

CALIFORNIA ASSOCIATION FOR MEDICAL LABORATORY TECHNOLOGY

DISTANCE LEARNING COURSE

CYSTIC FIBROSIS AND MICROBIAL INFECTIONS

By

Lucy Treagan, Ph.D.

Prof. Biol. Emerita

University of San Francisco

Course Number: DL-966

2.0 CE/Contact Hours

Level of Difficulty: Intermediate

**CAMLT is approved by the California Department of Health Services
as a CA CLS Accrediting Agency (#0021)**

and courses are approved by ASCLS for the P.A.C.E.™ Program (#519)

1895 Mowry Ave, Suite 112

Fremont, CA 94538-1700

Phone: 510-792-4441

FAX: 510-792-3045

Notification of Distance Learning Deadline

DON'T PUT YOUR LICENSE IN JEOPARDY!

This is a reminder that all the continuing education units required to renew your license must be earned no later than the expiration date printed on your license. If some of your units are made up of Distance Learning courses, please allow yourself enough time to retake the test in the event you do not pass on the first attempt. CAMLT urges you to earn your CE units early!

CYSTIC FIBROSIS AND MICROBIAL INFECTIONS

INTRODUCTION

Cystic fibrosis is a genetic disorder resulting from mutations in a gene on the long arm of chromosome 7. This disorder is found predominantly in Caucasian populations of European ancestry. The gene defect results in numerous medical problems for the patient. These problems include progressive lung disease and multiple organ dysfunction caused by abnormal electrolyte transport. Many organs are affected, including the lungs, pancreas, intestines, sweat glands, and kidneys.

OBJECTIVES

Upon completion of this course the participant will be able to:

1. discuss the genetic basis of cystic fibrosis.
2. describe clinical symptoms.
3. list diagnostic methods.
4. explain the significance of microbial infections in cystic fibrosis patients.
5. list microorganisms involved in these infections.
6. outline a practical approach to identification of microbial pathogens isolated from cystic fibrosis patients.
7. summarize therapies useful in cystic fibrosis.
8. describe current experimental studies.

GENETIC AND CLINICAL ASPECTS OF CYSTIC FIBROSIS

The gene responsible for this disease was identified in 1989 as the cystic fibrosis transmembrane conductance regulator gene (CFTR gene). Over one thousand naturally occurring mutations have been described in the CFTR gene. Some of these mutations result in severe disease impacting many organ systems while other mutations produce mild symptoms. The most common CFTR mutation, accounting for approximately 70% of all mutant CFTR alleles, affects the delta F508 allele.

The CFTR gene product is the cystic fibrosis transmembrane conductance regulator, which regulates and facilitates the transport of electrolytes across the epithelial cell membrane and other cellular membranes. Normal CFTR protein is located at cell surfaces, while the misfolded (defective) CFTR protein is retained in the endoplasmic reticulum of the cell and is targeted for subsequent degradation. Consequently, cystic fibrosis patients have abnormalities with chloride conductance in and out of cells.

Normally, as secretions travel from the sweat glands to the surface of the skin the epithelial cells lining the sweat ducts act to reabsorb sodium chloride, resulting in hypotonic sweat. In cystic fibrosis patients the sweat ducts are impermeable to the chloride ion. This results in sodium chloride remaining in the secretions and the sweat is salty.

Cystic fibrosis patients suffer from an impaired ability to clear microbes, other particles, and mucus from the airways. In the normal lung foreign particles are removed from the airways by the beating cilia and by the surface liquid layer over the cilia. The liquid layer has two components: (1) fluid that covers the cilia and is approximately six micrometers deep, and (2) a top layer of liquid that contains secreted mucins that trap inhaled microbes and miscellaneous particles. The depth of the top liquid layer is regulated by a balance between the opposing

processes of sodium absorption and anion secretion. In cystic fibrosis patients anion secretion is impaired while sodium absorption is increased. This affects the volume of the top liquid layer, causes mucus to accumulate and compromises the clearance of particles.

Patients with classic cystic fibrosis lack a functional CFTR protein and experience severe chronic bacterial infections of the airways. Such infections typically lead to eventual lung failure by the time the patient is in the mid-30s. In addition, the patients may suffer from severe hepatobiliary disease, increased sweat chloride concentration, pancreatic insufficiency, and a condition known as obstructive azoospermia resulting in sterility. Patients with some functional CFTR protein (non classic cystic fibrosis) have better nutritional status and overall survival (1).

