Clostridium

There are four medically important species: *Clostridium tetani, Clostridium botulinum, Clostridium perfringens*, and *Clostridium difficile.* All clostridia are anaerobic, spore-forming, gram-positive rods

*Clostridium tetani*

Disease :*C. tetani* causes tetanus (lockjaw).

Transmission

Spores are widespread in soil. The portal of entry is usually a wound site, e.g., where a nail penetrates the foot, but the spores can also be introduced during "skin-popping," a technique used by drug addicts to inject drugs into the skin. Germination of spores is favored by necrotic tissue and poor blood supply in the wound. Neonatal tetanus, in which the organism enters through a contaminated umbilicus or circumcision wound, is a major problem in some developing countries.

Pathogenesis

Tetanus toxin (tetanospasmin) is an exotoxin produced by vegetative cells at the wound site. This polypeptide toxin is carried intra-axonally (retrograde) to the central nervous system, where it binds to ganglioside receptors and blocks release of inhibitory mediators (e.g., glycine) at spinal synapses. Tetanus toxin and botulinum toxin , are among the most toxic substances known. They are proteases that cleave the proteins involved in mediator release. Tetanus toxin has one antigenic type, unlike botulinum toxin, which has eight. There is therefore only one antigenic type of tetanus toxoid in the vaccine against tetanus.

Clinical Findings

Tetanus is characterized by strong muscle spasms (spastic paralysis, tetany). Specific clinical features include **lockjaw** (trismus) due to rigid contraction of the jaw muscles, which prevents the mouth from opening; a characteristic grimace known as **risus sardonicus;** and exaggerated reflexes. **Opisthotonos,** a pronounced arching of the back due to spasm of the strong extensor muscles of the back, is often seen. Respiratory failure ensues. A high mortality rate is associated with this disease. Note that in tetanus, **spastic paralysis** (strong muscle contractions) occurs, whereas in botulism, **flaccid paralysis** (weak or absent muscle contractions) occurs.

Laboratory Diagnosis

There is no microbiologic or serologic diagnosis. Organisms are rarely isolated from the wound site. *C. tetani* produces a **terminal spore,** i.e., a spore at the end of the rod. This gives the organism the characteristic appearance of a "tennis racket."

Treatment

Tetanus immune globulin is used to neutralize the toxin. The role of antibiotics is uncertain. If antibiotics are used, either metronidazole or penicillin G can be given. An adequate airway must be maintained and respiratory support given. Benzodiazepines, e.g., diazepam (Valium), should be given to prevent spasms.

Prevention

Tetanus is prevented by immunization with tetanus **toxoid** (formaldehyde-treated toxin) in childhood and every 10 years thereafter. Tetanus toxoid is usually given to children in combination with diphtheria toxoid and the acellular pertussis vaccine (DTaP). When trauma occurs, the wound should be cleaned and debrided and tetanus toxoid booster should be given. If the wound is grossly contaminated, tetanus immune globulin**,** as well as the toxoid booster, should be given and penicillin administered. Tetanus immune globulin (tetanus antitoxin) is made in humans to avoid serum sickness reactions that occur when antitoxin made in horses is used. The administration of both immune globulins and tetanus toxoid (at different sites in the body) is an example of passive-active immunity**.**

*Clostridium botulinum*

Disease

*C. botulinum* causes botulism.

Transmission

Spores, widespread in soil, contaminate vegetables and meats. When these foods are canned or vacuum-packed without adequate sterilization, spores survive and germinate in the anaerobic environment. Toxin is produced within the canned food and ingested preformed**.** The highest-risk foods are (1) alkaline vegetables such as green beans, peppers, and mushrooms and (2) smoked fish. The toxin is relatively heat-labile; it is inactivated by boiling for several minutes. Thus, disease can be prevented by sufficient cooking.

Pathogenesis

Botulinum toxin is absorbed from the gut and carried via the blood to peripheral nerve synapses, where it blocks release of acetylcholine. It is a protease that cleaves the proteins involved in acetylcholine release. The toxin is a polypeptide encoded by a lysogenic phage. Along with tetanus toxin, it is among the most toxic substances known. There are eight immunologic types of toxin; types A, B, and E are the most common in human illness. Botox is a commercial preparation of exotoxin A used to remove wrinkles on the face. Minute amounts of the toxin are effective in the treatment of certain spasmodic muscle disorders such as torticollis, "writer's cramp," and blepharospasm.

