Guidelines for Management of Adults with Cystic Fibrosis
during Hospitalization and Outpatient Parenteral Antibiotic Therapy

Tulane Medical Center - Tulane University Cystic Fibrosis Care Center

GENERAL NOTES

1. Introduction to Cystic Fibrosis:

   a) Cystic fibrosis (CF) is a multiorgan system disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR gene codes for CFTR protein which is a chloride channel and a regulator of other ion channels in epithelial cells. Many features of the CF phenotype are directly related to ion channel abnormalities attributable to the CFTR mutations. Disease causing mutations of the CFTR gene result in abnormalities of chloride and sodium transport across epithelial cells on mucosal surfaces. This leads to decreased hydration of mucus. As a result secretions in the respiratory tract, pancreas, GI tract, sweat glands, and other exocrine tissues have increased viscosity. In the respiratory tract the result is chronic inflammation and infection with resultant progressive lung destruction. Clinical disease requires disease-causing mutations in both copies of the CFTR gene. There is significant variability in the phenotypic expression of disease, related to the specific mutation (or mutations) present as well as the presence of modifier genes. Eighty percent of CF patients are pancreatic exocrine insufficient and are at risk for steatorrhea and nutritional deficiencies. Patients with “milder” CF disease who may not be diagnosed until adolescence or adulthood may be pancreatic sufficient.

   b) CF is the most common lethal inherited disorder affecting Northern Europeans and North Americans. CF is more common among Caucasians and is the most common lethal inherited disease affecting the Caucasian population. Cystic fibrosis occurs in about 1 in 3,200 live Caucasian births in the U.S. It is less common in other ethnic groups, affecting 1 in 15,000 African-Americans and 1 in 31,000 Asian-Americans. There are approximately 30,000 children and adults with CF in the United States and 70,000 worldwide. Approximately 1 in 31 persons in this country is a CF carrier. Carriers do not have clinically apparent disease. The current mean age at time of diagnosis is 3.6 years. Newborn screening for CF is now required in all fifty states and accounts for >55% of new diagnoses. The most common CFTR mutation is delta F508. More than 85% of patients in the US will have at least one copy of delta F508 and about half of the patients are homozygous for delta F508.

   c) Survival and quality of life for individuals with cystic fibrosis has progressively improved over the past 50 years. The projected median age of survival in 2010 for cystic fibrosis patients in the U.S. was 38.3 years, having increased from 28.0 years in 1990. Currently 47.4% of patients with CF in the US are 18 years old or older. Many patients live into their 50s and 60s. Pulmonary disease is the leading cause of morbidity and mortality in patients with CF. The median age at death in 2010 was 26.3 years. Cystic fibrosis is now a disease for the Internist and the adult Pulmonary Diseases Specialist.

2. Adult Cystic Fibrosis Program and Clinics:

   a) The Tulane Adult Cystic Fibrosis Program is an integral component of the Tulane University Cystic Fibrosis Care Center, which is one of 115 Centers supported and accredited by the national Cystic Fibrosis Foundation. Tulane has been an accredited CF Care Center since 1963. Adult patients with cystic fibrosis have been cared for at the Tulane Medical Center since its opening in 1976. The Adult CF Program was established in 1993 under the direction of Dr. Dean Ellithorpe as Adult Program Director. Patients now transition from the Pediatric CF Program between the ages of 18 and 21. The Tulane Adult CF Program serves patients from south Louisiana, south Mississippi, and Gulf south Alabama.

   b) Dr. Ross Klingsberg, Assistant Professor of Medicine in the Pulmonary Diseases Section, assumed the position of Associate Adult Program Director in July 2011. Dr. Reinaldo Rampolla, the Medical Director for the Ochsner Lung Transplant Program, joined Tulane’s Adult CF Team in October 2010. Our
Adult CF Program consists of a multidisciplinary team, including the three Physicians, a Clinic Nurse Coordinator (Cheryle Donoghue), a Nurse Practitioner (Jennifer Greenheck), a Dietician, Respiratory Therapists, a Social Worker, and a Research Coordinator. The three physicians staff clinics three days a week and the Nurse Practitioner has a clinic dedicated to follow-up of CF patients receiving IV antibiotics. Pulmonary Diseases Section Faculty and Pulmonary Diseases Fellows are available 24/7 to answer calls from our adult CF patients and outlying hospitals.