DIAGNOSIS OF CYSTIC FIBROSIS

Cystic fibrosis often presents with a typical combination of symptoms that include respiratory infections and gastrointestinal abnormalities leading to malabsorption and nutritional problems. The presumptive diagnosis of cystic fibrosis is usually made clinically. In some geographic areas the use of neonatal screening for enzymes implicated in pancreatic disease allows an early diagnosis. Definitive diagnosis requires genetic testing.

In clinical practice the diagnosis is generally made using a sweat test. A sweat chloride concentration of more than 60 mmol/liter determined on two or more occasions remains the “gold standard” for diagnosis of cystic fibrosis. An electrophoretic technique - the quantitative pilocarpine iontophoresis – is used. Since false-positive and false-negative results occur, the diagnosis is confirmed by genetic analysis. A negative genetic screen does not ensure a normal CFTR genotype since the commercial screens currently available detect only the 70 most prevalent CFTR mutations.

If questions remain about the diagnosis of cystic fibrosis after sweat testing and genotyping the diagnosis can be confirmed by a direct measurement of CFTR function: the nasal potential difference test measures the transepithelial electrical potential resulting from ion transport through channels (2).

MICROBIAL INFECTIONS ASSOCIATED WITH CYSTIC FIBROSIS

In the healthy respiratory system the upper respiratory tract is colonized by a wide variety of microorganisms comprising the normal flora, while the lower respiratory tract is maintained in a sterile state by the various innate defenses of the host. These defenses consist of physical barriers and endocytic/phagocytic barriers. Failure of any of these innate defenses of the host results in susceptibility to pulmonary infection. Cystic fibrosis patients have an abnormal mucus composition in the airways and are particularly vulnerable to microbial infection. Such infections are responsible for the early mortality associated with cystic fibrosis.

Microbial species clearly associated with cystic fibrosis lung disease are: 1. *Pseudomonas aeruginosa*, 2. *Staphylococcus aureus*, and 3. *Burkholderia cepacia* complex. Organisms having a secondary role in cystic fibrosis lung disease include (a) *Stenotrophomonas maltophilia* and *Alcaligenes xylosoxidans*, (b) *Hemophilus influenzae*, (c) *Aspergillus fumigatus*, (d) *Mycobacterium* species (not *M. tuberculosis*), and (e) respiratory viruses (3) (4).

1. *Pseudomonas aeruginosa*:

P. aeruginosa is an opportunistic pathogen widely distributed in nature. This bacterium has been demonstrated in whirlpools, hot tubs, baths, hand soap, dental equipment, home

nebulizers, toys, hospital equipment, showers, toilets, sinks, and various communal surfaces. Person-to-person transmission had also been demonstrated.

Infection with this microorganism may be acquired in infancy. Infection rate for all cystic fibrosis patients is approximately 60%. Among the adult patients and adolescents the infection rate reaches 80%. Patients infected with *P. aeruginosa* may suffer from impaired pulmonary function.

P. aeruginosa strains show considerable genetic variability. The original infecting strains express genes for infection and colonization. These “rough” or “planktonic” strains are motile, have smooth lipopolysaccharide and tend to be sensitive to a variety of antibiotics. At this stage of infection it is possible to eradicate the bacterial strain with aggressive antimicrobial therapy. Most patients, however, develop a chronic infection with *P. aeruginosa* as the pathogen undergoes a process referred to as “conversion to mucoidy.” Mucoid isolates are nonmotile, have rough lipopolysaccharide and are frequently resistant to a wide variety of antimicrobial agents. The conversion to mucoidy signals the beginning of chronic bacterial colonization. Mucoid strains grow as biofilms in the airways of cystic fibrosis patients. Examination of sputa from such patients shows gram negative rods in small clusters, surrounded by amorphous material that stains gram negative. This material is alginate, a polysaccharide polymer which forms the biofilm matrix and protects the embedded bacteria from clearance by the immune system (5).