Clinical Findings

Descending weakness and paralysis, including diplopia, dysphagia, and respiratory muscle failure, are seen. No fever is present. Two special clinical forms occur: (1) wound botulism, in which spores contaminate a wound, germinate, and produce toxin at the site; and (2) infant botulism, in which the organisms grow in the gut and produce the toxin there. Ingestion of honey containing the organism is implicated in transmission of infant botulism. Affected infants develop weakness or paralysis and may need respiratory support but usually recover spontaneously. In the United States, infant botulism accounts for about half of the cases of botulism, and wound botulism is associated with drug abuse.

Laboratory Diagnosis

The organism is usually not cultured. Botulinum toxin is demonstrable in uneaten food and the patient's serum by mouse protection tests. Mice are inoculated with a sample of the clinical specimen and will die unless protected by antitoxin.

Treatment

Trivalent antitoxin (types A, B, and E) is given, along with respiratory support. The antitoxin is made in horses, and serum sickness occurs in about 15% of antiserum recipients.

Prevention

Proper sterilization of all canned and vacuum-packed foods is essential. Food must be adequately cooked to inactivate the toxin. Swollen cans must be discarded (clostridial proteolytic enzymes form gas, which swells cans).

*Clostridium perfringens*

*C. perfringens* causes two distinct diseases, gas gangrene and food poisoning, depending on the route of entry into the body.

Disease: Gas Gangrene

Gas gangrene (myonecrosis, necrotizing fasciitis) is one of the two diseases caused by *C. perfringens.* Gas gangrene is also caused by other histotoxic clostridia such as *Clostridium histolyticum, Clostridium septicum, Clostridium novyi,* and *Clostridium sordellii*. (*C. sordellii* also causes toxic shock syndrome in postpartum and postabortion woman.)

Transmission

Spores are located in the soil; vegetative cells are members of the **normal flora of the colon and vagina.** Gas gangrene is associated with war wounds, automobile and motorcycle accidents, and septic abortions (endometritis).

Pathogenesis

Organisms grow in traumatized tissue (especially muscle) and produce a variety of toxins. The most important is **alpha toxin** (lecithinase), which damages cell membranes, including those of erythrocytes, resulting in hemolysis. Degradative enzymes produce gas in tissues.

Clinical Findings

Pain, edema, and cellulitis occur in the wound area. Crepitation indicates the presence of gas in tissues. Hemolysis and jaundice are common, as are blood-tinged exudates. Shock and death can ensue. Mortality rates are high.

Laboratory Diagnosis

Smears of tissue and exudate samples show large gram-positive rods. Spores are not usually seen because they are formed primarily under nutritionally deficient conditions. The organisms are cultured anaerobically and then identified by sugar fermentation reactions and organic acid production. *C. perfringens* colonies exhibit a double zone of hemolysis on blood agar. Egg yolk agar is used to demonstrate the presence of the lecithinase. Serologic tests are not useful.

Treatment

Penicillin G is the antibiotic of choice. Wounds should be debrided.

Prevention

Wounds should be cleansed and debrided. Penicillin may be given for prophylaxis. There is no vaccine.

Disease: Food Poisoning

**Food poisoning** is the second disease caused by *C. perfringens.*

Transmission

Spores are located in **soil** and can contaminate **food.** The heat-resistant spores survive cooking and germinate. The organisms grow to large numbers in reheated foods, especially meat dishes.

Pathogenesis

*C. perfringens* is a member of the normal flora in the colon but not in the small bowel, where the enterotoxin acts to cause diarrhea. The mode of action of the enterotoxin is the same as that of the enterotoxin of *S. aureus;* i.e., it acts as a superantigen.

Clinical Findings

The disease has an 8- to 16-hour incubation period and is characterized by watery diarrhea with cramps and little vomiting. It resolves in 24 hours.