3. Inpatient Care:

   a) When hospitalization is necessary adult CF patients are routinely admitted to the In-patient Pulmonary Service on 5 Center, which is the designated Medical-Surgical nursing unit for adult CF patients. If patients are admitted to 5 East or 7 East as overflow they are to be transferred to 5 Center as soon as a bed is available. Dependent on adult bed availability, patients <21 years old may be admitted to 6 West, the Pediatric nursing unit. Patients with significant (≥ 250 ml) gross hemoptysis, acute respiratory distress or those requiring antibiotic desensitization will usually require admission to an ICU. During administrative hours the designated Attending is normally Dr. Klingsberg who is the responsible staff physician for CF Inpatients. The Nurse Practitioner may assist with the attending responsibilities. The Pulmonary Fellow assigned to the TMC Consult Service is the Fellow responsible for the CF Inpatients. On holidays, weekends and after-hours the On-call Pulmonary Diseases Faculty is designated the Attending for admissions and is the responsible staff physician during those hours. If a patient is admitted to an ICU the Critical Care Attending is the Attending.

   b) CF patients are assigned to private rooms for infection control. Many patients with cystic fibrosis have MRSA, multidrug-resistant (MDR) *Pseudomonas* infections, and/or infections with other MDR gram-negative organisms. *Always observe Standard Precautions and use proper Hand Hygiene.* For all patients with MRSA, MDR *Pseudomonas, Burkholderia cepacia* complex or other MDR organisms observe Contact Precautions and place the patient on “Contact Isolation”. Patients with suspected acute viral-type respiratory illness should also be placed on Droplet Precautions. Respiratory isolation is not usually necessary. Patients and their families are encouraged to observe proper hand hygiene. Patients on Droplet Precautions are to wear masks when out of their room.

   c) The majority of hospitalizations are for a CF pulmonary exacerbation. There are several possible scenarios for admissions. Some patients with pulmonary exacerbation will have been evaluated during a CF Clinic visit and then admitted. Others with an acute illness may present directly to the TMC ED, or be directly admitted from home, or be transferred from an outlying facility. A third group of patients are admitted from Adult CF Clinic or directly from home for a “tune-up” because of progressive subjective and/or objective findings indicative of deteriorating pulmonary status. Occasionally a patient may require hospitalization for a non-pulmonary problem, e.g., abdominal pain (possible distal intestinal obstruction syndrome, pancreatitis, etc.), line infection, DVT, uncontrolled CF-related Diabetes mellitus, or other problem. These patients are usually admitted to the Pulmonary Service with the other appropriate services being consultants.

   d) During normal administrative hours the admitting Fellow should review all new admissions with the Associate Program Director, Dr. Ross Klingsberg. After usual working hours the Fellow should contact either the on-call Pulmonary Attending faculty or Dr. Klingsberg. If a patient is admitted from the ED or transferred from another facility, Dr. Klingsberg should be informed of the admission ASAP. Do not hesitate to contact Dr. Klingsberg or Dr. Ellithorpe regarding the CF patients! All new admissions must be reviewed with one of the CF Team Physicians, Drs. Klingsberg, Ellithorpe, or Rampolla.

4. Diagnoses:

   a) At admission select the appropriate CF diagnosis on the ADULT CYSTIC FIBROSIS ADMIT ORDERS form. Also select any comorbidities as appropriate.

5. Symptoms and Signs:

   a) **Pulmonary exacerbations** in CF are characterized by (1) **respiratory symptoms** of increased cough (frequency, duration or intensity), increased sputum volume, change in character of sputum (darker color,
more viscous), new onset or increased hemoptysis, decreased exercise tolerance, new or worsening dyspnea; (2) chest physical findings with new or increased crackles, wheezes, rhonchi and/or tachypnea; (3) systemic symptoms/signs of fever > 38°C, respiratory distress, recent malaise/fatigue, recent anorexia/ poor appetite, recent weight loss (≥ 5% decrease), and recent increase in school/work absenteeism; (4) spirometry demonstrating a ≥ 8% decrease in FEV1 and/or decreased oxygenation from baseline; and (5) new chest x-ray abnormalities (infiltrates, atelectasis, mucous plugging, or pneumothorax).

b) Cystic Fibrosis is a multiorgan system disease affecting the upper and lower respiratory tract (bronchiectasis, bronchitis, pneumonia, pneumothorax, sinusitis, nasal polyps), gastro-intestinal tract (gastro-esophageal reflux, gastroparesis, impaired intestinal motility, distal intestinal obstruction syndrome/ DIOS), hepato-biliary tract (cholestasis, steatosis, biliary cirrhosis, cholelithiasis, biliary duct obstruction), exocrine pancreas (enzyme insufficiency, pancreatic steatorrhea, pancreatitis); endocrine (CF-Related Diabetes mellitus/ CFRD or impaired glucose tolerance), genitourinary tract (BAVD/ congenital bilateral absence of the vas deferens, azoospermia, male hypogonadism, amenorrhea, nephrolithiasis); and musculoskeletal system (clubbing, CF-related arthropathy, osteopenia/ osteoporosis). Eighty percent of patients will manifest pancreatic exocrine insufficiency in early childhood. The majority of patients will have radiographic evidence of bronchiectasis by pre-teens.

