MEDICAL EDUCATION SYSTEMS,INC

Pseudomonas Aeruginosa

Medical Education Systems, Inc.

TOLL FREE 1-877-295-4719
FAX (619) 295-0252
EMAIL: Info@mededsys.com
www.mededsys.com
P.O Box 83939 San Diego, CA 92138-3939

Pseudomonas Aeruginosa

Learning Objectives

- List the signs and symptoms of Pseudomonas aeruginosa
- Identify the pathophysiology of P. aeruginosa
- Identify how Pseudomonas aeruginosa is diagnosed
- Identify the causes and possible treatments of P. aeruginosa

Introduction

Events in the world can often focus the spotlight on medical issues that normally are obscured from public attention. News item, January 24, 2009:

Brazilian Miss World contestant Mariana Bridi da Costa dies

A 20-YEAR-OLD model who was a finalist to represent Brazil in the Miss World contest has died after having her hands and feet amputated because she had contracted a severe urinary infection.

Doctors had been forced to amputate her hands and feet after she developed septicaemia. Health officials said in a statement that Mariana Bridi's condition deteriorated overnight and she died early this morning. The Espirito Santo State Health Secretariat said in the statement she died from complications related to a generalized infection, Associated Press has reported. It was caused by the bacteria Pseudomonas aeruginosa, which is known to be resistant to several kinds of antibiotics.

Bridi had been in the hospital in the city of Serra in south-eastern Brazil since January 3. She became ill in December and doctors originally diagnosed her with kidney stones, local media said. Mariana Bridi da Costa had been in a hospital in Serra, in the south-eastern state of Espirito Santo, and on artificial respiration following the procedures, according to several newspapers. Her boyfriend, Thiago Simoes, told the G1 news website that Bridi fell ill on December 30, but was initially misdiagnosed with kidney stones. The infection quickly spread, causing her to go back to hospital for tests that revealed her condition. Surgeons had to act to remove her damaged hands and feet. Bridi was twice a finalist in the Brazilian stage of the Miss World pageant.

Pseudomonas aeruginosa Infections

Introduction

Background

Pseudomonas is a gram-negative rod that belongs to the family Pseudomonadaceae. More than half of all clinical isolates produce the blue-green pigment pyocyanin. *Pseudomonas* often has a characteristic sweet odor.

These pathogens are widespread in nature, inhabiting soil, water, plants, and animals (including humans). *Pseudomonas aeruginosa* has become an important cause of infection, especially in patients with compromised host defense mechanisms. It is the most common pathogen isolated from patients who have been hospitalized longer than 1 week. It is a frequent cause of nosocomial infections such as pneumonia, urinary tract infections (UTIs), and bacteremia. Pseudomonal infections are complicated and can be life threatening.

Pathophysiology

P aeruginosa is an opportunistic pathogen. It rarely causes disease in healthy persons. In most cases of infection, the integrity of a physical barrier to infection (e.g., skin, mucous membrane) is lost or an underlying immune deficiency (e.g., neutropenia, immunosuppression) is present. Adding to its pathogenicity, this bacterium has minimal nutritional requirements and can tolerate a wide variety of physical conditions.

The pathogenesis of pseudomonal infections is multifactorial and complex. *Pseudomonas* species are both invasive and toxigenic. The 3 stages, according to Pollack (2000), are (1) bacterial attachment and colonization, (2) local infection, and (3) bloodstream dissemination and systemic disease.[1] The importance of colonization and adherence is most evident when studied in the context of respiratory tract infection in patients with cystic fibrosis and in those that complicate mechanical ventilation. Production of extracellular proteases adds to the organism's virulence by assisting in bacterial adherence and invasion.

Frequency

United States

According to the Centers for Disease Control and Prevention (CDC), the overall prevalence of *P aeruginosa* infections in US hospitals is approximately 4 per 1000 discharges (0.4%).[2] *P aeruginosa* is also the fourth most commonly isolated nosocomial pathogen, accounting for 10.1% of all hospital-acquired infections. It is found on the skin of some healthy persons and has been isolated from the throat and stool of 5% and 3% of nonhospitalized patients, respectively. The gastrointestinal carriage rates among hospitalized patients increases to 20% within 72 hours of admission.

International

P aeruginosa is common in immunocompromised patients with diabetes.

Mortality/Morbidity

All infections caused by *P aeruginosa* are treatable and potentially curable. Acute fulminant infections, such as bacteremic pneumonia, sepsis, burn wound infections, and meningitis, are associated with extremely high mortality rates.

Race

P aeruginosa endocarditis in individuals who abuse intravenous drugs is observed mainly among young black males.

Sex

Cases of endocarditis and vertebral osteomyelitis have been observed in young males who use intravenous drugs.

Age

- Vertebral osteomyelitis due to pseudomonal infection mainly occurs in elderly patients and often involves the lumbosacral spine. Young people who use intravenous drugs may also be affected.
- Involvement of the GI tract most commonly occurs in infants and patients with hematologic malignancies and neutropenia that has resulted from chemotherapy.
- The incidence of pseudomonal pneumonia in patients with cystic fibrosis has shown a shift towards patients who are older than 26 years.

Clinical

History

Pseudomonal infections can involve any part of the body.

- Respiratory tract
    - Pneumonia is observed in patients with immunosuppression and chronic lung disease. It can be acquired nosocomially in the intensive care unit (ICU) setting and is associated with positive-pressure ventilation and endotracheal tubes. The pneumonia may be primary, following aspiration of the organism from the upper respiratory tract, especially in patients on mechanical ventilation. Alternatively, it may occur as a result of bacteremic spread to the lungs. This is observed commonly in patients following chemotherapy-induced neutropenia.
    - Bacteremic pneumonia occurs in patients with neutropenia following chemotherapy and in patients with AIDS.
    - Chronic infection of the lower respiratory tract with *P aeruginosa* is prevalent among patients with cystic fibrosis. These patients may present with chronic productive cough, anorexia, weight loss, wheezing, and tachypnea.

    - Symptoms of pneumonia include fever, chills, severe dyspnea, cyanosis, productive cough, confusion, and other signs of a systemic inflammatory response.
- Bacteremia
    - Bacteremia may be acquired via medical devices in hospitals and nursing homes, and the mortality rate remains greater than 10%.
    - Signs and symptoms depend on the primary site of infection.
- Endocarditis
    - *P aeruginosa* may infect native heart valves in individuals who abuse intravenous drugs and may infect prosthetic heart valves.
    - Right-sided and left-sided valve infections may occur.
    - Nonspecific symptoms include fever and malaise, with more specific symptoms depending on which cardiac valve is involved. Left-sided endocarditis typically presents with symptoms of congestive heart failure and those resulting from systemic spread of septic emboli.
- Central nervous system
    - *P aeruginosa* infection can cause meningitis and brain abscess.
    - Most infections follow an extension from a contiguous parameningeal structure, such as an ear, a mastoid, paranasal sinus surgery, or diagnostic procedures. In some patients, the involvement of the CNS is due to hematogenous spread of the organism from infective endocarditis, pneumonia, or UTI.
    - Patients present with fever, headache, and confusion. The onset may be fulminant or subacute, often depending on the immune status of the patient.
- Ear
    - In otitis externa (swimmer's ear), patients present with pain, pruritus, and ear discharge. The pain is worsened by traction on the pinna.
    - *Pseudomonas* infection is a common cause of chronic otitis media. Malignant otitis externa is a manifestation of invasive infection predominantly observed in patients with uncontrolled diabetes. It begins as ordinary otitis externa that fails to respond to antibiotic therapy. Presenting symptoms are persistent pain, edema, and tenderness of the soft tissues of the ear, with a purulent discharge. Fever is uncommon, and some patients present with a facial nerve palsy. Extension of the infection to the temporal bone can result in osteomyelitis, and further extension can create cranial nerve palsies and possibly a CNS infection.
- Eye
    - The cornea, aqueous humor, and vitreous humor comprise an immunocompromised environment, and *Pseudomonas,* when introduced, produces extracellular enzymes that cause a rapidly progressive and destructive lesion. *P aeruginosa* is a common cause of bacterial keratitis, scleral abscess, and endophthalmitis in adults and ophthalmia neonatorum in children.
    - Predisposing conditions for corneal involvement are trauma, contact lens use, predisposing ocular conditions, exposure to an ICU environment, and AIDS. Corneal lesions can progress to endophthalmitis and orbital cellulitis. Symptoms are pain, redness, swelling, and impaired vision.
- Bones and joints

    - The most common sites of involvement are the vertebral column, the pelvis, and the sternoclavicular joint.
    - Infection may be blood-borne, as in individuals who abuse intravenous drugs or in patients with pelvic infections or UTI. Alternatively, the infection may be contiguous, related to penetrating trauma, surgery, or overlying soft tissue infections. Patients at risk for pseudomonal bone and joint infections include those with puncture wounds to the foot, peripheral vascular disease, intravenous drug abuse, or diabetes mellitus.
    - Vertebral osteomyelitis may involve the cervical spine, and patients present with neck or back pain lasting weeks to months. Occasionally, patients with complicated UTI may develop lumbosacral vertebral osteomyelitis.
    - Patients with pyoarthrosis present with swelling and pain in the affected joint. Patients are persistently febrile.
- Gastrointestinal
    - Pseudomonal infections can affect every portion of the GI tract. The disease is often underestimated but usually affects very young children and adults with hematologic malignancies and chemotherapy-induced neutropenia. Additionally, colonization of the GI tract is an important portal of entry for pseudomonal bacteremia in patients who are neutropenic. The spectrum of disease can range from very mild symptoms to severe necrotizing enterocolitis with significant morbidity and mortality.
    - Epidemics of pseudomonal diarrhea can occur in nurseries. Young infants may present with irritability, vomiting, diarrhea, and dehydration.
    - The infection can cause enteritis, with patients presenting with prostration, headache, fever, and diarrhea (Shanghai fever).
    - *Pseudomonas* typhlitis typically presents in patients with neutropenia resulting from acute leukemia, with a sudden onset of fever, abdominal distension, and worsening abdominal pain.
- Urinary tract infections
    - Pseudomonal UTIs are usually hospital-acquired and are associated with catheterization, instrumentation, and surgery.
    - These infections can involve the urinary tract through an ascending infection or through bacteremic spread. In addition, these infections are a frequent source of bacteremia.
    - No specific characteristics distinguish this type of infection from other forms of UTI.
- Skin
    - *Pseudomonas* does not grow on dry skin, but it flourishes on moist skin.
    - Green nail syndrome is a paronychial infection that can develop in individuals whose hands are frequently submerged in water.
    - Secondary wound infections occur in patients with decubiti, eczema, and tinea pedis. These infections may have a characteristic blue-green exudate with a fruity odor.
    - *Pseudomonas* is a common cause of hot tub or swimming pool folliculitis. Patients present with pruritic follicular, maculopapular, vesicular, or pustular lesions on any part of the body that was immersed in water.