Laboratory Diagnosis

This is not usually done. There is no assay for the toxin. Large numbers of the organisms can be isolated from uneaten food.

Treatment

Symptomatic treatment is given; no antimicrobial drugs are administered.

Prevention

There are no specific preventive measures. Food should be adequately cooked to kill the organism.

*Clostridium difficile*

Disease

*C. difficile* causes antibiotic-associated pseudomembranous colitis. *C. difficile* is the most common nosocomial cause of diarrhea.

Transmission

The organism is carried in the **gastrointestinal tract** in approximately 3% of the general population and up to 30% of hospitalized patients. Most people are not colonized, which explains why most people who take antibiotics do not get pseudomembranous colitis. It is transmitted by the fecal-oral route. The hands of hospital personnel are important intermediaries.

Pathogenesis

Antibiotics suppress drug-sensitive members of the normal flora, allowing *C. difficile* to multiply and produce exotoxins A and B. Both exotoxin A and exotoxin B are enzymes that glucosylate (add glucose to) a G protein called Rho GTPase. The main effect of exotoxin B in particular is to cause depolymerization of actin, resulting in a loss of cytoskeletal integrity, apoptosis, and death of the enterocytes.

Clindamycin was the first antibiotic to be recognized as a cause of pseudomembranous colitis, but many antibiotics are known to cause this disease. At present, second- and third-generation cephalosporins are the most common causes because they are so frequently used. Ampicillin and fluoroquinolones are also commonly implicated. In addition to antibiotics, cancer chemotherapy also predisposes to pseudomembranous colitis. *C. difficile* rarely invades the intestinal mucosa.

Clinical Findings

*C. difficile* causes diarrhea associated with **pseudomembranes** (yellow-white plaques) on the colonic mucosa. The diarrhea is usually not bloody, and neutrophils are found in the stool in about half of the cases. Fever and abdominal cramping often occur. The pseudomembranes are visualized by sigmoidoscopy. Toxic megacolon can occur, and surgical resection of the colon may be necessary. Pseudomembranous colitis can be distinguished from the transient diarrhea that occurs as a side effect of many oral antibiotics by testing for the presence of the toxin in the stool. In 2005, a new, more virulent strain of *C. difficile* emerged. This new strain causes more severe disease, is more likely to cause recurrences, and responds less well to metronidazole than the previous strain. The strain is also characterized by resistance to quinolones. It is thought that the widespread use of quinolones for diarrheal disease may have selected for this new strain.

Laboratory Diagnosis

The presence of exotoxins in a filtrate of the patient's stool specimen is the basis of the laboratory diagnosis. There are two types of tests usually used to detect the exotoxins. One is an enzyme-linked immunosorbent assay (ELISA) using known antibody to the exotoxins. The ELISA tests are rapid but are less sensitive than the cytotoxicity test. In the cytotoxicity test, human cells in culture are exposed to the exotoxin in the stool filtrate and the death of the cells is observed. This test is more sensitive and specific but requires 24–48 hours' incubation time. To distinguish between cytotoxicity caused by the exotoxins and cytotoxicity caused by a virus possibly present in the patient's stool, antibody against the exotoxins is used to neutralize the cytotoxic effect.

Treatment

The causative antibiotic should be withdrawn. Oral metronidazole or vancomycin should be given and fluids replaced. Metronidazole is preferred because using vancomycin may select for vancomycin-resistant enterococci. In many patients, treatment does not eradicate the carrier state and repeated episodes of colitis can occur.

Prevention

There are no preventive vaccines or drugs. Antibiotics should be prescribed only when necessary.

Mycobacteria: Introduction

Mycobacteria are aerobic, **acid-fast** bacilli (rods). They are neither gram-positive nor gram-negative; i.e., they are stained poorly by the dyes used in Gram stain. They are virtually the only bacteria that are acid-fast. (One exception is *Nocardia asteroides,* the major cause of nocardiosis, which is also acid-fast.) The term "acid-fast" refers to an organism's ability to retain the carbolfuchsin stain despite subsequent treatment with an ethanol-hydrochloric acid mixture. The high lipid content (approximately 60%) of their cell wall makes mycobacteria acid-fast.