c) Pay special attention to general health, dental care and hygiene, mental status and psychosocial issues, nutritional intake and weight loss, and pancreatic enzyme & vitamin intake. Review history for respiratory allergies, allergic rhinitis, asthma, allergic bronchopulmonary aspergillosis (ABPA), nasal polyps, and previous sinus surgery. Asthma is reported in 20+% of adult CF patients. Allergy with positive prick tests to inhalants is present in 20+% of CF patients.

d) CF-related diabetes occurs in 30+% of adult CF patients with an increasing incidence with age. Inquire re home insulin schedule, CBG monitoring and most recent Hemoglobin A1C and urine microalbumin. Note that CFRD is not typical Type 1 or Type 2 Diabetes mellitus. Most will require insulin therapy. They rarely develop ketoacidosis or hyperosmolar states. Inquire re the most recent eye exam. Glucose intolerance is frequently present during episodes of pulmonary exacerbations.

e) Depression, anxiety, mood disorders, panic attacks, and sleep disorders are common problems with adult CF patients! Do they routinely see a Psychiatrist or Psychologist?

f) Pain is another common problem. Acute chest pain, usually pleuritic in character, may occur with pulmonary exacerbations. Chronic chest and back pain are frequent complaints. Episodes of acute polyarthritis or polyarthralgia may occur. Grade severity of a patient’s pain on a scale of 0-10.

g) Inquire re exposure to passive smoking; use of tobacco, alcohol, mood-altering prescription medications (whether prescribed or not), and marijuana or other illicit drugs.

h) Assess the patient’s compliance with all of their CF related treatments at home, especially airway clearance therapies (ACT) - Vest, Acapella or Flutter device, CPT, nebulized/ inhaled meds, aerobic exercise, etc. Non-compliance with ACT is a major problem!

i) Verify immunization status: One time only pneumococcal vaccine for adults before age 65 years. Influenza vaccine (annually September thru February). Pertussis vaccine (Tdap booster) one time after age 15 years. See: http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf

j) All patients are to have a dictated “Esig” History and Physical (work-type #3731) for the on-service Pulmonary Diseases Attending. Do not use the Consult work-type. The H&P should be done the day of admission. It should appear in Meditech/hCare within several hours of dictation.

6. Vital signs, weight, and height:

a) Vital signs should be ordered as indicated or per nursing unit routine. Actual weight and height must be obtained on admission. Do not rely on patient’s self-reported weight. Patients are to be weighed every Monday, Wednesday and Friday while in the hospital. You must insist that the nursing staff documents patient’s actual weights.
7. Diet and Nutrition:

a) Optimal BMI for adult CF patients (>20 years old) is ≥22 for females and is ≥23 for males. BMI <20 is indicative of malnutrition. To calculate BMI see [http://www.nhlbisupport.com/bmi/](http://www.nhlbisupport.com/bmi/).

b) Consult the In-patient Dietician for nutritional assessment and recommendations re dietary supplements, enzyme and vitamin supplementation.

c) The standard CF diet is high calorie, high protein (HCHP) with supplement of choice. The Dieticians will specify the Supplements. If the patient receives night-time g-tube feedings at home (e.g. Nutren 2.0) continue the same feedings in hospital. Standard ADA diabetic diets are NEVER appropriate for CF patients with CFRD. Do not restrict calorie or fat intake for CF patients.

d) Order brand name pancreatic enzymes (Creon® or Zenpep® are formulary) per patient’s home schedule (same brand, strength and number of capsules). You must specify the strength. The number of the specific enzyme capsule indicates the units of lipase x 1000/ capsule. The typical enzyme dose is 1000-2500 units of lipase/Kg BW per meal taken immediately before the meal. Lower doses are taken with snacks. Enzymes should be left at the patient’s bedside to take as needed. If the patient’s home enzyme is non-formulary (e.g., Pancreaze®) they may use their own enzymes from home. Many patients receiving pancreatic enzyme supplementation also take either PPIs or H2- blockers as enzymes may be degraded by gastric acid.

e) Order AquADEKs® Softgels multivitamin (formulated specifically for adult CF patients) one capsule twice daily with a meal. AquADEKs® is the only formulary CF multivitamin at TMC. Patients who take Source CF® Softgels at home may take AquADEKs® while in the hospital. Many CF patients are also taking additional vitamin supplementation with OTC Beta carotene (Vitamin A), OTC Vitamin D3 (cholecalciferol), OTC Vitamin E, and/or prescription Vitamin K (Mephyton®). Check for results of most recent fat-soluble vitamin levels in Meditech. Note that OTC Beta carotene is non-formulary at TMC and Vitamin A may be substituted.

f) Many patients will be taking iron supplements at home. Anemia either due to iron deficiency or chronic disease or both is common. Iron malabsorption in CF patients appears to be a factor.