- Pseudomonal bacteremia produces distinctive skin lesions known as ecthyma gangrenosum.
- *Pseudomonas* also has emerged as an important source of burn wound sepsis. Invasive burn wound sepsis is defined as the bacterial proliferation of 100,000 organisms per gram of tissue, with subjacent involvement of subjacent unburned tissue.

Physical

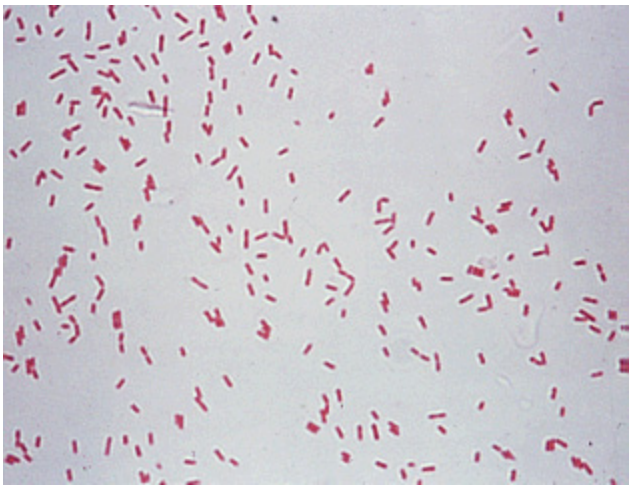
- Endocarditis
  - Cardinal features of bacterial endocarditis include fever, murmur, and positive blood culture findings.
  - A new onset of cardiac murmur or a change in character of a preexisting murmur may develop, although these may be absent on presentation.
  - Peripheral stigmata of endocarditis include Roth spots, Janeway lesions, Osler nodes, splinter hemorrhages, and splenomegaly.
- Pneumonia
  - Patients have rales, rhonchi, fever, cyanosis, retractions, and hypoxia.
  - Shock may develop in patients with bacteremic pneumonia.
  - Patients with cystic fibrosis may develop clubbing, increased anteroposterior (AP) diameter, and malnutrition.
- Gastrointestinal tract
  - Young infants with diarrhea may have fever, signs of dehydration, abdominal distension, and signs of peritonitis.
  - Physical findings of Shanghai fever may include fever, splenomegaly, and rose spots. Depending on the severity of the illness, prostration, dehydration, and vascular collapse may be observed.
- Skin and soft tissue infections
  - Ecthyma gangrenosum lesions are hemorrhagic and necrotic, with surrounding erythema. These characteristic lesions are almost always caused by *Pseudomonas* infection and usually are found in the axilla, groin, or perianal area but may involve any part of body.
  - Subcutaneous nodules, deep abscesses, cellulitis, and fasciitis may also occur.
  - Pseudomonal burn wound infections appear black or as a violaceous discoloration or eschar. Systemic manifestations of burn wound sepsis may include fever or hypothermia, disorientation, hypotension, oliguria, ileus, and leukopenia.
- Skeletal infections
  - Vertebral osteomyelitis manifests as local tenderness and a decreased range of motion.
  - Osteomyelitis may complicate puncture wounds.
  - Neurological deficits, when present, suggest spinal cord involvement.
- With eye infections, the physical examination reveals lid edema, conjunctival erythema and chemosis, and severe mucopurulent discharge adherent to an underlying corneal ulcer.
- Malignant otitis externa

    - The external auditory canal is erythematous, swollen, and inflamed, and a discharge may be observed.
    - The tympanic membrane is hidden from view because of edema and may be ruptured.
    - Local lymphadenopathy may be present.
- Bacteremia
    - Patients have fever, tachypnea, and tachycardia.
    - Hypotension and shock may develop.
    - Jaundice may occur.
    - Skin shows characteristic skin lesions called ecthyma gangrenosum.

Causes

- Pseudomonal bacteremia occurs in association with malignancy, chemotherapy, AIDS, burn wound sepsis, and diabetes.
- Certain populations of patients are especially susceptible to pseudomonal infections. Predisposing conditions include placement of intravenous lines, severe burns, urinary tract catheterization, surgery, trauma, and premature birth (infants).
- Conditions predisposing to pseudomonal infections and major manifestations include the following:
    - Diabetes - Malignant otitis externa
    - Drug addiction - Endocarditis, osteomyelitis
    - Leukemia - Sepsis, typhlitis
    - Cancer - Pneumonia, sepsis
    - Burn wound - Cellulitis, sepsis
    - Cystic fibrosis - Pneumonia
    - Surgery involving CNS - Meningitis
    - Tracheostomy - Pneumonia
    - Neonatal period - Diarrhea
    - Corneal ulcer - Panophthalmitis
    - Vascular catheterization - Bacteremia, suppurative thrombophlebitis
    - Urinary catheterization - UTI

Samer Qarah, MD, Pulmonary Critical Care Consultant, Department of Internal Medicine, Division of Pulmonary and Critical Care, The Brooklyn Hospital Center and Cornell University
Burke A Cunha, MD, Professor of Medicine, State University of New York School of Medicine at Stony Brook; Chief, Infectious Disease Division, Winthrop-University Hospital; **Pratibha Dua, MD, MBBS,** Staff Physician, Department of Internal Medicine, The Brooklyn Hospital Center; **Klaus-Dieter Lessnau, MD, FCCP,** Clinical Assistant Professor of Medicine, New York University School of Medicine; Medical Director, Pulmonary Physiology Laboratory, Director of Research in Pulmonary Medicine, Department of Medicine, Section of Pulmonary Medicine, Lenox Hill Hospital; **Tarun Madappa, MD, MPH,** Pulmonary Fellow, Section of Pulmonary Medicine, Lenox Hill Hospital



Gram stain of *Pseudomonas aeruginosa* cells

Pseudomonas aeruginosa is member of the Gamma Proteobacteria class of Bacteria. It is a Gram-negative, aerobic rod belonging to the bacterial family Pseudomonadaceae. Since the revisionist taxonomy based on conserved macromolecules (e.g. 16S ribosomal RNA) the family includes only members of the genus Pseudomonas which are cleaved into eight groups. Pseudomonas aeruginosa is the type species of its group. which contains 12 other members.

Like other members of the genus, *Pseudomonas aeruginosa* is a free-living bacterium, commonly found in soil and water. However, it occurs regularly on the surfaces of plants and occasionally on the surfaces of animals. Members of the genus are well known to plant microbiologists because they are one of the few groups of bacteria that are true pathogens of plants. In fact, *Pseudomonas aeruginosa* is occasionally a pathogen of plants. However, *Pseudomonas aeruginosa* has become increasingly recognized as an emerging opportunistic pathogen of clinical relevance. Several different epidemiological studies track its occurrence as a nosocomial pathogen and indicate that antibiotic resistance is increasing in clinical isolates.

Pseudomonas aeruginosa is an opportunistic pathogen, meaning that it exploits some break in the host defenses to initiate an infection. In fact, *Pseudomonas aeruginosa* is the epitome of an opportunistic pathogen of humans. The bacterium almost never infects uncompromised tissues, yet there is hardly any tissue that it cannot infect if the tissue defenses are compromised in some manner. It causes urinary tract infections, respiratory system infections, dermatitis, soft tissue infections, bacteremia, bone and joint infections, gastrointestinal infections and a variety of systemic infections, particularly in patients with severe burns and in cancer and AIDS patients who are immunosuppressed. Pseudomonas aeruginosa infection is a serious problem in patients hospitalized with cancer, cystic fibrosis, and burns. The case fatality rate in these patients is near 50 percent.

Pseudomonas aeruginosa is primarily a nosocomial pathogen. According to the CDC, the overall incidence of *P. aeruginosa* infections in U.S. hospitals averages about 0.4 percent (4 per 1000 discharges), and the bacterium is the fourth most commonly-isolated nosocomial pathogen accounting for 10.1 percent of all hospital-acquired infections.

Characteristics

Pseudomonas aeruginosa is a Gram-negative rod measuring 0.5 to 0.8 μm by 1.5 to 3.0 μm. Almost all strains are motile by means of a single polar flagellum.

The bacterium is ubiquitous in soil and water, and on surfaces in contact with soil or water. Its metabolism is respiratory and never fermentative, but it will grow in the absence of O_2 if NO_3 is available as a respiratory electron acceptor.

The typical *Pseudomonas* bacterium in nature might be found in a biofilm, attached to some surface or substrate, or in a planktonic form, as a unicellular organism, actively swimming by means of its flagellum. *Pseudomonas* is one of the most vigorous, fast-swimming bacteria seen in hay infusions and pond water samples.

In its natural habitat *Pseudomonas aeruginosa* is not particularly distinctive as a pseudomonad, but it does have a combination of physiological traits that are noteworthy and may relate to its pathogenesis.

• *Pseudomonas aeruginosa* has very simple nutritional requirements. It is often observed "growing in distilled water", which is evidence of its minimal nutritional needs. In the laboratory, the simplest medium for growth of *Pseudomonas aeruginosa* consists of acetate as a source of carbon and ammonium sulfate as a source of nitrogen.

• *P. aeruginosa* possesses the metabolic versatility for which pseudomonads are so renowned. Organic growth factors are not required, and it can use more than seventy-five organic compounds for growth.

• Its optimum temperature for growth is 37 degrees, and it is able to grow at temperatures as high as 42 degrees.