Infections with mucoid *P. aeruginosa* are associated with heightened inflammation, tissue destruction, fever, elevated white blood cell count, increased sputum production and decreased pulmonary function. Typically, the infecting strain becomes increasingly resistant to antibiotics. Once *P. aeruginosa* colonizes the lungs it cannot be eradicated by the most aggressive antimicrobial therapy. Chronic lung infection with *P. aeruginosa* leads to cardiopulmonary failure and is a major cause of death in cystic fibrosis patients.

The inflammatory response in the lungs of cystic fibrosis patients chronically infected with *P. aeruginosa* may be due in part to the massive induction of bacterial genes encoding lipoproteins which act as proinflammatory toxins. An additional possibility is that some of the lung pathology is due to the host’s immune response directed against pseudomonal biofilms.

Pseudomonas can be readily isolated on agar selective for gram negative organisms, such as MacConkey and eosin methylene blue agars. A positive oxidase test, pigment production, growth at 42 degrees celsius, and in some cases mucoid colony morphology allow presumptive identification. Some of these phenotypic characteristics may be lost in chronic infections. As a result of these changes it may be difficult to identify some strains of *P. aeruginosa* with the use of commercial identification systems.

2. *Staphylococcus aureus*:

S. aureus was the first pathogen recognized in cystic fibrosis patients. This bacterium caused substantial morbidity and mortality in infants with cystic fibrosis in the pre-antibiotic era.

Colonization of anterior nares with *S. aureus* is common in healthy individuals. *S. aureus* strains spread within families and are shared among children in daycare centers, summer camps and similar group living situations. Nasal colonization with *S. aureus* is a risk factor for subsequent staphylococcal disease. Consequently, antibiotic therapy is frequently used for cystic fibrosis patients colonized with *S. aureus*. Common use of

prophylactic anti-staphylococcal therapy has raised questions whether such treatment may enhance susceptibility to other bacterial pathogens, such as *P. aeruginosa*.

Although clinical observations support a pathogenic role for *S. aureus*, the primary role of this microorganism in the pathogenesis of lung disease has been questioned.

Nevertheless, *S. aureus* can be recovered from approximately 50% of cystic fibrosis patients.

Laboratory isolation and identification is complicated by the increased frequency of *S. aureus* small-colony variants (auxotrophic isolates) found in cystic fibrosis patients. These organisms yield small, nonhemolytic, nonpigmented, slowly growing colonies on sheep blood or chocolate agars thus making identification more difficult. Mannitol salt agar is useful for isolation of *S. aureus* auxotrophs while preventing overgrowth by gram negative rods.

S. aureus isolates from cystic fibrosis patients are frequently resistant to antibiotics. Approximately 6% to 20% of isolates are oxacillin resistant. Methicillin resistance is also common, particularly in isolates from cystic fibrosis patients who had been hospitalized.

3. *Burkholderia cepacia* complex:

B. cepacia complex organisms were first described as pathogens in cystic fibrosis patients in the late 1970s and early 1980s. Initial description emphasized the multidrug resistance of these organisms and their marked virulence. Infected cystic fibrosis patients suffer from high fever and bacteremia. These organisms are able to invade the airway epithelium leading to rapid pulmonary deterioration. The disease has a very high mortality rate of 62% to nearly 100% and was given the name of “cepacia syndrome.” Pulmonary hypertension is associated with this syndrome and probably contributes to the high mortality rate.

Subsequent studies have shown that in contrast to the initial description of the cepacia syndrome, many cystic fibrosis patients have chronic infection with *B. cepacia* complex and others appear to have transient or intermittent infection or colonization. The cepacia syndrome develops in approximately 20% of cystic fibrosis patients colonized with these organisms.

Strains of *B. cepacia* complex are widely distributed in nature and have been isolated from soil, water, plants, and industrial settings. Cystic fibrosis patients may acquire the infection from the environment or by direct contact with infected individuals. These microorganisms are found in high concentration in the sputum of infected persons and are able to survive for prolonged periods on surfaces.

Taxonomic studies have shown that *Burkholderia cepacia*-like organisms constitute a very heterogeneous group of strains. There are at least nine genomic species or genomovars. Although most of the genomovars have been isolated from cystic fibrosis patients, not all genomic species have a primary role in lung disease.

