoes reabsorption and is excreted in urine. Adverse effects include allergic rashes, reversible neutropenia or thrombocytopenia and the rare occurrence of erythema multiforme and anaphylaxis. Pseudomembranous colitis, caused by overgrowth of C. difficile and toxin production, is associated with use of clindamycin and is treated with oral metronidazole or vancomycin.

Inhibitors of Metabolism

The sulfa drugs and trimethoprim exert their antimicrobial effect by interfering with folate metabolism. Purine and pyrimidine synthesis requires folic acid coenzymes and interference with their
production inhibits cell growth and replication. The combination of the two drugs is synergistic by inhibiting two sequential steps in this enzymatic process.

**Sulfonamides**

Sulfonamides were originally identified from the dye prontosil, which is metabolized in the body to the antibacterial compound sulfanilamide. These drugs are structurally similar to p-Aminobenzoic acid which, in the bacterial cell, serves as a precursor to folic acid after conversion by dihydropterotate synthetase. The sulfas are bacteriostatic and are effective for Enterobacter, Chlamydia, Nocardia, Pneumocystis, and Toxoplasma when used in combination with pyrimethamine. These drugs achieve good tissue levels, penetrate the CSF fairly well, and cross the placenta. They are metabolized to an inactive product in the liver and excreted in the kidney. Adverse effects include rashes, angioedema, Stevens-Johnson syndrome, hemolytic anemia, kernicturus and possible precipitation of crystals of the inactive metabolite in the kidney causing nephrotoxicity. Sulfas should be avoided in pregnancy and in children under 2 months of age.

**Trimethoprim**

Trimethoprim blocks the conversion of folic acid to tetrahydrofolic acid by inhibiting the enzyme dihydrofolate reductase. This drug has a strong affinity for the bacterial reductase enzyme and is a 20-50 times more potent enzyme inhibitor than the sulfonamides. Its antibacterial spectrum, absorption and excretion are all similar to the sulfas. Adverse effects include folate deficiency anemia, leukopenia or granulocytopenia.

**Co-trimoxazole**

The sulfonamide sulfamethoxazole is used primarily in combination with trimethoprim forming a compound, co-trimoxazole or TMP/SMX. This drug has greater activity that either drug as a single agent. The combination is very effective against many agents causing infections in the head and neck. It is useful for acute and chronic otitis media, acute sinusitis, and as an alternative for pneumococcal, Neissera or Haemophilus meningitis in the penicillin allergic patient. Although the mechanism of action is unclear, TMP-SMX is effective against disease progression in Wegener’s granulomatosis.

**Inhibitors of Nucleic Acid Function/Synthesis**

**Fluoroquinolones**

The fluoroquinolones are synthetic antibiotics made by the addition of fluorine molecules onto the quinolone ring of nalidixic acid. This group includes ofloxacin, ciprofloxacin and levofloxacin, as well as the newer agents, gemifloxacin and grepafloxacin. They are bactericidal and exert their effect by binding to bacterial DNA gyrase, thereby interfering with DNA replication. The fluoroquinolones are very effective against aerobic gram-negative rods and are useful in the treatment of Pseudomonas infections. In addition they can be used for mycobacterial infections and for the organisms causing atypical pneumonia—Mycoplasma, Chlamydia and Legionella. These drugs have excellent tissue penetration, including cartilage and bone, and are concentrated in the mucosa of the middle ear and sinuses. Their anti-pseudomonal activity makes them highly useful for malignant external otitis, chronic otitis media and auricular perichondriits. They can also be employed for the treatment of sinusitis and tonsillopharyngitis. Fluoroquinolones are either metabolized in the liver and excreted in the feces or urine or are eliminated unchanged by the kidneys. Adverse reactions include nausea, dizziness, phototoxicity and crystalluria with nephrotoxicity. These drugs should not be used in pregnant women or nursing mothers. Children under 18 should be given the drug with caution as articular cartilage erosion and arthropathy may develop.