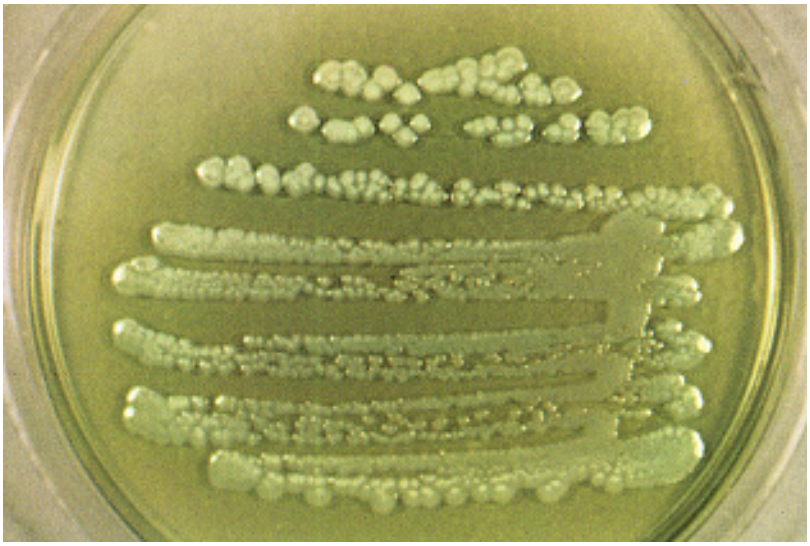
• It is tolerant to a wide variety of physical conditions, including temperature. It is resistant to high concentrations of salts and dyes, weak antiseptics, and many commonly used antibiotics.

• *Pseudomonas aeruginosa* has a predilection for growth in moist environments, which is probably a reflection of its natural existence in soil and water.

These natural properties of the bacterium undoubtedly contribute to its ecological success as an opportunistic pathogen. They also help explain the ubiquitous nature of the organism and its prominence as a nosocomial pathogen.

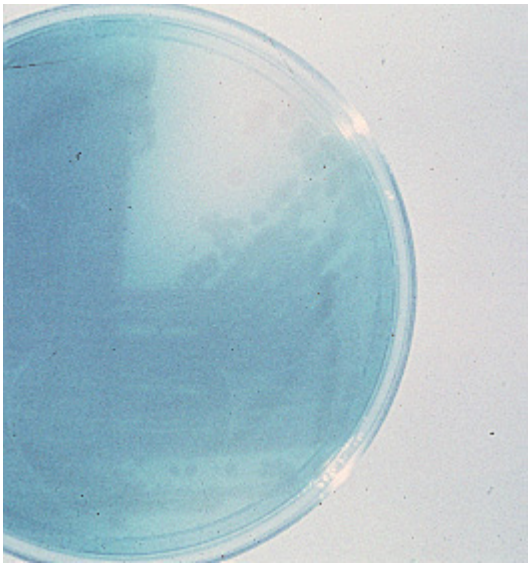
P. aeruginosa isolates may produce three colony types. Natural isolates from soil or water typically produce a small, rough colony. Clinical samples, in general, yield one or another of two smooth colony types. One type has a fried-egg appearance which is large, smooth, with flat edges and an elevated appearance.

Another type, frequently obtained from respiratory and urinary tract secretions, has a mucoid appearance, which is attributed to the production of alginate slime. The smooth and mucoid colonies are presumed to play a role in colonization and virulence.



***Pseudomonas aeruginosa* colonies on agar**

P. aeruginosa strains produce two types of soluble pigments, the fluorescent pigment pyoverdin and the blue pigment pyocyanin. The latter is produced abundantly in media of low-iron content and functions in iron metabolism in the bacterium. Pyocyanin (from "pyocyaneus") refers to "blue pus", which is a characteristic of suppurative infections caused by *Pseudomonas aeruginosa*.



The soluble blue pigment pyocyanin is produced by many, but not all, strains of *Pseudomonas aeruginosa*

Resistance to Antibiotics

Pseudomonas aeruginosa is notorious for its resistance to antibiotics and is, therefore, a particularly dangerous and dreaded pathogen. The bacterium is naturally resistant to many antibiotics due to the permeabiliity barrier afforded by its Gram-negative outer membrane. Also, its tendency to colonize surfaces in a biofilm form makes the cells impervious to therapeutic concentrations antibiotics. Since its natural habitat is the soil, living in association with the bacilli, actinomycetes and molds, it has developed resistance to a variety of their naturally-occuring antibiotics. Moreover, *Pseudomonas* maintains antibiotic resistance plasmids, both R-factors and RTFs, and it is able to transfer these genes by means of the bacterial mechanisms of horizontal gene transfer (HGT), mainly transduction and conjugation.

Only a few antibiotics are effective against *Pseudomonas aeruginosa*, including fluoroquinolones, gentamicin and imipenem, and even these antibiotics are not effective against all strains. The futility of treating *Pseudomonas* infections with antibiotics is most dramatically illustrated in cystic fibrosis patients, virtually all of whom eventually become infected with a strain that is so resistant that it cannot be treated.

Diagnosis

Diagnosis of *P.aeruginosa* infection depends upon isolation and laboratory identification of the bacterium. It grows well on most laboratory media and commonly is isolated on blood agar or eosin-methylthionine blue agar. It is identified on the basis of its Gram morphology, inability to ferment lactose, a positive oxidase reaction, its fruity odor, and its ability to grow at 42°C. Fluorescence under ultraviolet light is helpful in early identification of *P.s aeruginosa* colonies. Fluorescence is also used to suggest the presence of *P. aeruginosa* in wounds.

Pathogenesis

For an opportunistic pathogen such as *Pseudomonas aeruginosa*, the disease process begins with some alteration or circumvention of normal host defenses. The pathogenesis of *Pseudomonas*s infections is multifactorial, as suggested by the number and wide array of virulence determinants possessed by the bacterium. Multiple and diverse determinants of virulence are expected in the wide range of diseases caused, which include septicemia, urinary tract infections, pneumonia, chronic lung infections, endocarditis, dermatitis, and osteochondritis.

Most *Pseudomonas* infections are both invasive and toxinogenic. The ultimate *Pseudomonas* infection may be seen as composed of three distinct stages: (1) bacterial attachment and colonization; (2) local invasion; (3) disseminated systemic disease. However, the disease process may stop at any stage. Particular bacterial determinants of virulence mediate each of these stages and are ultimately responsible for the characteristic syndromes that accompany the disease.

Colonization

Although colonization usually precedes infections by *Pseudomonas aeruginosa*, the exact source and mode of transmission of the pathogen are often unclear because of its ubiquitous presence in the environment. It is sometimes present as part of the normal flora of humans, although the prevalence of colonization of healthy individuals outside the hospital is relatively low (estimates range from 0 to 24 percent depending on the anatomical locale).

The pili of *Pseudomonas aeruginosa* will adhere to the epithelial cells of the upper respiratory tract and, by inference, to other epithelial cells as well. These adhesins appear to bind to specific galactose or mannose or sialic acid receptors on epithelial cells. Colonization of the respiratory tract by *Pseudomonas* requires pili adherence and may be aided by production of a protease enzyme that degrades fibronectin in order to expose the underlying pilus receptors on the epithelial cell surface. Tissue injury may also play a role in colonization of the respiratory tract, since *P. aeruginosa* will adhere to tracheal epithelial cells of mice infected with influenza virus but not to normal tracheal epithelium. This has been called opportunistic adherence, and it may be an important step in *Pseudomonas* keratitis and urinary tract infections, as well as infections of the respiratory tract.

The receptor on tracheal epithelial cells for *Pseudomonas* pili is probably sialic acid (N-acetylneuraminic acid). Mucoid strains, which produce an exopolysaccharide (alginate), have an additional or alternative adhesin which attaches to the tracheobronchial mucin (N-acetylglucosamine). Besides pili and the mucoid polysaccharide, there are possibly other cell surface adhesins utilized by *Pseudomonas* to colonize the respiratory epithelium or mucin. Also, it is possible that surface-bound exoenzyme S could serve as an adhesin for glycolipids on respiratory cells.

The mucoid exopolysaccharide produced by *P. aeruginosa* is a repeating polymer of mannuronic and glucuronic acid referred to as alginate. Alginate slime forms the matrix of the *Pseudomonas* biofilm which anchors the cells to their environment and in medical situations, it protects the bacteria from the host defenses such as lymphocytes, phagocytes, the ciliary action of the respiratory tract, antibodies and complement. Biofilm mucoid strains of *Pseudomonas* are also less susceptible to antibiotics than their planktonic counterparts. Mucoid strains of *P. aeruginosa* are most often isolated from patients with cystic fibrosis and they are usually found in lung tissues from such individuals.

Invasion

The ability of *Pseudomonas aeruginosa* to invade tissues depends upon production of extracellular enzymes and toxins that break down physical barriers and damage host cells, as well as resistance to phagocytosis and the host immune defenses. As mentioned above, the bacterial capsule or slime layer effectively protects cells from opsonization by antibodies, complement deposition, and phagocyte engulfment.

Two extracellular proteases have been associated with virulence that exert their activity at the invasive stage: elastase and alkaline protease. Elastase has several activities that relate to virulence. The enzyme cleaves collagen, IgG, IgA, and complement.

It also lyses fibronectin to expose receptors for bacterial attachment on the mucosa of the lung. Elastase disrupts the respiratory epithelium and interferes with ciliary function. Alkaline protease interferes with fibrin formation and will lyse fibrin. Together, elastase and alkaline protease destroy the ground substance of the cornea and other supporting structures composed of fibrin and elastin. Elastase and alkaline protease together are also reported to cause the inactivation of gamma interferon (IFN) and tumor necrosis factor (TNF).

Pseudomonas aeruginosa produces three other soluble proteins involved in invasion: a cytotoxin (mw 25 kDa) and two hemolysins. The cytotoxin is a pore-forming protein. It was originally named leukocidin because of its effect on neutrophils, but it appears to be cytotoxic for most eucaryotic cells. Of the two hemolysins, one is a phospholipase and the other is a lecithinase. They appear to act synergistically to break down lipids and lecithin. The cytotoxin and hemolysins contribute to invasion through their cytotoxic effects on neutrophils, lymphocytes and other eucaryotic cells.

One *Pseudomonas* pigment is probably a determinant of virulence for the pathogen. The blue pigment, pyocyanin, impairs the normal function of human nasal cilia, disrupts the respiratory epithelium, and exerts a proinflammatory effect on phagocytes. A derivative of pyocyanin, pyochelin, is a siderophore that is produced under low-iron conditions to sequester iron from the environment for growth of the pathogen. It could play a role in invasion if it extracts iron from the host to permit bacterial growth in a relatively iron-limited environment. No role in virulence is known for the fluorescent pigments.