The diagnosis of *B. cepacia* complex infection has serious consequences for the cystic fibrosis patient. Stringent infection control practices are required to prevent person-to-person spread of this infection. Cystic fibrosis patients colonized with *B. cepacia* complex are generally excluded from contact with uninfected patients. Furthermore, infected patients may be rejected as potential lung transplant recipients at many cystic fibrosis centers due to generally poor outcomes.

The diversity of *B. cepacia* complex organisms makes identification difficult. The nine genomic species of *B. cepacia* complex are genetically distinct but difficult to distinguish phenotypically and can be differentiated only by molecular testing. Genomovars I to VIII have been isolated from cystic fibrosis patients. *B. multivorans* (genomovar II) and *B. cenocepacia* (genomovar III) have a definitive correlation with cystic fibrosis lung disease. These two species constitute over 85% of *B. cepacia* complex isolates found in cystic fibrosis patients (*B. cenocepacia* representing approximately 50%). *B. cepacia* and *B. stabilis* species are also of clinical importance. Another newly characterized member of this family, *B. dolosa*, genomovar VI, has been found to accelerate the decline in lung function as well as carry an epidemic risk.

Three types of media are used to recover *B. cepacia* complex organisms from respiratory specimens: PC (*Pseudomonas cepacia*) agar, OFPBL (oxidative-fermentative base, polymyxin B, bacitracin, lactose) agar, and BCSA (*B. cepacia* selective agar). These culture media inhibit the growth of *P. aeruginosa*. BCSA gives superior results in the recovery of *B. cepacia* complex. Isolates from selective media are subjected to conventional biochemical analysis and tested with commercial bacterial identification systems. Genomovars II and VI are phenotypically indistinguishable, while genomovars I and III cannot be separated phenotypically. Commercial test system identification of *B. cepacia* complex should be confirmed with growth on selective media and additional biochemical tests. Differentiation of *B. cepacia* complex from similar organisms can be accomplished by whole-cell protein analysis, whole-cell fatty acid analysis, and by 16S rRNA gene sequencing. Different genomovars can be identified by molecular techniques, such as amplified fragment length polymorphism fingerprinting. Molecular identification of suspected *B. cepacia* complex organisms is available through the Cystic Fibrosis Foundation *B. cepacia* Research Laboratory and Repository.

B. cepacia complex is commonly resistant to many antimicrobial agents. However, in the absence of previous exposure to antibiotics, these bacteria are typically susceptible to piperacillin, piperacillin-tazobactam, cefoperazone, ceftazidime, chloramphenicol, and trimethoprim-sulfamethoxazole. Eradication of *B. cepacia* complex with antibiotics is difficult, making prevention of infection of primary importance.

Organisms having secondary role in cystic fibrosis lung disease

(a) *Stenotrophomonas* and *Alcaligenes*:

S. maltophilia and *A. xylosoxidans* are among the emerging pathogens in cystic fibrosis infections. These bacteria are being seen with increasing frequencies in adult patients. The overall prevalence of *S. maltophilia* in American cystic fibrosis patients is 8.4%, with different values reported by various cystic fibrosis care centers. The role of these organisms in cystic fibrosis lung disease has not been determined by case-control studies.

(b) *Hemophilus influenzae*:

Data collected in a 1998 study indicate that *H. influenzae* can be isolated from sputum or respiratory secretions of 16% of cystic fibrosis patients. The pathogenic potential of nontypable *H. influenzae* is difficult to assess, although there are

indications that this organism may be involved in chronic lung infections and acute exacerbations of disease in cystic fibrosis patients.

A recent study of cystic fibrosis patients colonized with *H. influenzae* showed that more than one strain may be present. The better-adapted strains can persist for long periods of time. Some of the strains have a decreased susceptibility to the antibiotics ampicillin or ciprofloxacin. There is a significant correlation between antibiotic resistance of bacterial strains and long-term colonization.

(c) Aspergillus and other fungi:

Filamentous fungi are frequently recovered from respiratory specimens of cystic fibrosis patients. Among these isolates *Aspergillus* (*A. fumigatus* in particular) has been associated with pulmonary symptoms in cystic fibrosis patients.

Aspergillus infections are acquired through environmental exposure and cannot be completely prevented since the fungus is widely spread in nature. Dust containment during construction, renovation, gardening, and lawn cutting helps to limit exposure to fungal spores. In the health care environment, water leaks that are not completely dried within 72 hours may be a source of *Aspergillus*. Prophylactic antibiotic treatment represents a risk factor for colonization with *Aspergillus*.