The major pathogens are *Mycobacterium tuberculosis,* the cause of tuberculosis, and *Mycobacterium leprae,* the cause of leprosy. Atypical mycobacteria, such as *Mycobacterium avium-intracellulare* complex and *Mycobacterium kansasii,* can cause tuberculosis like disease but are less frequent pathogens. Rapidly growing mycobacteria, such as *Mycobacterium chelonei,* occasionally cause human disease in immunocompromised patients or those in whom prosthetic devices have been implanted .

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| ***Mycobacterium tuberculosis***  **Disease**  This organism causes tuberculosis.  **Important Properties**  *M. tuberculosis* **grows slowly** (i.e., it has a doubling time of 18 hours, in contrast to most bacteria, which can double in number in 1 hour or less). Because growth is so slow, cultures of clinical specimens must be held for 6–8 weeks before being recorded as negative. *M. tuberculosis* can be cultured on bacteriologic media, whereas *M. leprae* cannot. Media used for its growth (e.g., Löwenstein-Jensen medium) contain complex nutrients (e.g., egg yolk) and dyes (e.g., malachite green). The dyes inhibit the unwanted normal flora present in sputum samples. *M. tuberculosis* is an **obligate aerobe;** this explains its predilection for causing disease in highly oxygenated tissues such as the upper lobe of the lung and the kidney. Its cell wall contains several complex lipids: (1) long-chain (C78–C90) fatty acids called **mycolic acids,** which contribute to the organism's acid-fastness; (2) wax D, one of the active components in Freund's adjuvant, which is used to enhance the immune response to many antigens in experimental animals; and (3) phosphatides, which play a role in caseation necrosis.  **Cord factor** (trehalose dimycolate) is correlated with virulence of the organism. Virulent strains grow in a characteristic "serpentine" cordlike pattern, whereas a virulent strains do not. The organism also contains several proteins, which, when combined with waxes, elicit delayed hypersensitivity. These proteins are the antigens in the **PPD (purified protein derivative)** skin test (also known as the tuberculin skin test). A lipid located in the bacterial cell wall called phthiocercol dimycoserosate is required for pathogenesis in the lung. *M. tuberculosis* is relatively resistant to acids and alkalis. NaOH is used to concentrate clinical specimens; it destroys unwanted bacteria, human cells, and mucus but not the organism. *M. tuberculosis* is resistant to dehydration and so survives in dried expectorated sputum; this property may be important in its transmission by aerosol.  **Transmission & Epidemiology**  *M. tuberculosis* is transmitted from person to person by respiratory aerosol, and its initial site of infection is the lung. In the body, it resides chiefly within reticuloendothelial cells, e.g., **macrophages. Humans are the natural reservoir** of *M. tuberculosis;* there is no animal reservoir. Most transmission occurs by aerosols generated by the coughing of "smear-positive" people, i.e., those whose sputum contains detectable bacilli in the acid-fast stain. However, about 20% of people are infected by aerosols produced by the coughing of "smear-negative" people.  In the United States, tuberculosis is almost exclusively a human disease. In developing countries, *Mycobacterium bovis* also causes tuberculosis in humans. *M. bovis* is found in cow's milk, which, unless pasteurized, can cause gastrointestinal tuberculosis in humans. The disease tuberculosis occurs in only a small number of infected individuals. In the United States, most cases of tuberculosis are associated with reactivation in elderly, malnourished men. The risk of infection and disease is highest among socioeconomically disadvantaged people, who have poor housing and poor nutrition. These factors, rather than genetic ones, probably account for the high rate of infection among Native Americans, African-Americans, and Eskimos.  **Pathogenesis**  *M. tuberculosis* produces no exotoxins and does not contain endotoxin in its cell wall. In fact, no mycobacteria produce toxins. The organism preferentially infects macrophages and other reticuloendothelial cells. *M. tuberculosis* survives and multiplies within a cellular vacuole called a phagosome. The organism produces a protein called "exported repetitive protein" that prevents the phagosome from fusing with the lysosome, thereby allowing the organism to escape the degradative enzymes in the lysosome. Lesions are dependent on the presence of the organism and the host response. There are two types of lesions:   1. **Exudative lesions,** which consist of an acute inflammatory response and occur chiefly in the lungs at the initial site of infection. 