Dissemination

Blood stream invasion and dissemination of *Pseudomonas* from local sites of infection is probably mediated by the same cell-associated and extracellular products responsible for the localized disease, although it is not entirely clear how the bacterium produces systemic illness. *P. aeruginosa* is resistant to phagocytosis and the serum bactericidal response due to its mucoid capsule and possibly LPS. The proteases inactivate complement, cleave IgG antibodies, and inactivate IFN, TNF and probably other cytokines. The Lipid A moiety of *Pseudomonas* LPS (endotoxin) mediates the usual pathologic aspects of Gram-negative septicemia, e.g. fever, hypotension, intravascular coagulation, etc. It is also assumed that *Pseudomonas* Exotoxin A exerts some pathologic activity during the dissemination stage (see below).

Toxinogenesis

Pseudomonas aeruginosa produces two extracellular protein toxins, Exoenzyme S and Exotoxin A. Exoenzyme S has the characteristic subunit structure of the A-component of a bacterial toxin, and it has ADP-ribosylating activity (for a variety of eucaryotic proteins) characteristic of many bacterial exotoxins.

Exoenzyme S is produced by bacteria growing in burned tissue and may be detected in the blood before the bacteria are. It has led to the suggestion that exoenzyme S may act to impair the function of phagocytic cells in the bloodstream and internal organs as a preparation for invasion by *P. aeruginosa*.

Exotoxin A has exactly the same mechanism of action as the diphtheria toxin; it causes the ADP ribosylation of eucaryotic elongation factor 2 resulting in inhibition of protein synthesis in the affected cell. Although it is partially-identical to diphtheria toxin, it is antigenically-distinct. It utilizes a different receptor on host cells than diphtheria toxin, but otherwise it enters cells in the same manner and has the exact enzymatic mechanism. The production of Exotoxin A is regulated by exogenous iron, but the details of the regulatory process are distinctly different in *C. diphtheriae* and *P. aeruginosa*.

Exotoxin A appears to mediate both local and systemic disease processes caused by *Pseudomonas aeruginosa*. It has necrotizing activity at the site of bacterial colonization and is thereby thought to contribute to the colonization process. Toxinogenic strains cause a more virulent form of pneumonia than nontoxinogenic strains. In terms of its systemic role in virulence, purified Exotoxin A is highly lethal for animals including primates. Indirect evidence involving the role of exotoxin A in disease is seen in the increased chance of survival in patients with *Pseudomonas* septicemia that is correlated with the titer of anti-exotoxin A antibodies in the serum. Also, tox- mutants show a reduced virulence in some models.

Table 1 (below) is a summary of the virulence determinants of *Pseudomonas aeruginosa*. Table 2 (is a brief description of the diseases caused by *Pseudomonas aeruginosa*.)

Table 1. Summary of the Virulence Determinants of Pathogenic *Pseudomonas aeruginosa*

Adhesins
pili (N-methyl-phenylalanine pili)
polysaccharide capsule (glycocalyx)
alginate slime (biofilm)

Invasins
elastase
alkaline protease
hemolysins (phospholipase and lecithinase)
cytotoxin (leukocidin)
siderophores and siderophore uptake systems
pyocyanin diffusible pigment

Motility/chemotaxis
flagella
Retractile pili

Toxins
Exoenzyme S

Exotoxin A
Lipopolysaccharide

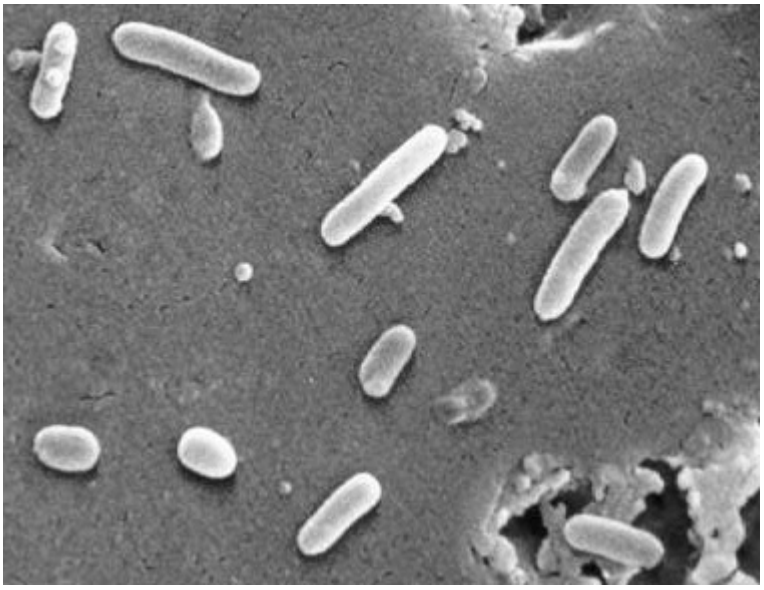
Antiphagocytic surface properties
capsules, slime layers
LPS
Biofilm construction

Defense against serum bactericidal reaction
slime layers, capsules, biofilm
LPS
protease enzymes

Defense against immune responses
capsules, slime layers, biofilm
protease enzymes

Genetic attributes
genetic exchange by transduction and conjugation
inherent (natural) drug resistance
R factors and drug resistance plasmids

Ecological criteria
adaptability to minimal nutritional requirements
metabolic diversity
widespread occurrence in a variety of habitats



Pseudomonas aeruginosa **Scanning electron micrograph. CDC**

Table 2. Diseases caused by *Pseudomonas aeruginosa*

Endocarditis. *Pseudomonas aeruginosa* infects heart valves of IV drug users and prosthetic heart valves. The organism establishes itself on the endocardium by direct invasion from the blood stream.

Respiratory infections. Respiratory infections caused by *Pseudomonas aeruginosa* occur almost exclusively in individuals with a compromised lower respiratory tract or a compromised systemic defense mechanism. Primary pneumonia occurs in patients with chronic lung disease and congestive heart failure. Bacteremic pneumonia commonly occurs in neutropenic cancer patients undergoing chemotherapy. Lower respiratory tract colonization of cystic fibrosis patients by mucoid strains of *Pseudomonas aeruginosa* is common and difficult, if not impossible, to eradicate.

Bacteremia and septicemia. *Pseudomonas aeruginosa* causes bacteremia primarily in immunocompromised patients. Predisposing conditions include hematologic malignancies, immunodeficiency relating to AIDS, neutropenia, diabetes mellitus, and severe burns. Most *Pseudomonas* bacteremia is acquired in hospitals and nursing homes. *Pseudomonas* accounts for about 25 percent of all hospital acquired Gram-negative bacteremias.

Central nervous system infections. *Pseudomonas aeruginosa* causes meningitis and brain abscesses. The organism invades the CNS from a contiguous structure such as the inner ear or paranasal sinus, or is inoculated directly by means of head trauma, surgery or invasive diagnostic procedures, or spreads from a distant site of infection such as the urinary tract.

Ear infections including external otitis. *Pseudomonas aeruginosa* is the predominant bacterial pathogen in some cases of external otitis, including "swimmer's ear". The bacterium is infrequently found in the normal ear, but often inhabits the external auditory canal in association with injury, maceration, inflammation, or simply wet and humid conditions.

Eye infections. *Pseudomonas aeruginosa* can cause devastating infections in the human eye. It is one of the most common causes of bacterial keratitis, and has been isolated as the etiologic agent of neonatal ophthalmia. *Pseudomonas* can colonize the ocular epithelium by means of a fimbrial attachment to sialic acid receptors. If the defenses of the environment are compromised in any way, the bacterium can proliferate rapidly through the production of enzymes such as elastase, alkaline protease and exotoxin A, and cause a rapidly destructive infection that can lead to loss of the entire eye.

Bone and joint infections. *Pseudomonas* infections of bones and joints result from direct inoculation of the bacteria or the hematogenous spread of the bacteria from other primary sites of infection. Blood-borne infections are most often seen in IV drug users and in conjunction with urinary tract or pelvic infections. *Pseudomonas aeruginosa* has a particular tropism for fibrocartilagenous joints of the axial skeleton. *Pseudomonas aeruginosa* causes chronic contiguous osteomyelitis, usually resulting from direct inoculation of bone and is the most common pathogen implicated in osteochondritis after puncture wounds of the foot.

Urinary tract infections. Urinary tract infections (UTI) caused by Pseudomonas aeruginosa are usually hospital-acquired and related to urinary tract catheterization, instrumentation or surgery. *Pseudomonas aeruginosa* is the third leading cause of hospital-acquired UTIs, accounting for about 12 percent of all infections of this type. The bacterium appears to be among the most adherent of common urinary pathogens to the bladder uroepithelium. As in the case of *E. coli*, urinary tract infection can occur via an ascending or descending route. In addition, *Pseudomonas* can invade the bloodstream from the urinary tract, and this is the source of nearly 40 percent of *Pseudomonas* bacteremias.

Gastrointestinal infections. *Pseudomonas aeruginosa* can produce disease in any part of the gastrointestinal tract from the oropharynx to the rectum. As in other forms of *Pseudomonas* disease, those involving the GI tract occur primarily in immunocompromised individuals. The organism has been implicated in perirectal infections, pediatric diarrhea, typical gastroenteritis, and necrotizing enterocolitis. The GI tract is also an important portal of entry in *Pseudomonas* septicemia and bacteremia.

Skin and soft tissue infections, including wound infections, pyoderma and dermatitis. *Pseudomonas aeruginosa* can cause a variety of skin infections, both localized and diffuse. The common predisposing factors are breakdown of the integument which may result from burns, trauma or dermatitis; high moisture conditions such as those found in the ear of swimmers and the toe webs of athletes, hikers and combat troops, in the perineal region and under diapers of infants, and on the skin of whirlpool and hot tub users. Individuals with AIDS are easily infected. *Pseudomonas* has also been implicated in folliculitis and unmanageable forms of acne vulgaris.

Host Defenses

Most strains of *P. aeruginosa*are resistant to killing in serum alone, but the addition of polymorphonuclear leukocytes results in bacterial killing. Killing is most efficient in the presence of type-specific opsonizing antibodies, directed primarily at the antigenic determinants of LPS. This suggests that phagocytosis is an important defense and that opsonizing antibody is the principal functional antibody in protecting from *P. aeruginosa* infections. Once *P. aeruginosa* infection is established, other antibodies, such as antitoxin, may be important in controlling disease.