**Antimycobacterial Agents**

Treating and eradicating mycobacterial infections can be a therapeutic challenge. Therapy must address the fact that there are typically two distinct groups of tubercle bacilli infecting the patient. The first is a group of rapidly dividing, actively growing organisms, while the second is a more latent population that grows slowly, multiplying only episodically. The first group will be readily affected by antimycobacterial drugs. However, within this group are drug resistant organisms, which necessitates multi-drug therapy so as not to select for resistant pathogens. The slow growing characteristic of the second group dictates prolonged drug therapy to prevent resurgence of infection after a latent phase. For tuberculosis, first line
therapy usually consists of a 3 or 4 drug regimen for a time period from 6 months to 2 years. Second line drugs are reserved for infections with known multi-drug resistant bacilli or infections unresponsive to first line therapy. Second line agents include aminosalicylic acid, cycloserine, ethionamide, capreomycin, ciprofloxacin, and others. New drugs that may prove to be useful against the mycobacteria include minocycline, clarithromycin, sparfloxacin, and grepafloxacin.

**Isoniazide**

Isoniazide (INH) is a synthetic analog of pyridoxine and is the most potent anti-tubercular drug. Its mechanism of action is inhibition of the enzyme which forms the outer mycolic acid layer of the cell membrane. This drug has a bactericidal effect against actively dividing cells and a bacteriostatic effect on the latent population. It should never be used as a single agent to prevent emergence of resistant organisms. INH achieves good tissue levels and penetrates the CSF. It is metabolized to inactive products in the liver and is excreted in the urine, saliva, and sputum. Potential adverse effects include hypersensitivity, peripheral neuropathy and hepatotoxicity.

**Rifampin**

Rifampin is a semisynthetic compound derived from Streptomyces. Its antibacterial effect is due to interaction with RNA polymerase, thereby interfering with RNA transcription. It is a bactericidal agent with activity against many Mycobacteria species as well as N. meningitidis and H. influenzae. It is widely distributed in tissues and achieves therapeutic levels in the CSF. It is taken up and partially metabolized in the liver, excreted in bile and enters the enterohepatic cycle. Metabolites and parent compound enter the feces, urine and tears, imparting an orange-red color that patients should be told to expect. Adverse effects include rash, fever, GI upset, and hepatotoxicity. Rifampin can lower serum levels of some medications by inducing the P-450 system in the liver.

**Pyrazinamide**

Pyrazinamide is a synthetic antimycobacterial that is hydrolyzed to pyrazinoic acid, the active form of the drug. It is bactericidal to actively dividing cells by an unclear mechanism. It penetrates most tissues, including CSF, very well. Its activity is essentially limited to M. tuberculosis. Adverse effects include GI upset, hepatotoxicity, and hyperuricemia with the rare precipitation of a gouty attack.

**Ethambutol**

Ethambutol is a synthetic drug that has antimycobacterial action by inhibiting cell wall synthesis and maintenance. It distributes throughout the body and into the CSF. It is partially metabolized and both parent drug and metabolites are excreted in the urine. The most important potential adverse effect is optic neuritis and patients should have monthly visual acuity exams while taking this drug. This effect is dose-related and reversible by discontinuing therapy.

**Streptomycin**

This aminoglycoside has both anti-tubercule and antibacterial effects. It inhibits protein synthesis by binding to 30S ribosomal subunits. It is usually given intramuscularly and achieves therapeutic concentrations in synovial, pleural, pericardial and ascitic fluids, but does not penetrate into CSF. It is excreted, unchanged, by the kidneys. Adverse effects include hypersensitivity, paraesthesias, auditory or vestibular dysfunction and nephrotoxicity.

**Dapsone**

Dapsone is a synthetic compound that is structurally related to the sulfonamides. Its mechanism of action is that of a PABA antagonist. It is weakly bactericidal or bacteriostatic against M. leprae, and is also used in the treatment of Pneumocystis pneumonia and brown recluse spider bites. It is widely distributed in the body, undergoes acetylation in the liver, and is excreted in the urine. Adverse effects include erythema nodosum leprosum, peripheral neuropathy, methemoglobinemia, and hemolytic anemia, especially in the presence of G6PD deficiency.

**Clofazimine**

Clofazimine is a synthetic phenazine dye that is a weak bactericidal agent used against M. leprae and MAI. It works by binding to DNA and inhibiting replication and transcription. It also produces oxygen
free radicals that are cytotoxic to bacteria. It is widely distributed but does not penetrate the CSF. It is partially metabolized and excreted in the bile. Side effects include GI distress and reddish/purple discoloration of the skin and body fluids.