8. Home treatments:

a) Make certain that you order all of patient’s at-home medicines and treatments. CF patients may be on numerous scheduled medications, e.g. insulin, nasal and inhaled steroids (e.g. Fluticasone/ Flonase®, Flovent®, Advair®, Symbicort®, etc.), anti-histamines (e.g. Allegra®, etc.), azithromycin (Zithromax®), H2-blockers (e.g. famotidine/ Pepcid®), PPIs (e.g. pantoprazole/ Protonix, etc.), prokinetic agents (metoclopramide/ Reglan®, laxatives (Miralax® or Go-lytely®), fiber tablets (Benefiber®), ursodiol (Actigall® or Urso®), nasal saline irrigation (e.g. Sinus-Rinse™ or Waterpik®), antidepressants (Zoloft®, Lexapro®, etc.). When a patient is “on-cycle” with nebulized tobramycin (TOBI®), compounded tobramycin, compounded colistin, or Cayston at home, it is not normally continued in the hospital. In-hospital medications should generally be limited to items included in the TMC Formulary. Non-formulary items are not stocked by the TMC Pharmacy. If desired a patient may use their own home supply. An order to that effect is required and a TMC pharmacist must identify and label the medication.

9. Consultations:

a) Evaluate the need for any in-patient medical subspecialty consults: Allergy-Immunology (antibiotic allergy and need for desensitization, possible ABPM), Gastroenterology/ Hepatology (gastroparesis, DIOS, abnormal LFTs), Nephrology (renal insufficiency, proteinuria), Interventional Radiology (massive or persistent hemoptysis), Otolaryngology (nasal polyps, sinusitis), and others as indicated. Psychiatry consult may be indicated for evaluation of anxiety, depression, or drug-seeking behavior. Routinely consult the Diabetic Educator and/or Endocrinology for patients with new onset CFRD or poorly controlled CFRD. Consider an Infectious Disease consult when “line infections” are an issue or there are unusual infecting organisms. Most issues with pulmonary infections should initially be addressed with Dr. Dean Ellithorpe.
10. Social Service:

   a) Consult the Cystic Fibrosis Center Social Worker (pager 552-7387 or 988-4106 (Ascom)), for evaluation of psychosocial issues, support systems, assistance with health insurance issues and discharge planning.

CLINICAL INVESTIGATIONS

1. Clinical Laboratory studies:

   a) Initial admission labs are to include CBC with differential, CMP/CH12 (comprehensive chemistry panel), magnesium, phosphorous, prealbumin, high-sensitivity C-reactive protein, and urinalysis, unless obtained in ED or CF Clinic immediately prior to admit. Note that the CMP includes LFTs.

   b) Order other labs as indicated: Hgb A1C (if known CFRD or glucose intolerance); GGT (if elevated alkaline phosphatase); Prothrombin time and PTT; serum iron profile and ferritin (if hypochromic, microcytic anemia), total IGE, and 25-hydroxy vitamin D assays (if not done within past 12 months). The complete CF Vitamin profile, which includes vitamin A, D, E and K is not routinely ordered for in-patients. Some vitamin assays, e.g. vitamin A, may not be reliable during an acute illness. If a patient has acute abdominal pain, consider ordering a serum amylase and lipase. For patients who are to receive an aminoglycoside or colistin order a random urine microalbumin/creatinine ratio. If there is concern re possible substance use/abuse, order a urine drug screen. If there are new abnormal LFT results, consider ordering a hepatitis panel. For female patients of child-bearing potential obtain urine pregnancy test.

   c) Review previous lab results in Meditech or hCare Clinician Portal. Be alert to significant increase (≥ 0.4 mg/dl) in serum creatinine.

   d) Order stool for fecal pancreatic elastase-1 (PE-1) if patient is having symptoms indicative of steatorrhea (abdominal bloating, cramping, increased flatulence and/or loose, bulky, malodorous stools).

   e) Blood glucose monitoring: Order periodic CBG if patient has CFRD, history of glucose intolerance, or elevated random glucose on in-hospital labs.