The observation that patients with diminished antibody responses (caused by underlying disease or associated therapy) have more frequent and more serious *P. aeruginosa* infections underscores the importance of antibody-mediated immunity in controlling *Pseudomonas* infections. unfortunately, cystic fibrosis is the exception. Most cystic fibrosis patients have high levels of circulating antibodies to bacterial antigens, but are unable to clear *P. aeruginosa* efficiently from their lungs. Cell-mediated immunity does not seem to play a major role in resistance or defense against *Pseudomonas* infections.

Epidemiology and Control of *Pseudomonas aeruginosa* Infections

Pseudomonas aeruginosa is a common inhabitant of soil, water, and vegetation. It is found on the skin of some healthy persons and has been isolated from the throat (5 percent) and stool (3 percent) of nonhospitalized patients. In some studies, gastrointestinal carriage rates increased in hospitalized patients to 20 percent within 72 hours of admission.

Within the hospital, *P. aeruginosa* finds numerous reservoirs: disinfectants, respiratory equipment, food, sinks, taps, toilets, showers and mops. Furthermore, it is constantly reintroduced into the hospital environment on fruits, plants, vegetables, as well by visitors and patients transferred from other facilities. Spread occurs from patient to patient on the hands of hospital personnel, by direct patient contact with contaminated reservoirs, and by the ingestion of contaminated foods and water.

The spread of *P. aeruginosa* can best be controlled by observing proper isolation procedures, aseptic technique, and careful cleaning and monitoring of respirators, catheters, and other instruments. Topical therapy of burn wounds with antibacterial agents such as silver sulfadiazine, coupled with surgical debridement, dramatically reduces the incidence of *P. aeruginosa* sepsis in burn patients.

Pseudomonas aeruginosa is frequently resistant to many commonly used antibiotics. Although many strains are susceptible to gentamicin, tobramycin, colistin, and fluoroquinolins, resistant forms have developed. The combination of gentamicin and carbenicillin is frequently used to treat severe *Pseudomonas* infections. Several types of vaccines are being tested, but none is currently available for general use.

Glossary

A

ABSORB/ABSORPTION: The passage of substances into or across tissues, such as the passage of food and water from the intestines into the bloodstream. Because of a lack of digestive enzymes, some foods eaten by people with CF may not be well absorbed and used by the body (see DIGESTIVE SYSTEM, ENZYMES, PANCREAS, INTESTINE and MALABSORPTION).

ADVERSE REACTION: Unwanted side effect resulting from a drug or mixture of drugs. It may appear quickly or over time (see SIDE EFFECTS).

AIRWAYS: Tubes that bring outside air into the lungs. The lungs have many airways of varied sizes. The largest is the trachea between the throat and the lungs. It branches into smaller airways in the lungs called bronchi. These divide into still smaller branches called bronchioles. These turn into alveoli, the very smallest airways.

AMINOGLYCOSIDES: A group of antibiotics used to treat bacterial infections. Tobramycin and gentamicin are examples of aminoglycosides used in CF treatment (see ANTIBIOTIC and BACTERIA).

ANTIBIOTIC: A drug that kills bacteria or slows bacterial growth. Antibiotics are often used to treat lung infections (see AMINOGLYCOSIDES, BACTERIA and CEPHALOSPORINS).

ANTI-INFLAMMATORY AGENT: Medication to reduce inflammation or irritation of body tissue. Ibuprofen is an example of an anti-inflammatory agent used in CF treatment.

ANTIBODY: molecule in the body that combines with a foreign bacteria or virus to stop its activity or signal other molecules in the body to become active in fighting the foreign germ.

ANTIMICROBIAL: Can stop the growth of disease-causing germs.

APPROVED DRUG: In the United States, only drugs approved by the Food and Drug Administration (FDA) can be sold. The approval process involves several steps, including pre-clinical laboratory and animal studies, clinical trials for safety and effectiveness, filing a New Drug Application by the drug manufacturer, FDA review and approval of the application (see FOOD AND DRUG ADMINISTRATION).

ARM: Any of the treatment groups in a randomized trial. Most randomized trials have two arms, but some have three or more (see RANDOMIZED TRIAL).

ASSAY: A way to measure how many parts of a certain ingredient are in a larger system, object or mixture.

AUTOSOMAL RECESSIVE: A genetic trait or disorder that appears only when a person inherits a pair of chromosomes, each of which has the gene for the trait. One chromosome of the pair comes from the father and the other from the mother. Autosomal recessive disorders occur only if each parent is either a carrier of the trait or has the trait. CF is an autosomal recessive disease (see CARRIER and GENE).

B

BACTERIA: Tiny one-celled creatures that are often the cause of infections. People with CF are prone to bacterial lung infections (often caused by the bacteria Staphylococcus aureus and Pseudomonas aeruginosa). Some bacteria normally found in the body are helpful. For example, Escherichia coli live in the intestines and help with digestion (see ANTIBIOTIC, INTESTINE, ***PSEUDOMONAS AERUGINOSA*** and STAPHYLOCOCCUS AUREUS).

BALANCED STUDY: When a particular type of participant (for instance, females, people with certain lung function levels, African Americans, etc.) is equally represented in each study group.

BIAS: A point of view that impairs fair judgment. In clinical trials, bias is controlled by blinding and randomization (see BLIND TRIAL and RANDOMIZATION).

BIOFILM: A substance that sticks to wet surfaces. Biofilms can form on solid or liquid surfaces as well as on soft tissue in living organisms. They are usually difficult to dissolve. In CF, a biofilm, or protective coating, is formed by *Pseudomonas aeruginosa* bacteria and prevents drugs from killing the bacteria.

BIOMARKERS: A biochemical or a substance in the body that can be used to measure disease activity or effects of treatment.

BLIND TRIAL: A clinical trial in which participants are unaware whether they are taking the experimental drug, placebo or standard treatment. (see SINGLE BLIND TRIAL and DOUBLE BLIND TRIAL).

BMI (Body Mass Index): A measurement comparing fat to muscle in the human body. Weight in kilograms is divided by height in meters to figure out the degree of nutritional health, such as determining malnutrition or obesity.

BRONCHO-ALVEOLAR FLUID: Fluid found in the bronchiole and alveoli part of the lungs.

BRONCHO-ALVEOLAR LAVAGE: A diagnostic test where fluid is taken from the bronchioles and alveoli part of the lungs.

BRONCHOSCOPY: A procedure using a small tube (bronchoscope) to look down the throat and inside the lungs.

BURKHOLDERIA CEPACIA COMPLEX: Bacteria that can live in the lungs of people with CF and cause infection. This bacterium is resistant to antibiotics and easily spread between people with CF, and can cause life-threatening lung infections.

C

CADAVERIC: Having to do with a dead body (a cadaver).

CARRIER: A person having a single gene for a genetic trait or disorder like CF. Carriers show no signs of the disease. In CF, each parent of a child with CF either has CF or is a CF carrier (see GENE and HEREDITARY).

CELL: The basic unit of living organisms.

CEPHALOSPORINS: A group of antibiotics used to treat bacterial infections (see ANTIBIOTIC and BACTERIA).

CFTR: see CYSTIC FIBROSIS CONDUCTANCE TRANSMEMBRANE REGULATOR

CHROMOSOME: The thread-like material that carriers genes, the units of heredity. Chromosomes are in the nucleus of every living cell. Every person should have 23 pairs of chromosomes in each cell.

CHRONIC: A disease or condition that lasts and is continuous. CF is a chronic disease.

CLINICAL: Related to the study and treatment of people in a medical setting or clinic.

CLINICAL ASSESSMENT: An evaluation of the symptoms and progression of a disease.

CLINICAL INVESTIGATOR: A medical researcher, most often a medical doctor, responsible for carrying out a clinical research protocol (see PROTOCOL and PRINCIPAL INVESTIGATOR).

CLINICAL STUDY: A type of research—also called observational research—in which participants are observed. While these studies do not use drugs or treatments, they are very important for developing new ideas about how diseases or progression of disease could be prevented or treated.

CLINICAL TRIAL: A type of research—also called interventional research—that follows certain government guidelines for testing the effect of drugs on people. Researchers observe how the drug affects the body under highly controlled conditions and whether the treatment is helpful.

CLINICALLY STABLE: When symptoms are not changing or progressing and, for the time being, are not expected to.

COMPASSIONATE USE: When experimental drugs are provided to people before final FDA approval. Typically used only with individuals who may receive benefit but have no other treatment options and cannot enroll in a clinical trial.

COMPLEX DOSAGE REQUIREMENTS: When clinical trial participants are required to take an experimental drug or treatment several times a day or to take a combination of drugs and treatments.

COMPUTED TOMOGRAPHY (CT scan): A three-dimensional image or picture of the body showing three measurements, such as height, width and depth. Created by a computer from a series of cross-sectional pictures.

CONDENSATE: Something that has turned into liquid, such as a liquid reduced from a gas or vapor, like water from steam.

CONFIDENTIALITY: The FDA and medical ethics require that the identities and medical information of all clinical trial participants be kept confidential. When a person joins a clinical trial, they must agree to share their medical records with researchers. The Principal Investigator must guarantee these records remain confidential (see FDA and PRINCIPAL INVESTIGATOR).

CONTRAINDICATED: Used to describe when certain medicines or treatments should not be used.

CONTROL GROUP: In many clinical trials, one group of patients receives the experimental drug or treatment, while the control group receives either a standard treatment or placebo (see PLACEBO and STANDARD TREATMENT).

CONVENTIONAL: Following what is traditional or customary. Not new or experimental.

CULTURE: Sputum or throat swab is put on a medium for germs to grow in the laboratory, so the germ can be identified.

CYSTIC FIBROSIS CONDUCTANCE TRANSMEMBRANE REGULATOR (CFTR): A protein in the cell that makes the channel where chloride moves in and out. The defect in the channel causes CF.

CYSTIC FIBROSIS-RELATED DIABETES (CFRD): The body's inability to move sugar from the blood into the cells for energy. A special form of diabetes found in people with CF.

D

DATA SAFETY MONITORING BOARD (DSMB): An independent committee of clinical research experts and community representatives that reviews ongoing information from a clinical trial. The committee's job is to watch for safety issues and ensure participants are not exposed to unnecessary risk. The DSMB can recommend that a trial be stopped.