Infection with *Aspergillus fumigatus* may be localized or disseminated and may induce either an acute inflammatory response or a chronic granulomatous response. Lung tissue damage may occur. In addition, patients who have asthma or cystic fibrosis may develop allergic bronchopulmonary aspergillosis leading to damage to the large airways. These patients usually show elevated serum IgE levels. By contrast, elevated specific antibody of the IgA class has a protective effect in aspergillosis, while elevated titers of specific antibody of the IgG class serve as an indication of fungal colonization.

A. fumigatus may be isolated from the airways of 16 to 45% of cystic fibrosis patients. Other fungi frequently isolated from cystic fibrosis patients are the *Pseudallescheria boydii*/*Scedosporium apiospermum* complex and *Aspergillus terreus*. *S. apiosporium* presents a special risk as it has a tendency to disseminate in immunocompromised patients.

(d) Mycobacterium species:

Cystic fibrosis patients are at increased risk of infection with mycobacteria. Occasionally, *M. tuberculosis* is implicated, but nontuberculous mycobacteria are much more common. *M. avium-intracellulare*, *M. abscessus*, *M. kansasii*, *M. goodii*, *M. chelonae* and *M. fortuitum* have been isolated from cystic fibrosis patients. The extent of colonization ranges from 3% to 28%, depending on the patient population and the culture technique used. *M. avium* complex is most common, followed by *M. abscessus*. The clinical significance of mycobacterial colonization is not clear, although infection with *M. abscessus* can cause considerable damage.

(e) Viruses:

Respiratory viruses are important pathogens in cystic fibrosis patients. Viruses such as respiratory syncytial virus, influenza virus, parainfluenza virus, adenovirus, and rhinovirus may be transmitted through direct contact with infected persons or through indirect contact by touching contaminated objects. These viruses infect the respiratory epithelium, decreasing ciliary movement and increasing production of mucus. Although children with cystic fibrosis do not have an increased susceptibility to viral infections, the respiratory illness can be more severe in these patients. Respiratory syncytial virus, for example, can cause severe illness that requires hospitalization and may cause residual impairment in lung function. Prevention of respiratory syncytial virus infections with immune globulin or monoclonal antibody (palivizumab) has been suggested. A subunit vaccine is under investigation.

Adenovirus and influenza virus infections can cause deterioration in lung function in cystic fibrosis patients. Influenza vaccine is recommended for cystic fibrosis patients older than six months of age and for close contacts of all cystic fibrosis patients.

PRACTICAL APPROACH TO IDENTIFICATION OF MICROBIAL PATHOGENS FROM CYSTIC FIBROSIS PATIENTS

Culture of respiratory tract specimens from cystic fibrosis patients and identification of presumptive pathogens is highly labor-intensive and expensive. The clinical microbiology laboratories at the University of North Carolina Hospitals have developed a streamlined approach to microbiology for cystic fibrosis patients. The following protocol is used for specimens from these patients:

- a. Routine gram stains from cultures of sputum specimens are eliminated
- b. Complete identification and susceptibility testing of significant isolates from respiratory specimens is done every 3 months
- c. Cultures of outpatient specimens submitted less than 3 months after an extensive workup are sight read and reported. Complete identification and sensitivity testing are done by physician request.
- d. The same strategy is used for inpatients: initial sputum and deep pharyngeal specimens receive complete identification, but subsequent specimens are sight read.
- e. Bronchoscopy specimens receive complete identification and sensitivity testing.
- f. Identification of filamentous fungi is limited to once per calendar year because of long-term colonization with *Aspergillus* species.
- g. Complete *S. aureus* susceptibility testing is performed once per calendar year. Otherwise, these isolates are tested by an oxacillin screening plate. Oxacillin-resistant isolates are given complete susceptibility testing.
- h. Disk diffusion susceptibility testing is done for *P. aeruginosa* once every 3 months for outpatients or at admission of inpatients. The same strategy is used for *A. xylosoxidans* and *B. cepacia* complex organisms.
- i. *S. maltophilia* susceptibility testing is performed by MIC methodologies.

- j. Isolates resistant to multiple antibiotics may be sent to the US Cystic Fibrosis Foundation Reference Laboratory. This laboratory evaluates the drug resistant isolates and determines the best antimicrobial combination with which to treat the patient.