2. **Granulomatous lesions,** which consist of a central area of giant cells containing tubercle bacilli surrounded by a zone of epithelioid cells. These giant cells, called **Langhans' giant cells,** are an important pathologic finding in tuberculous lesions. A **tubercle** is a granuloma surrounded by fibrous tissue that has undergone central caseation necrosis. Tubercles heal by fibrosis and calcification. The primary lesion of tuberculosis usually occurs in the lungs. The parenchymal exudative lesion and the draining lymph nodes together are called a **Ghon complex.** Primary lesions usually occur in the lower lobes, whereas reactivation lesions usually occur in the apices. Reactivation lesions also occur in other well-oxygenated sites such as the kidneys, brain, and bone. Reactivation is seen primarily in immunocompromised or debilitated patients.   Spread of the organism within the body occurs by two mechanisms:   1. A tubercle can erode into a bronchus, empty its caseous contents, and thereby spread the organism to other parts of the lungs, to the gastrointestinal tract if swallowed, and to other persons if expectorated. 2. It can disseminate via the bloodstream to many internal organs. Dissemination can occur at an early stage if cell-mediated immunity fails to contain the initial infection or at a late stage if a person becomes immunocompromised.   **Immunity & Hypersensitivity**  After recovery from the primary infection, resistance to the organism is mediated by **cellular immunity,** i.e., by CD4-positive T cells and macrophages. Circulating antibodies also form, but they play no role in resistance and are not used for diagnostic purposes. Patients deficient in cellular immunity, such as AIDS patients, are at much higher risk for disseminated, life-threatening tuberculosis. Mutations in the mhtml:mk:@MSITStore:F:\Microbiology\Review%20of%20Medical%20Microbiology%20&%20Immunology,%20Tenth%20Edition%202008.chm::/Chapter%2021_%20Mycobacteria.mht!http://www.accessmedicine.com/images/special/gammalower.gif-interferon receptor gene are another cause of defective cellular immunity that predisposes to severe tuberculosis. This emphasizes the importance of activation of macrophages by mhtml:mk:@MSITStore:F:\Microbiology\Review%20of%20Medical%20Microbiology%20&%20Immunology,%20Tenth%20Edition%202008.chm::/Chapter%2021_%20Mycobacteria.mht!http://www.accessmedicine.com/images/special/gammalower.gif-interferon in the host defense against *M. tuberculosis.*  Prior infection can be detected by a positive **tuberculin skin test** result, which is due to a delayed hypersensitivity reaction. **PPD** is used as the antigen in the tuberculin skin test. The intermediate-strength preparation of PPD, which contains 5 tuberculin units, is usually used. The skin test is evaluated by measuring the diameter of the **induration** surrounding the skin test site. Note that induration (thickening), not simply erythema (reddening), must be observed. The diameter required to judge the test as positive varies depending upon the status of the individual being tested. Induration of 15 mm or more is positive in a person who has no known risk factors. Induration of 10 mm or more is positive in a person with high-risk factors, such as a homeless person, intravenous drug users, or nursing home residents. Induration of 5 mm or more is positive in a person who has deficient cell-mediated immunity, e.g., AIDS patients, or has been in close contact with a person with active tuberculosis.  The tuberculin test becomes positive 4–6 weeks after infection. Immunization with BCG vaccine can cause a positive test, but the reactions are usually only 5–10 mm and tend to decrease with time. People with PPD reactions of 15 mm or more are assumed to be infected with *M. tuberculosis* even if they have received the BCG vaccine. A positive skin test reverts to negative in about 5–10% of people.  Tuberculin reactivity is mediated by the cellular arm of the immune system; it can be transferred by CD4-positive T cells but not by serum. Infection with measles virus can suppress cell-mediated immunity, resulting in a loss of tuberculin skin test reactivity . A gene called *Nramp* determines natural resistance to tuberculosis. People who have mutations in the *Nramp* gene have a much higher rate of clinical tuberculosis than those with a normal allele. The NRAMP protein is located in the membrane of the phagosome in macrophages and plays an important role in killing the organism within the phagosome.  **Clinical Findings**  Clinical findings are protean; many organs can be involved. Fever, fatigue, night sweats, and weight loss are common. Pulmonary tuberculosis causes cough and hemoptysis. Scrofula is mycobacterial cervical adenitis that presents as swollen nontender lymph nodes, usually unilaterally. Both *M. tuberculosis* and *Mycobacterium scrofulaceum* cause scrofula. Erythema nodosum, characterized by tender nodules along the extensor surfaces of the tibia and ulna, is a manifestation of primary infection seen in patients who are controlling the infection with a potent cell-mediated response. Miliary tuberculosis is characterized by multiple disseminated lesions that resemble millet seeds. Tuberculous meningitis and tuberculous osteomyelitis, especially vertebral osteomyelitis (Pott's disease), are important disseminated forms.  **Gastrointestinal tuberculosis** is characterized by abdominal pain and diarrhea accompanied by more generalized symptoms of fever and weight loss. Intestinal obstruction or hemorrhage may occur. The ileocecal region is the site most often involved. Tuberculosis of the GI tract can be caused by either *M. tuberculosis* when it is swallowed after being coughed up from a lung lesion or by *M. bovis* when it is ingested in unpasteurized milk products. Oropharyngeal tuberculosis typically presents as a painless ulcer accompanied by local adenopathy.  In **renal tuberculosis,** dysuria, hematuria, and flank pain occur. "Sterile pyuria" is a characteristic finding. The urine contains white blood cells, but cultures for the common urinary tract bacterial pathogens show no growth. However, mycobacterial cultures are often positive.  **Laboratory Diagnosis**  **Acid-fast staining** of sputum or other specimens is the usual initial test. For rapid screening purposes, auramine stain, which can be visualized by fluorescence microscopy, can be used.  After digestion of the specimen by treatment with NaOH and concentration by centrifugation, the material is cultured on special media, such as Löwenstein-Jensen agar, for up to 8 weeks. It will *not* grow on a blood agar plate. In liquid BACTEC medium, radioactive metabolites are present and growth can be detected by the production of radioactive carbon dioxide in about 2 weeks. A liquid medium is preferred for isolation because the organism grows more rapidly and reliably than it does on agar. If growth in the culture occurs, the organism can be identified by biochemical tests. For example, *M. tuberculosis* produces **niacin,** whereas almost no other mycobacteria do. It also produces catalase. More rapid identification tests using DNA probes are also available.  Because drug resistance, especially to INH , is a problem, susceptibility tests should be performed. However, the organism grows very slowly and susceptibility tests usually take several weeks, which is too long to guide the initial choice of drugs. The **luciferase assay,** which can detect drug-resistant organisms in a few days, is a distinct improvement. Luciferase is an enzyme isolated from fireflies that produces flashes of light in the presence of adenosine triphosphate (ATP). If the organism isolated from the patient is resistant, it will not be damaged by the drug; i.e., it will make a normal amount of ATP, and the luciferase will produce the normal amount of light. If the organism is sensitive to the drug, less ATP will be made and less light produced.  There are two approaches to the diagnosis of latent infections. One is the PPD skin test. Because there are problems both in the interpretation of the PPD test and with the person returning for the skin test to be read, a quantifiable laboratory-based test is valuable. This laboratory test is the interferon-gamma release assay called QuantiFERON-TB. In this assay, blood cells from the patient are exposed to antigens from *M. tuberculosis* and the amount of interferon-gamma released from the cells is measured.    **Treatment & Resistance**  **Multidrug** therapy is used to prevent the emergence of drug-resistant mutants during the long (6- to 9-month) duration of treatment. (Organisms that become resistant to one drug will be inhibited by the other.) **Isoniazid** (INH), a bactericidal drug, is the mainstay of treatment. Treatment for most patients with pulmonary tuberculosis is with three drugs: INH, rifampin, and pyrazinamide. INH and rifampin are given for 6 months, but pyrazinamide treatment is stopped after 2 months. In patients who are immunocompromised ,who have disseminated disease, or who are likely to have INH-resistant organisms, a fourth drug, ethambutol, is added and all four drugs are given for 9–12 months. Although therapy is usually given for months, the patient's sputum becomes **noninfectious within 2–3 weeks.** The necessity for protracted therapy is attributed to (1) the intracellular location of the organism; (2) caseous material, which blocks penetration by the drug; (3) the slow growth of the organism; and (4) metabolically inactive "persisters" within the lesion. Because metabolically inactive organisms may not be killed by antitubercular drugs, treatment may not eradicate the infection and reactivation of the disease may occur in the future.  