DEFICIENCY: A lack of something necessary to good health. An insufficiency. Example: a Vitamin D deficiency in people with CF.

DETECT: To discover the existence, presence, or fact of. To uncover something that has been hidden or is not as it should be.

DETERIORATION: The process of becoming worse. Example: when someone's health deteriorates.

DIAGNOSE: To find the cause of health problems.

DIGESTION: The process of breaking down the food we eat and absorbing its nutrients into the body for energy (see ABSORPTION).

DIGESTIVE SYSTEM: The organs that take in, digest and get rid of food. Includes the mouth, salivary glands, pharynx (throat), esophagus, stomach, intestines, liver, pancreas, colon, rectum and anus. In CF, thick mucus blocks some passages in the digestive system, like that between the pancreas and intestines.

DOSAGE: The prescribed amount of a drug that must be taken to get the benefit or intended result.

DOUBLE BLIND TRIAL: A clinical trial in which neither the participants nor the staff knows which patients are receiving the experimental drug and which are receiving a placebo or standard therapy. Double blind trials are thought to be more objective because expectations of the physician and the participants don't affect the outcomes (see BLIND TRIAL, SINGLE BLIND TRIAL and PLACEBO).

DRUG-DRUG INTERACTION: Changes in the effect of a drug when taken with another drug. The effect may be an increase or a decrease in the action of either drug, or it may be an adverse effect normally not associated with either drug (see ADVERSE REACTION).

DSMB: See DATA SAFETY MONITORING BOARD.

DUCT: A tube or passageway for secretions. Ducts are found in organs, such as the pancreas, organ systems and exocrine glands. In CF, thick mucus can block these ducts (see SECRETION).

E

EFFICACY: The ability of a drug to produce a desired effect. A drug will pass efficacy trials if it is effective at the dose tested against the illness for which it was prescribed.

ELIGIBILITY CRITERIA: Reasons for selection of participants to be excluded from a clinical trial (see INCLUSION/EXCLUSION CRITERIA).

ENERGY INTAKE: Energy helps cells perform all of their functions, including building proteins and other substances the body may require. Energy intake is based on food that is eaten.

ENROLL: Joining a clinical trial, after meeting all necessary criteria and signing the Informed Consent Form (see INCLUSION/EXCLUSION CRITERIA and INFORMED CONSENT DOCUMENT).

ENZYMES: Proteins that help make and increase certain chemical processes in the body, like the breaking down of foods in digestion. Because people with CF have mucus that often blocks

the passageways (or ducts) through which digestive enzymes from the pancreas flow, they may need enzyme replacements to digest food (see ABSORPTION, DIGESTIVE SYSTEM, MUCUS and PANCREAS).

ESOPHAGUS: The tube that leads from the throat (pharynx) to the stomach.

EXACERBATION: Signs and symptoms that show a need for treatment.

EXCLUSION/INCLUSION CRITERIA: Standards used to decide whether a person may or may not enroll in a clinical trial. Criteria are based on such factors as age, gender, disease, previous treatment history, and other medical conditions. These criteria are not used to keep people out of clinical trials, but rather to identify the right participants and keep them safe in a trial.

EXPANDED ACCESS: Refers to any of the FDA procedures for distributing experimental drugs to patients who are no longer benefiting from currently available treatments and unable to participate in ongoing clinical trials (see COMPASSIONATE USE, PARALLEL TRACK and TREATMENT IND).

EXPERIMENTAL DRUG: A drug not licensed by the FDA for use in humans (see OFF-LABEL USE).

F

FDA: See FOOD AND DRUG ADMINISTRATION.

FAILURE TO THRIVE: Not gaining weight or growing at a normal rate.

FOOD AND DRUG ADMINISTRATION (FDA): The agency of the U.S. Department of Health and Human Services (DHHS) responsible for monitoring the safety and effectiveness of all drugs, biologics, vaccines and medical devices, including those used in the diagnosis, treatment and prevention of CF and other diseases (see http://www.fda.gov/).

FORMULATION: A prescribed recipe for making a drug.

G

GASTROESOPHAGEAL REFLUX DISEASE (GERD): a condition in which food or liquid travels backwards from the stomach to the esophagus (the tube from the mouth to the stomach). This action can irritate the esophagus, causing heartburn and other symptoms.

GENE: The main unit of heredity. Each chromosome carries hundreds of genes. Genes decide body traits like eye and hair color, height, facial features and many health problems. CF is caused by an alteration of a gene. A child inherits CF when two CF genes are received, one from each parent (see AUTOSOMAL RECESSIVE, CARRIER and HEREDITARY).

GENETIC: Hereditary or inherited. Material that is passed on from parents to children (see GENE).

GLAND: A group of cells that make substances so that other parts of the body can work. The pancreas is a gland that makes enzymes so food can be broken down and absorbed by the body.

GLUCOSE: A sugar.

GOOD CLINICAL PRACTICE (GCP): The standard for clinical trial design, conduct, performance, monitoring, auditing, recording, analyzing and reporting. GCP ensures that reported results will be credible and accurate, and that the rights, integrity and confidentiality of patients are protected.

H

HEREDITARY: Traits or conditions, like eye color or CF, that are genetically passed from parents to their children (see GENE and GENETIC).

HIGH-RESOLUTION COMPUTER TOMOGRAPHY (CT scan): A three-dimensional image or picture of the body. Created by a computer from a series of cross-sectional pictures with edge-defining qualities to sharpen the image, sometimes with a closer view of a smaller area. A close-up CT scan. Used often to create images of a person's lungs (see COMPUTED TOMOGRAPHY).

HORMONE: Secretion from glands. Hormones regulate body functions like growth and heart rate.

HYPERGLYCEMIA: Higher than normal blood glucose or blood sugar in the bloodstream.

HYPOTHESIS: Theory or assumption used as a guide in clinical research.

I

IND: See INVESTIGATIONAL NEW DRUG.

IRB: See INSTITUTIONAL REVIEW BOARD.

IMMUNE: Resistant to infection by a specific germ.

IMPAIRED GLUCOSE TOLERANCE: A fasting blood sugar of 100 to 125 mg/dL and /or a blood sugar of 140 to 199 mg/dL 2 hours after an oral glucose load during an oral glucose tolerance test (OGTT).

INACTIVE (Inert): Having no effect.

INCLUSION/EXCLUSION CRITERIA: Standards used to decide whether a person may or may not enroll in a clinical trial. Criteria are based on such factors as age, gender, disease, previous treatment history, and other medical conditions. These criteria are not used to keep people out of clinical trials, but rather to identify the right participants and keep them safe in a trial.

INDICATION: Something that points to or suggests the proper treatment of a disease, as required by the cause or symptoms. Like a tip-off, or clue, that certain action is required.

INDUCTANCE PLETHYSMOGRAPHY: A machine to measure lung volume and lung health in people ages 6 years of age and older. Sometimes called a “body box.”

INFLAMMATION: The swelling of body tissues due to irritation or injury. Inflammation occurs with an infection.

INFORMED CONSENT: The process of learning about a clinical study or trial before deciding whether to join. Doctors and nurses involved in the trial fully explain the study and answer any questions. The goal is to have people participate who are informed about the study or trial.

INFORMED CONSENT DOCUMENT: A document that describes the rights of clinical research participants and details about the study or trial. It includes the study’s purpose, length, required procedures, and staff contact information. It also explains any risks and potential benefits. The patient should ask the study staff any questions before signing.

INHALE: To breathe in.

INHERITED: Traits or conditions, like eye color or CF, that are genetically passed from parents to their children (see GENE and GENETIC).

IN-PATIENT (IN-PATIENT STUDY/TRIAL): Hospitalized patient. Study or trial that requires time in a hospital.

INSTITUTIONAL REVIEW BOARD (IRB): Committee of research and disease experts, and community advocates working to ensure that a clinical trial is fair and ethical, and that the rights of all participants are protected. All clinical trials in the United States must be approved by an IRB before they can begin. This group approves the initial research and reviews the research as it progresses to help protect the rights and safety of participants. The IRB also must approve all materials prepared for participants, including the informed consent document, promotional posters, flyers, brochures, Web sites, and other items.

INTERVENTIONS: Approach to treating a disease or condition. Intervention is a word frequently used to describe a treatment or therapy.

INTESTINE: Tube in the digestive system that connects the stomach to the anus. The long, narrow, upper part is the small intestine. The short, wide, lower part is the large intestine. Also called the bowel.

INTRAMUSCULAR: In the muscle. Example: a "shot" or intramuscular injection.

INTRAVENOUS (IV): Putting a medicine right into a blood vessel, usually a vein, using a thin needle and a tube.

INVESTIGATIONAL NEW DRUG (IND): An experimental drug that is approved by the FDA for use in clinical trials.

INVESTIGATIONAL TREATMENT: An unapproved treatment, or a treatment used for a new purpose in clinical research. This is usually a drug.

IN VITRO: Latin for "in glass." Usually refers to research in a laboratory, outside the body.

IN VIVO: Latin for "in living (body)." Usually refers to research done in living animals and humans.

L

LIVING DONOR: A living person who donates a body part for transplantation into another person. Many different types of organs can come from living donors, like a kidney, or a lobe of a lung or liver.

LIVING SYSTEMS: Human, animal, or cell environments used for experimental purposes in clinical trials (see IN VITRO and IN VIVO).

LOBAR: A well-defined part of an organ or gland. The lungs have several distinct lobes.

LUPUS: Any of several diseases, which first affect the skin and joints, but often involve other parts of the body.

M

MACROLIDES: A group of antibiotics used to treat lung infections, including azithromycin and erythromycin.

MALABSORPTION: Poor uptake of nutrients from food for use by the body. In CF, mucus may plug ducts of digestive organs and block the secretion of enzymes and hormones. This makes many nutrients unavailable for use in body maintenance and growth (see ABSORPTION, DIGESTION, DIGESTIVE SYSTEM, DUCT, ENZYME, FAILURE TO THRIVE, HORMONE, MUCUS, ORGAN, PANCREAS and SECRETION).

MARKERS: A substance in the body that, when present in large or abnormal amounts, suggests the presence of disease. Also called a biomarker.

MICROBIOLOGY: The branch of biology that deals with microorganisms and their effects on other living organisms. The study of microscopic forms of life (such as bacteria, viruses, and fungi).