THERAPIES FOR CYSTIC FIBROSIS LUNG DISEASE

Clearance of the purulent pulmonary secretions in cystic fibrosis lung disease can be accomplished by various methodologies. All are based on the premise that these techniques relieve airway obstruction, enhance the clearance of pulmonary secretions, improve ventilation, and promote expectoration of elastase-laden sputum. Improved airway clearance slows the progression of lung disease. Lung transplantation is the ultimate treatment of cystic fibrosis patients.

Physical techniques:

- a. Standard chest physiotherapy with postural drainage. The treatment is time-consuming and must be carried out by a trained person.
- b. High frequency chest compression with an inflatable vest.
- c. Active forced expiration.
- d. Positive expiratory pressure.
- e. Autogenic drainage.
- f. Use of oscillators, such as the Flutter device.

All of the above treatment options are capable of increasing the quantity of expectorated sputum.

Use of recombinant deoxyribonuclease (DNase):

Cystic fibrosis sputum contains many neutrophils that release DNA upon autolysis. The DNA aggregates into large fibrils, markedly increasing sputum viscosity. DNase decreases the sputum viscosity and aids in sputum clearance.

Chemotherapy:

Antibiotic therapy leads to improvement in lung function, the best prediction of survival in cystic fibrosis patients. The decisions--when to treat and with which antibiotics--are based on the patient's age, the colonizing organisms, and the severity of pulmonary symptoms.

Current prophylactic regimen in the United States utilizes 300mg of tobramycin administered on a twice-daily basis for alternating 28-day on-off cycles. This is aimed at prevention of *P. aeruginosa* colonization and development of resistant strains.

Treatment of *P. aeruginosa* infections with oral antibiotics includes the quinolones, particularly ciprofloxacin. Double antibiotic therapy appears more effective than monotherapy and ciprofloxacin may be combined with inhaled tobramycin.

In cases of *S. aureus* colonization, patients may receive oxacillin, nafcillin, or cephalothin.

The emergence of resistant strains remains a major problem in the treatment of infections of cystic fibrosis patients.

EXPERIMENTAL STUDIES

Animal models of cystic fibrosis

1. Mouse Models

Ion transport imbalance is of critical importance in the pathogenesis of cystic fibrosis lung disease. A mouse model of this disease had been developed with

transgenic mice that absorb excess sodium in their airways. These mice show key abnormalities of cystic fibrosis including airway obstruction with dehydrated mucus, airway inflammation, and inflammatory cytokines in airway liquid despite the maintenance of these mice in a sterile environment. When challenged with bacteria, the airways of these mice are unable to clear the microorganisms.

This experimental model has potential use for evaluating therapeutic agents for cystic fibrosis. However, mice with a disrupted CFTR gene do not develop all of the characteristic manifestations of human cystic fibrosis, including abnormalities of the pancreas, intestines, liver, lungs, and other organs.

2. Newborn pigs model

Recently a new model of cystic fibrosis has been developed in pigs. These animals are more similar to humans than mice in terms of anatomy, biochemistry, physiology, size, life span, and genetics.

Pigs were generated with a specific disruption of both CFTR alleles. Genetically altered newborn pigs showed defective chloride transport and developed pathological abnormalities in the pancreas, intestines, and liver. These abnormalities were similar to those observed in human newborns affected with cystic fibrosis.

Summary:

Cystic fibrosis is a genetic disorder found predominantly in persons of European ancestry. The gene affected is called the cystic fibrosis transmembrane conductance regulator gene (CFTR). The CFTR gene product regulates and facilitates the transport of electrolytes across cell membranes. Cystic fibrosis patients have a high concentration of salt in their sweat. They have difficulty in clearing foreign particles from the airways and suffer from respiratory infections. Severe chronic lung infections frequently result in lung failure and are a primary cause of early mortality associated with cystic fibrosis.

Cystic fibrosis is diagnosed by clinical symptoms and by a sweat test. The diagnosis can be confirmed by genetic analysis. A negative genetic screen does not rule out cystic fibrosis. A direct measurement of CFTR function can be performed to confirm the diagnosis.