Treatment of latent (asymptomatic) infections consists of INH taken for 6–9 months. (This regimen used to be considered prophylactic because it reduced the risk of symptomatic infection appearing in the future.) This approach is most often used in asymptomatic patients whose PPD skin test recently converted to positive. The risk of symptomatic infection is greatest within the first 2 years after infection, so INH is particularly indicated for these "recent converters." INH is also used in children exposed to patients with symptomatic tuberculosis. Patients who receive INH should be evaluated for drug-induced hepatitis, especially those over the age of 35 years. Rifampin can be used in those exposed to INH-resistant strains. A combination of rifampin and pyrazinamide should not be used because it caused a high rate of severe liver injury.  Resistance to INH and other antituberculosis drugs is being seen with increasing frequency in the United States, especially in immigrants from Southeast Asia and Latin America. Strains of *M. tuberculosis* **resistant to multiple drugs** (MDR strains) have emerged, primarily in AIDS patients. The most common pattern is resistance to both INH and rifampin, but some isolates are resistant to three or more drugs. The treatment of MDR organisms usually involves the use of four or five drugs, including ciprofloxacin, amikacin, ethionamide, and cycloserine.  Previous treatment for tuberculosis predisposes to the selection of these MDR organisms. **Noncompliance,** i.e., the failure of patients to complete the full course of therapy, is a major factor in allowing the resistant organisms to survive. One approach to the problem of noncompliance is directly observed therapy (DOT), in which health care workers observe the patient taking the medication. The strains of *M. tuberculosis* resistant to INH, rifampin, a fluoroquinolone, and at least one additional drug are called XDR (extensively drug resistant) strains.  **Prevention**  The incidence of tuberculosis began to decrease markedly even before the advent of drug therapy in the 1940s. This is attributed to better housing and nutrition, which have improved host resistance , prevention of the spread of the organism depends largely on the prompt identification and adequate treatment of patients who are coughing up the organism. The use of masks and other respiratory isolation procedures to prevent spread to medical personnel is also important. Contact tracing of individuals exposed to patients with active pulmonary disease who are coughing should be done.  An important component of prevention is the use of the PPD skin test to detect recent converters and to institute treatment for latent infections as described above. Groups that should be screened with the PPD skin test include people with HIV infection, close contacts of patients with active tuberculosis, low-income populations, alcoholics and intravenous drug users, prison inmates, and foreign-born individuals from countries with a high incidence of tuberculosis.  Because there are some problems associated with PPD skin tests, such as the measurement and the interpretation of results and the inconvenience of the patient having to return for the skin test to be read.  BCG vaccine can be used to induce partial resistance to tuberculosis. The vaccine contains a strain of live, attenuated *M. bovis* called bacillus Calmette-Guérin. The vaccine is effective in preventing the appearance of tuberculosis as a clinical disease, especially in children, although it does not prevent infection by *M. tuberculosis.* However, a major problem with the vaccine is its variable effectiveness, which can range from 0% to 70%. It is used primarily in areas of the world where the incidence of the disease is high. The skin test reactivity induced by the vaccine given to children wanes with time, and the interpretation of the skin test reaction in adults is not altered by the vaccine. For example, skin test reactions of 10 mm or more should not be attributed to the vaccine unless it was administered recently. In the United States, use of the vaccine is limited to young children who are in close contact with individuals with active tuberculosis and to military personnel. BCG vaccine should not be given to immunocompromised people because the live BCG organisms can cause disseminated disease. BCG vaccine is also used to treat bladder cancer. The vaccine is instilled into the bladder and serves to nonspecifically stimulate cell-mediated immunity, which can inhibit the growth of the carcinoma cells. Pasteurization of milk and destruction of infected cattle are important in preventing intestinal tuberculosis. |