MICROORGANISMS: A form of life that can be seen under a microscope. Germs are microorganisms.

MODELS: Represents a living system and used in research.

MUCOCILIARY CLEARANCE: In the airways of the lungs, this system works to move mucus and particles breathed in to upper airways so they can be coughed out of the lungs.

MUCOID: Resembling mucus; forming large moist sticky colonies of bacteria.

MUCOSAL: A fluid made by mucous membranes and glands. Normally thin and slippery. In CF, mucus is thick and sticky.

MUCUS: A fluid made by membranes and glands. Mucus is normally thin and slippery. In CF, the mucus is often thick and sticky (see GLAND, MUCUS MEMBRANE, PHLEGM and SPUTUM).

MUCUS MEMBRANE: Tissue that contains mucus-making glands. Mucus membranes are found in the nose, mouth, lungs, esophagus, stomach, and intestines (see ESOPHAGUS, GLAND, INTESTINE, MUCUS and TISSUE).

MULTI-CENTER: More than one medical or research institution, such as a multi-center clinical study.

MUTATION: A change in a gene (see AUTOSOMAL RECESSIVE, CARRIER, CHROMOSOME, GENE, GENETIC, HEREDITARY and INHERITED).

N

NSAIDS: Non Steroidal Anti-Inflammatory Drugs, such as ibuprofen and aspirin (see ANTI-INFLAMMATORY AGENT).

NATIONAL INSTITUTES OF HEALTH (NIH): The agency of the U.S. Department of Health and Human Services (DHHS) responsible for health and medical research. NIH conducts research in its own laboratories and funds billions of dollars in research at other facilities, including universities, in the United States and abroad.

NEUTROPHIL: A white blood cell that destroys foreign bacteria in the body.

NEW DRUG APPLICATION (NDA): An application for a new drug submitted to the FDA to review and approve an experimental drug. The application is submitted after the completion of clinical trials and before a drug can be available to the general public.

NONINVASIVE: Not penetrating the body, as by incision. Used to describe a diagnostic procedure that does not invade healthy tissue.

NOVEL TECHNIQUE: A newly used skill or procedure.

O

OFF-LABEL USE: When a drug is prescribed for conditions other than those approved by the FDA.

OPEN-LABEL TRIAL: A clinical trial where all parties, including physicians and participants, know if they are using an investigational drug. Also when all participants get to receive the investigational drug once its safety and effectiveness have been established and before the FDA approves it.

ORAL: Taken by mouth.

ORAL GLUCOSE TOLERANCE TEST (OGTT): This test is used to diagnose not just diabetes and CFRD but also the varied types of abnormal glucose tolerance in CF. You must first fast (nothing to eat or drink) for 12 hours. Then, blood is drawn to measure your "baseline" or "fasting" glucose level. You are then asked to drink glucose. Your blood sugar is measured again 2 hours later. Often, blood sugar is measured at 1, 2, and 3 hours later.

ORGAN: A part of the body that performs a specific function or group of functions. Some common organs are the heart, lungs, and brain. A group of related organs is an organ system, such as the digestive system.

ORGANISM: A form of life, such as a plant, animal, bacterium (single bacteria) or fungus.

ORPHAN DRUGS: An FDA category of medications used to treat rare diseases and conditions which affect fewer than 200,000 people. Orphan drug status gives a drug manufacturer a greater financial incentive to develop and provide such drugs. CF is an orphan disease.

OSCILLOMETRY: Measurement of changes, used in studying cardiovascular and respiratory functions.

OUTCOME: Overall results of a study or trial offered up for evaluation. Also called an endpoint.

OXIDANT: A substance that oxidizes another substance.

OXIDIZES: To combine with oxygen.

P

PFTs: See PULMONARY FUNCTION TESTS.

PANCREAS: A long organ with glands found behind the stomach. The pancreas secretes enzymes through ducts into the intestine to break down food. In CF, mucus may obstruct the pancreatic ducts, preventing digestion. Another part of the pancreas has endocrine tissue, which makes a hormone called insulin. Insulin controls storage and use of sugar (see ENZYMES and MUCUS).

PANCREATIC INSUFFICIENCY (PI): The failure to properly digest food due to a lack of digestive enzymes made by the pancreas.

PARALLEL TRACK TRIAL: A system of making experimental drugs available to individuals who are unable to participate in clinical trials.

PARAMETER: Used to measure the quantity or function of something. Example: FEV_1 is a measurement, or parameter, for lung function.

PEER REVIEW: Careful review of a clinical trial by experts who consider its scientific merit, participant safety and ethics.

PHARMACOKINETICS: The processes (in a living organism) of absorption, distribution, metabolism, and excretion of a drug or vaccine.

PHASE 1 TRIALS: First step in drug development to test a drug's safety and to find out how the human body reacts to the drug. The purpose of Phase 1 trials is to discover the side effects of

increased doses and collect early evidence of drug effectiveness. Healthy volunteers or people who do not have the disease or condition being studied, are often included.

PHASE 2 TRIALS: Research that tests the effectiveness and safety of a new drug. Identifies common side effects and risks.

PHASE 3 TRIALS: Usually the last type of clinical trial before a drug is approved by the FDA. Intended to gather more information about 1) the general risk-benefit of the drug, and 2) how to administer the drug (see RISK-BENEFIT).

PHASE 4 TRIALS: Research conducted after FDA approval to get additional information about the drug's long-term risks, benefits, and best possible use.

PHLEGM: Mucus made from glands in the airways of the lung.

PLACEBO: A pharmaceutical preparation that contains no active substance (a sugar pill), and looks like the drug that is being tested.

PLACEBO CONTROLLED: A drug is studied by giving an inactive substance (a placebo) to one group of participants, while the drug being tested is given to another.

PLACEBO EFFECT: A change that occurs after a person takes a placebo.

PNEUMONIA: An inflammation of the lungs often caused by a bacterial or viral infection. Pneumonia is a problem in people with CF.

POLYMERASE CHAIN REACTION (PCR): A laboratory technique for quickly fusing large amounts of DNA together from a single DNA segment.

PORCINE: Of or derived from pigs.

PRECLINICAL: Testing of experimental drugs in the test tube or in animals. Occurs before clinical trials in humans are done.

PREVENTION TRIALS or STUDIES: Research to find better ways to prevent disease in people who have never had the disease or prevent disease from returning.

PRINCIPAL INVESTIGATOR (PI): Person responsible for the conduct of the clinical trial at a research site.

PROCEDURE: Something done to fix a health problem or learn more about it. For example, surgery, tests and putting in an IV (intravenous line) are procedures.

PROTEIN: Proteins are a basic part of all living cells. Found in foods such as meat, proteins are essential in the diet for growth and repair of tissue.

PROTOCOL: A detailed plan for a clinical trial. It describes what types of people may participate in the trial; the schedule of tests, procedures, medications and dosages; and the length of the study.

PSEUDOMONAS AERUGINOSA: A type of bacteria that often lives in the lungs of people with CF and causes lung infections (see ANTIBIOTIC, BACTERIA and STAPHYLOCOCCUS AUREUS).

PULMONARY: Relating to the lungs.

PULMONARY FUNCTION TESTS (PFTs): Tests to check lung function. Along with the patient's history and physical exam, PFTs help doctors diagnose a health problem, and decide what therapy to prescribe. They can be used with children five years and older. PFTs measure air flow and lung volumes.

Q

QUALITY OF LIFE: A concept that considers a person's physical, mental, and emotional health, level of independence, social relationships, personal beliefs and relationship to their environment.

R

RANDOMIZATION: Commonly used to assign clinical trial participants to a treatment arm, based on chance (see ARM).

RANDOMIZED TRIAL: Participants are assigned by chance to one of two or more treatment arms of a clinical trial (see ARM).

RECRUITMENT: Act of enrolling people in a clinical trial.

RECRUITMENT PERIOD: Time frame allowed to recruit for a clinical trial.

REPRODUCIBLE: To make a counterpart, image, or copy. To produce again or anew. To re-create. In clinical research, it refers to the ability of one study to recreate the results of a different study, thereby showing that the results are valid.

RESEARCH:

Applied Research
Studies that apply basic research findings to problems like diseases and symptoms. Examples:

creating new respiratory equipment or studying cell defects in the sweat glands of people with CF (see CELL and GLAND).

Basic Science Research
Studies that increase knowledge of basic life processes. To learn the causes of CF, scientists do basic science studies like gene studies and research on how cells work (see CELL, GENE and GENETIC).

Clinical Research
Studies in people that improve diagnosis and treatment. Examples: studies on drugs, lung function, nutrition, and sweating. (see DIAGNOSE, PULMONARY FUNCTION TESTS and SWEAT TEST).

RESEARCH COORDINATOR: A staff person chosen by the principal investigator to assist him/her in conducting the clinical trial (see PRINCIPAL INVESTIGATOR).

RESISTANCE: The ability of an organism to defend itself, either from disease or from being harmed. Example: bacteria can become resistant to antibiotics and no longer be killed by the drugs.

RISK-BENEFIT RATIO: The known risk of participating in a clinical trial weighed against the potential benefits.

S

SAFETY: The condition or state of being safe. In clinical trials, this refers to an absence of harmful side effects resulting from use of the product and may be assessed by special tests and procedures, psychiatric evaluation, and/or physical examination of participants.

SAFETY PROFILE: A summary of clinical data that explains the possible side effects of a certain drug or treatment.

SCREENING: Identifying a potential clinical trial participant by finding out if the person meets the eligibility criteria (see ELIGIBILITY CRITERIA).

SCREENING STUDIES: Refers to studies that test how to identify diseases or conditions.

SECRETION: A product of a gland, like sweat or saliva (see GLAND).

SENSITIVE: Responsive to a stimulus. Easily irritated or inflamed.

SIDE EFFECTS: Any unexpected results from taking an investigational drug or treatment (see ADVERSE REACTION).

SINGLE BLIND TRIAL: A trial where either the investigator or participant is unaware of which treatment arm the participant is assigned to (see BLIND TRIAL, DOUBLE BLIND TRIAL and ARM).

SPACER DEVICE: A hollow chamber that fits on the mouthpiece of a metered dose inhaler. It makes the inhaler easier to use and more efficient in delivering medicine.

SPIROMETER: A device that measures air flow and lung volumes (see PULMONARY FUNCTION TESTS).