**Antimicrobial Use for Perioperative Prophylaxis**

The second most common hospital acquired infection is post-operative wound infection. Each year, approximately .04% of patients undergoing surgical therapy will develop a wound infection. The estimated cost of these infections approaches $5 billion annually. Contributing to this expense are factors such as necessity of prolonged antibiotic treatment course, utilization of excess hospital supplies and labor for wound care, and prolonged hospital stay. In a study evaluating the cost effectiveness of prophylactic antibiotics in neck dissection, a clean head and neck surgery, Blair et al. found no statistically significant difference in the occurrence of wound infection between the treatment and nontreatment groups. However, they did demonstrate that those patients who developed wound infection had, on average, a hospital stay 15 days longer than those patients without infection. The average additional cost of this prolonged stay was $36,000/patient. In contrast, the cost of perioperative antibiotic prophylaxis for 100 patients using clindamycin or cefoperozone was $14,600 and $49,600 respectively.

Prophylactic antibiotic therapy should not be employed randomly, but rather systematically, based on scientific evidence and logic. Clean wounds—Class I—are those in which strict sterile technique is utilized and no contamination occurs. These wounds have an infection rate of 1-5% and routine antibiotic prophylaxis is not indicated. Class II, or clean-contaminated wounds, are those in which surgical wounds are contaminated by entrance into the aerodigestive or genitourinary tracts with spillage of bacteria contaminated secretions. Generally, these wounds are characterized by an infection rate of 8-11% but increased length and/or complexity of procedure has been associated with a higher incidence of infection to between 28-87%. Contaminated wounds—Class III—have an infection rate of 15-17% and include traumatic wounds and those with gross spillage from the GI tract. Most head and neck surgeries involve Class I or II wounds, necessitating coverage of skin and oral flora for these cases. Skin flora consists primarily of gram-positive aerobic cocci, whereas the normal bacterial flora in the oral cavity is 90% anaerobes and 10% gram-positive aerobic cocci. The number of gram-negative aerobes is normally quite small but may be increased in patients who have been hospitalized or treated with XRT.

When choosing a prophylactic antibiotic, coverage of the above mentioned organisms should be of primary concern. Additionally, it is important to consider individual patient hypersensitivities, drug toxicities, and local patterns of bacterial resistance. It is generally accepted that the first dose of antibiotic should be administered within 2 hours before or 3 hours after surgery has begun. Optimally, the drug is given such that there are therapeutic blood levels when the wound becomes contaminated. Lengthy procedures may require more than one dose so that therapeutic drug levels are maintained. Duration of prophylaxis has been frequently studied and trials of 1 day versus 2,3, and 5 day treatments have been compared. Conclusions are all essentially the same. There appears to be no benefit to prolonged antibiotic therapy beyond the 24 hour period surrounding surgery.

There have been many clinical trials evaluating the efficacy of various antibiotic regimens. Examples of antibiotics shown to be effective in Class II head and neck wound prophylaxis include cefazolin alone or in combination with metronidazole, cefoperozone, clindamycin alone or in combination with gentamicin or amikacin, amoxicillin/clavulanate, ampicillin/sulbactam, and ticarcillin/clavulanate.. The use of topical perioperative antibiotics has also been studied. Both clindamycin and peroxide rinses have been shown to significantly reduce bacterial counts in the oral cavity. This effect is immediate but also persists for 4 hours after rinsing. In small clinical trials these antibiotics used alone or in combination with parenteral antibiotics have been shown to reduce post-operative wound infectious complications.

The efficacy of prophylactic antibiotic therapy has been proven by several clinical studies for use in clean-contaminated head and neck procedures, tonsillectomy, neurotologic or skull base surgery, and open mandible fractures. Alternatively, basic sinonasal procedures, otologic surgery and repair of midface or closed mandible fractures have not been shown to benefit from antibiotic prophylaxis. The use antibiotic therapy in these situations where prophylaxis is not indicated contributes to patient colonization with alternative pathogens, encourages development of bacterial resistance to antibiotics, and unnecessarily increases cost of hospital stay.
References