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| **Atypical Mycobacteria**  Several species of mycobacteria are characterized as atypical, because they differ in certain respects from the prototype, *M. tuberculosis.* For example, atypical mycobacteria are widespread in the **environment** and are not pathogenic for guinea pigs, whereas *M. tuberculosis* is found only in humans and is highly pathogenic for guinea pigs.  The atypical mycobacteria are classified into four groups according to their rate of growth and whether they produce pigment under certain conditions . Group I organisms produce a yellow-orange-pigmented colony only when exposed to light (**photochromogens**), whereas group II organisms produce the pigment chiefly in the dark (**scotochromogens**). Group III mycobacteria produce little or no yellow-orange pigment, irrespective of the presence or absence of light (**nonchromogens**). In contrast to the organisms in the previous three groups, which grow slowly, group IV organisms grow rapidly, producing colonies in fewer than 7 days. |

*Mycobacterium leprae*

Disease

This organism causes leprosy.

Important Properties

*M. leprae* has **not been grown** in the laboratory, either on artificial media or in cell culture. It can be grown in the mouse footpad or in the armadillo. Humans are the natural hosts, although the armadillo may also be a reservoir for human infection. The optimal temperature for growth (30°C) is lower than body temperature; it therefore grows preferentially in the skin and superficial nerves. It grows very slowly, with a doubling time of 14 days. This makes it the slowest-growing human bacterial pathogen. One consequence of this is that antibiotic therapy must be continued for a long time, usually several years.

Transmission

Infection is acquired by **prolonged contact with patients** with lepromatous leprosy, who discharge *M. leprae* in large numbers in nasal secretions and from skin lesions

Pathogenesis

The organism replicates intracellularly, typically within skin histiocytes, endothelial cells, and the Schwann cells of nerves. There are two distinct forms of leprosy—**tuberculoid** and **lepromatous**—with several intermediate forms between the two extremes .

**Clinical Findings**

The incubation period averages several years, and the onset of the disease is gradual. In tuberculoid leprosy, hypopigmented macular or plaque-like skin lesions, thickened superficial nerves, and significant anesthesia of the skin lesions occur. In lepromatous leprosy, multiple nodular skin lesions occur, resulting in the typical **leonine** (lionlike) **facies.** After the onset of therapy, patients with lepromatous leprosy often develop **erythema nodosum leprosum** (ENL), which is interpreted as a sign that cell-mediated immunity is being restored. ENL is characterized by painful nodules, especially along the extensor surfaces of the tibia and ulna; neuritis; and uveitis.

The disfiguring appearance of the disease results from several factors: (1) the skin anesthesia results in burns and other traumas, which often become infected; (2) resorption of bone leads to loss of features such as the nose and fingertips; and (3) infiltration of the skin and nerves leads to thickening and folding of the skin. In most patients with a single skin lesion, the disease resolves spontaneously. Patients with forms of the disease intermediate between tuberculoid and lepromatous can progress to either extreme.

**Laboratory Diagnosis**

In lepromatous leprosy, the bacilli are easily demonstrated by performing an acid-fast stain of skin lesions or nasal scrapings. Lipid-laden macrophages called "foam cells" containing many acid-fast bacilli are seen in the skin. In the tuberculoid form, very few organisms are seen and the appearance of typical granulomas is sufficient for diagnosis. Cultures are negative because the organism does not grow on artificial media. No serologic tests are useful. False-positive results in the nonspecific serologic tests for syphilis, such as the VDRL and RPR tests, occur frequently in patients with lepromatous leprosy.

**Treatment**

The mainstay of therapy is **dapsone** (diaminodiphenylsulfone), but because sufficient resistance to the drug has emerged, combination therapy is now recommended, e.g., dapsone, rifampin, and clofazimine for lepromatous leprosy and dapsone and rifampin for the tuberculoid form. Treatment is given for at least 2 years or until the lesions are free of organisms. Thalidomide is the treatment of choice for severe ENL reactions.

**Prevention**

Isolation of all lepromatous patients, coupled with chemoprophylaxis with dapsone for exposed children, is required. There is no vaccine