A number of microbial species have been linked to respiratory infections that are common in cystic fibrosis patients. Of these, *P. aeruginosa*, *B. cepacia* complex and *S. aureus* are of primary importance.

P. aeruginosa plays a major role in lung infections of cystic fibrosis patients. Original infecting strains are generally susceptible to antibiotics and can be eradicated with aggressive treatment. As the infection becomes chronic, *P. aeruginosa* strains convert to “mucoidy”. These mucoid strains are resistant to most antibiotics and grow as biofilms in the airways of cystic fibrosis patients. These strains cannot be eradicated by the most aggressive antibacterial therapy.

S. aureus is frequently found in healthy persons in the anterior nares and can be recovered from approximately 50% of cystic fibrosis patients.

B. cepacia complex organisms are a heterogeneous group of bacteria widely distributed in the environment. These organisms are important pathogens because of their ability to invade the airway epithelium causing severe lung disease accompanied by bacteremia and a high mortality rate. This condition is called “the cepacia syndrome.” The bacteria can be transmitted person-to-

person and frequently exhibit multidrug resistance. Strict infection control is required for prevention.

The therapeutic approach to cystic fibrosis is to clear the purulent secretions from the airways. This can be achieved by physical methods, by using DNase to decrease the viscosity of respiratory secretions, or by chemotherapy directed at the infecting pathogen. Multidrug resistance of some of the pathogens presents a major obstacle to successful chemotherapy.

References:

1. Knowles MR, Durie PR. What is Cystic Fibrosis? *N.Engl.J.Med.* 2002;347:439-442
2. Lyczak JB, Cannon CL, Pier GB. Lung Infections Associated with Cystic Fibrosis. *Clin.Microb.Rev.* 2002;15:194-222
3. Gilligan PH, Miller MB. Laboratory Aspects of Management of Chronic Pulmonary Infections in Patients with Cystic Fibrosis. *J.Clin.Microb.* 2003;41:4009-4015
4. Saiman L, Siegel J. Infection Control in Cystic Fibrosis. *Clin.Microb.Rev.* 2004;17:57-71
5. Firoved AM, Ornatowski W, Deretic V. Microarray Analysis Reveals Induction of Lipoprotein Genes in Mucoid *Pseudomonas aeruginosa*: Implications for Inflammation in Cystic Fibrosis. *Infection and Immunity* 2004;72:5012-5018

Review Questions:

Course #DL-966

Select the **one** best answer

1. The disease cystic fibrosis:
 - a. is transmitted by arthropod vectors
 - b. is transmitted by bats
 - c. is a genetic disorder
 - d. affects only the elderly
2. The gene affected in cystic fibrosis:
 - a. is located on the sex chromosome
 - b. is known as the cystic fibrosis transmembrane conductance regulator gene
 - c. is not present in persons of European ancestry
 - d. undergoes only one type of mutation
3. Cystic fibrosis can be diagnosed by:
 - a. clinical symptoms alone
 - b. fecal occult blood test
 - c. clinical symptoms and a sweat test
 - d. serologic tests
4. A major pathogen in cystic fibrosis lung disease is:
 - a. *Pseudomonas aeruginosa*
 - b. *Staphylococcus epidermidis*
 - c. *Escherichia coli*
 - d. measles virus
5. Mucoid strains of *P. aeruginosa*:
 - a. are linked to chronic infections
 - b. are susceptible to most antibiotics
 - c. never cause inflammation
 - d. can be easily eradicated with therapy
6. Colonization of healthy individuals with *S. aureus*:
 - a. does not occur
 - b. is universal
 - c. involves the anterior nares
 - d. is not related to subsequent staphylococcal disease
7. *B. cepacia* complex organisms:
 - a. are widely distributed in nature
 - b. have very low virulence
 - c. do not invade the airway epithelium
 - d. are not transmitted person-to-person
8. The “cepacia syndrome” is a term used for:
 - a. *P. aeruginosa* pulmonary infection
 - b. transient infection by *B. cepacia* complex organisms
 - c. staphylococcal septicemia
 - d. bacteremia and invasion of the airway epithelium by *B. cepacia* complex organisms