SPONSOR: Individual, company, institution or organization responsible for initiation, management and financing of a study.

SPUTUM: Mucus or phlegm coughed up from lungs (see MUCUS and PHLEGM).

SPUTUM CULTURE: A test to see what germs may be growing in the sputum (see SPUTUM).

SPUTUM DENSITY: A measurement of mucus or phlegm coughed up from lungs.

STANDARD TREATMENT: An effective treatment or drug approved by the FDA for a specific disease or condition.

STANDARD OF CARE: Treatment or medical management based on state-of-the-art health care (see STANDARD TREATMENT).

STAPHYLOCOCCUS AUREUS (STAPH): A type of bacteria that can cause infections. In CF, "staph" often causes lung infections. It is treated with antibiotics (see ANTIBIOTIC and BACTERIA).

STATISTICAL SIGNIFICANCE: The probability that an event or change did or did not occur by chance.

STUDY ENDPOINT: Results from a clinical trial used to judge the effectiveness of a drug treatment (see OUTCOME).

SUB-STUDY: A smaller study that is part of a larger study.

SURFACTANT: A chemical that can reduce the surface tension of a liquid in which it is dissolved so that it spreads out more easily.

SUSCEPTIBILITY: Being prone to, sensitive to, or lacking the ability to resist something.

SWEAT TEST: A test to diagnose CF. Measures the salt (sodium and chloride) in sweat.

SYSTEMIC: Affecting the body as a whole.

T

THERAPEUTIC: Refers to a substance that has a healing effect on a specific condition.

TISSUE: A group of cells of a similar type and function.

TOLERABILITY: Ability to tolerate, put up with, or endure.

TOLERABLE DOSAGE: Highest recommended amount of a substance that does not have adverse results (see ADVERSE REACTION and SIDE EFFECTS).

TOXICITY: The degree to which a drug is harmful or poisonous. A drug's toxicity will vary depending on amount and use.

TREATMENT IND: IND stands for Investigational New Drug, and is part of the FDA's approval process to market a new prescription drug. This process makes promising investigational drugs available to patients outside of clinical trials early in the drug development process, before the FDA approves it as a new drug.

TREATMENT TRIALS: Refers to trials that test new drugs, new combinations of drugs, or new approaches to standard medical treatments.

TRIGGER: A device used to release or activate a mechanism. An event that causes other events to happen.

U

UNDUE OR UNNECESSARY RISK: IRBs review clinical trial protocols to ensure participants are not required to do anything that would be harmful to their health (see INSTITUTIONAL REVIEW BOARDS).

V

VALIDATE: To confirm or make true. To give official sanction or approval. In clinical trials, it is the process by which the correctness of data are established.

VIRUS: An organism, smaller than bacteria, that causes infections like influenza, viral pneumonia, colds, and hepatitis (see BACTERIA and PNEUMONIA).

W

WASHOUT PERIOD: A time during a clinical trial when participants receive no drugs for the study so the effects of previous study drugs are removed.

WITHDRAW: The point at which a clinical trial participant, for any reason, stops participating in the trial.

Glossary for Pneumonia caused by serotype O11 Pseudomonas Aeruginosa

Abdominal pain: A condition which is characterized by the sensation of pain that is located in the abdomen

Anxiety: A feeling of apprehension, and fear without apparent stimulus that is associated sometime with somatic responses

Blue skin: Blueness of the skin

Chest pain: Pain in the chest area.

Chills: Excessive feeling of coldness.

Clammy skin: Moist, cool and pale skin.

Confusion: Mental confusion and impaired thinking.

Fatigue: Excessive tiredness or weakness.

Fever: Elevation of the body temperature above the normal 37 degrees celsius

Poor appetite: Loss or reduction in appetite for food

Productive cough: The noise produced from the sudden expulsion of air from the lungs

Rapid breathing: Excessively rapid breathing

Rapid heart beat: Excessively fast heart beat (fast pulse) called "tachycardia"

Stress: Emotional stress (sometimes refers to physical stress)

Sweating: Sweating more than normal

Exam

Select the ***best*** answer to each of the following items. Mark your responses on the Answer Form.

1. *Pseudomonas* is a gram-negative rod that belongs to the family Pseudomonadaceae. More than half of all clinical isolates produce the blue-green pigment pyocyanin. *Pseudomonas* often has a characteristic _____.

a. grainy texture
b. sour odor
c. sweet odor
d. orange color

2. *Pseudomonas aeruginosa* has become an important _____, especially in patients with compromised host defense mechanisms.

a. viral disease
b. immune deficiency
c. cause of hospitalization
d. cause of infection

3. The 3 stages of *Pseudomonas*, according to Pollack (2000), are (1) bacterial attachment and colonization, (2) local infection, and (3) bloodstream dissemination and systemic disease. The importance of colonization and adherence is most evident when studied in the context of respiratory tract infection in patients with cystic fibrosis and in those that _____.

a. have a long history of smoking
b. complicate mechanical ventilation
c. are COPD patients
d. are younger patients

4. According to the Centers for Disease Control and Prevention (CDC), the overall prevalence of *P aeruginosa* infections in US hospitals is approximately _____ per 1000 discharges.

a. 2
b. 4
c. 8
d. 12

5. All infections caused by *P aeruginosa* are treatable and potentially curable. Acute fulminant infections, such as bacteremic pneumonia, sepsis, burn wound infections, and meningitis, are associated with _____.

a. immune deficient patients
b. elderly patients
c. extremely high mortality rates
d. females more often than males

6. The incidence of pseudomonal pneumonia in patients with cystic fibrosis has shown a shift towards patients who are _____.

a. younger than 26 years
b. older than 26 years
c. in their mid-50's
d. older than 65 years of age

7. *P aeruginosa* is also the fourth most commonly isolated nosocomial pathogen, accounting for _____% of all hospital-acquired infections.

a. 5
b. 10.1
c. 15.6
d. 21.5

8. Chronic infection of the lower respiratory tract with *P aeruginosa* is prevalent among patients with cystic fibrosis. These patients may present with _____.

a. chronic productive cough
b. anorexia
c. wheezing
d. All of the above

9. Pseudomonal infections can affect every portion of the GI tract. The disease is often underestimated but usually affects very young children and adults with hematologic malignancies and chemotherapy-induced neutropenia. Additionally, colonization of the GI tract is an important portal of entry for pseudomonal bacteremia in patients who are _____. The spectrum of disease can range from very mild symptoms to severe necrotizing enterocolitis with significant morbidity and mortality.

a. immuno-comprised
b. neutropenic
c. sleep-deprived
d. IV drug users

10. *P aeruginosa* endocarditis in individuals who abuse intravenous drugs is observed mainly among young black males.

a. True
b. False

11. *Pseudomonas* also has emerged as an important source of burn wound sepsis. Invasive burn wound sepsis is defined as the bacterial proliferation of _____organisms per gram of tissue, with subjacent involvement of subjacent unburned tissue.

a. 10,000
b. 76,000
c. 100,000
d. 300,000

12. Ecthyma gangrenosum lesions are hemorrhagic and necrotic, with surrounding erythema. These characteristic lesions are almost always caused by *Pseudomonas* infection and usually are found in the _____.

a. axilla
b. groin
c. perianal area
d. may involve any part of body

13. *Pseudomonas aeruginosa* is member of the Gamma Proteobacteria class of Bacteria. Since the revisionist taxonomy based on conserved macromolecules (e.g. 16S ribosomal RNA) the family includes only members of the genus Pseudomonas which are cleaved into eight groups. Pseudomonas aeruginosa is the type species of its group. which contains _____ other members.

a. 3
b. 6
c. 9
d. 12

14. Certain populations of patients are especially susceptible to pseudomonal infections. Predisposing conditions include placement of intravenous lines, severe burns, urinary tract catheterization, surgery, trauma, and premature birth (infants).

a. True
b. False

15. Pseudomonas aeruginosa infection is a serious problem in patients hospitalized with cancer, cystic fibrosis, and burns. The case fatality rate in these patients is near _____ percent.

a. 12
b. 25
c. 50
d. 70

16. The typical *Pseudomonas* bacterium in nature might be found in a biofilm, attached to some surface or substrate, or in a planktonic form, as a unicellular organism, actively swimming by means of its_____. *Pseudomonas* is one of the most vigorous, fast-swimming bacteria seen in hay infusions and pond water samples.

a. acetate
b. flagellum
c. synapses
d. elongated shape

17. *Pseudomonas aeruginosa* has very simple nutritional requirements. It is often observed "growing in distilled water", which is evidence of its minimal nutritional needs. In the laboratory, the simplest medium for growth of *Pseudomonas aeruginosa* consists of acetate as a source of carbon and ammonium sulfate as a source of_____.

a. oxygen
b. nitrogen
c. calcium
d. vitamins

18. The optimum temperature for *Pseudomonas aeruginosa* growth is 37 degrees, and it is able to grow at temperatures as high as _____ degrees.

a. 42
b. 51
c. 59
d. 64

19. *Pseudomonas aeruginosa* has a predilection for growth in moist environments, which is probably a reflection of its natural existence in soil and water.

a. True
b. False

20. *Pseudomonas aeruginosa* is notorious for its _____ and is, therefore, a particularly dangerous and dreaded pathogen.

a. virulence
b. resistance to antibiotics
c. ability to defy diagnosis
d. infectious nature

21. Diagnosis of *P.aeruginosa* infection depends upon isolation and laboratory identification of the bacterium. It grows well on most laboratory media and commonly is isolated on blood agar or eosin-methylthionine blue agar.

a. True
b. False

22. For an opportunistic pathogen such as *Pseudomonas aeruginosa*, the disease process begins with some alteration or circumvention of _____. The pathogenesis of *Pseudomonas*s infections is multifactorial, as suggested by the number and wide array of virulence determinants possessed by the bacterium.

a. antibiotics
b. antivirals
c. normal host defenses
d. detection

23. Although colonization usually precedes infections by *Pseudomonas aeruginosa*, the exact source and mode of transmission of the pathogen are often unclear because of its ubiquitous presence in the environment. It is sometimes present as part of the normal flora of humans, although the prevalence of colonization of healthy individuals outside the hospital is relatively low (estimates range from 0 to _____ percent depending on the anatomical locale).

a. 9
b. 12
c. 24
d. 30

MEDEDSYS
PO BOX 83939, San Diego, CA, 92138-3939
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