9. Genomic species of *B. cepacia* complex involved most frequently in cystic fibrosis infections are:
 - a. all genomovars are equally involved
 - b. genomovar I is the only genomic species involved in infections
 - c. genomovars II and III
 - d. genomovars V and IX
10. *B. cepacia* complex organisms:
 - a. frequently exhibit multidrug resistance
 - b. are very homogeneous genetically
 - c. invariably cause fatal infections
 - d. are transmitted by mosquitoes
11. Infection with *Alcaligenes*:
 - a. has not been reported in the US
 - b. occurs only in infants
 - c. has been reported in adult cystic fibrosis patients
 - d. invariably results in severe lung disease
12. *Hemophilus influenzae* strains:
 - a. can be isolated from 80% of cystic fibrosis patients
 - b. may show decreased susceptibility to ampicillin
 - c. are never involved in long-term colonization of cystic fibrosis patients
 - d. cause azoospermia in cystic fibrosis patients
13. Diagnosis of cystic fibrosis can be confirmed by:
 - a. the nasal potential difference test
 - b. a skin test
 - c. a white blood cell count
 - d. urinalysis
14. Viral respiratory pathogens of cystic fibrosis patients include:
 - a. respiratory syncytial virus
 - b. poliovirus
 - c. hepatitis C virus
 - d. rabies virus
15. An animal model of cystic fibrosis:
 - a. does not exist
 - b. has been established in guinea pigs
 - c. has been established in monkeys
 - d. has been established in mice
16. Prophylactic treatment with antibiotics is:
 - a. used to prevent symptomatic *P. aeruginosa* colonization
 - b. never used for infections of cystic fibrosis patients
 - c. used to prevent aspergillosis
 - d. used to prevent infection with respiratory viruses

17. Oxacillin, nafcillin, or cephalothin may be used in cases of colonization by:
- adenovirus
 - Rhizopus*
 - S. aureus*
 - Alcaligenes*
18. Sputum viscosity may be decreased by treating the patient with:
- deoxyribonuclease
 - ribonuclease
 - aspirin
 - Advil
19. Chest physiotherapy with postural drainage is:
- a procedure that can be self-administered
 - designed to enhance the clearance of pulmonary secretions
 - never done to cystic fibrosis patients
 - done to improve the patient's posture
20. Use of oscillators:
- improves airway clearance
 - is harmful to patients
 - is an excellent exercise technique
 - is never used in cystic fibrosis treatment

Course #: DL-966 Cystic Fibrosis Select the **one** best answer for each question
 2.0 CE Credits

Name _____ CLS Lic. # _____ Date _____

Signature (Required) _____

Address _____

Street _____ City _____ State/Zip _____
 Payment Method ___ Check or ___ Credit Card # _____ Type -Visa / MC
 Exp. Date _____ Signature _____

2.0 CE Fee = \$24.00 for members (\$30.00 for non-members)

- | | | | | | | | | | |
|-----|---|---|---|---|----|---|---|---|---|
| 1. | a | b | c | d | 11 | a | b | c | d |
| 2. | a | b | c | d | 12 | a | b | c | d |
| 3. | a | b | c | d | 13 | a | b | c | d |
| 4. | a | b | c | d | 14 | a | b | c | d |
| 5. | a | b | c | d | 15 | a | b | c | d |
| 6. | a | b | c | d | 16 | a | b | c | d |
| 7. | a | b | c | d | 17 | a | b | c | d |
| 8. | a | b | c | d | 18 | a | b | c | d |
| 9. | a | b | c | d | 19 | a | b | c | d |
| 10. | a | b | c | d | 20 | a | b | c | d |

Distance Learning Evaluation Form

According to state regulations, this evaluation must be completed and returned in order to receive CE hours. Your comments help us to provide you with better continuing education materials in the distance learning format. Please circle the number that agrees with your assessment.

- Overall, I was satisfied with the quality of this Distance Learning course.
 (strongly agree) 5 4 3 2 1 (strongly disagree)
- The objectives of this Distance Learning course were met.
 (strongly agree) 5 4 3 2 1 (strongly disagree)
- The difficulty of this Distance Learning course was consistent with the number of CE hours.
 (strongly agree) 5 4 3 2 1 (strongly disagree)
- I will use what I learned from this Distance Learning course.
 (strongly agree) 5 4 3 2 1 (strongly disagree)
- The time to complete this Distance Learning course was: _____ hours
- Please comment on this Distance Learning course on the back of this sheet.
 What did you like or dislike?