   f) Periodic labs should be ordered as clinically indicated. Obtain repeat CBC with diff, BMP and Mg on hospital day 3. Obtain repeat CBC with diff, BMP and Mg every 7 days and/or at discharge. Check renal function (BMP and Mg) every 3 days if receiving an aminoglycoside. Note the CMP includes the BMP plus albumin, hepatic enzymes and total bilirubin. If the initial prealbumin and/or CRP are abnormal, repeat weekly. Obtain drug levels as appropriate - random tobramycin level 12-16 hours after the first Q 24 hour dose or any changed dose and vancomycin trough before the 4th Q 8 hour dose. Per our Nephrology Consultants, serum Mg and urine microalbumin/creatinine ratio are the most sensitive indicators of renal injury from antibiotics. These should be checked weekly for patients receiving aminoglycosides or colistin.

   g) DAILY LABS ARE RARELY EVER NECESSARY!

2. Respiratory cultures:

   a) Order sputum for CF culture (CUCF), not routine respiratory culture, if it has not been obtained within the week prior to admission. Sputum should be obtained within 24 hours of admit. Make certain that requested sputum sample is obtained! If necessary, order sputum induction with hypertonic saline (3 -7%) by RT. If a patient is unable to produce a sputum sample, perform a throat swab after a deep cough and submit for CUCF. Note that final results of CF cultures are generally not available for at least 5-7 days. Mucoid strains of Pseudomonas are slow growers. The Microbiology Lab at TMC utilizes specialized culture media and procedures for a CF culture to adequately identify CF pathogens. Kirby-Bauer disc susceptibility tests are utilized for Pseudomonas. The automated broth systems are unreliable with mucoid pseudomonas. Order AFB smear/culture if not done within past year or if there has been a positive AFB culture within the past year. Non-tuberculous mycobacteria isolates, especially MAI Complex and M. abscessus, are common in CF patients.

   b) If purulent nasal discharge is present submit nasal swab for CUCF.
3. **Blood cultures:**
   a) Blood cultures are not routinely done. Significant fever is unusual in CF patients. If a patient has significant fever (oral temp ≥38.5°C) or if there is possible line infection obtain blood cultures, including one from implanted venous access if present.

4. **Imaging studies:**
   a) Always obtain EPA & lateral chest radiograph on admission. Compare with previous studies! If there is airspace disease or pleural abnormality present on the admission chest x-ray repeat the study in 2-3 days. In these cases the chest x-ray should also be repeated at the end of antibiotic treatment.
   b) If there has been a significant change in respiratory signs and symptoms, especially gross hemoptysis or a significant change in plain radiograph findings, consider ordering a high-resolution chest CT scan. Be cautious with ordering CT scans due to radiation exposure.
   c) If there are significant sinus complaints consider ordering sinus CT scan.
   d) When there are significant GI complaints of bloating, cramping, pain, constipation and/or decreased frequency of BMs, order abdominal radiographs (supine AP of the abdomen). In DIOS there will be stool throughout the entire colon to the ileo-cecal valve.
   e) Patients with abnormal LFTs, especially significant elevations of alkaline phosphatase or ALT, should be evaluated with abdominal ultrasound if it has not been performed recently.

5. **Cardio-pulmonary diagnostic studies:**
   a) If a PFT was not done in the Adult CF Clinic within 72 hours prior to admission, order spirometry ASAP. Repeat spirometry every 7 days while on IV antibiotics. Order room air ABG if room air pulse oxygen saturation is ≤90% or CO2 on chemistry panel is ≥37 meq/l.
   b) Order ECG if significant tachycardia (HR >110/min) or arrhythmia present. Be alert to QTc prolongation (≥120 milliseconds) from some drugs and electrolyte abnormalities.
   c) Order Echocardiogram with Doppler flow studies if at risk for pulmonary hypertension.

**RESPIRATORY THERAPY SERVICES**

1. **Airway clearance therapy (ACT):** Request Respiratory Therapy to perform a “CF patient evaluation”. RT should review and assess the patient’s home ACT program. Aggressive ACT is an essential component of the in-patient treatment program for pulmonary exacerbations. The RT staff should also reinforce patient education re ACT (REACT) at home.

2. **Bronchodilators:** Routinely order combined albuterol 2.5 mg +/- ipratropium (Atrovent®) 0.5 mg nebulized q 4-6 hours/ TID - QID, while awake. If a patient is not in any respiratory distress you may omit nebulized bronchodilators between 12 midnight and 6 am, except PRN. Levalbuterol (Xopenex®) is non-formulary but may be ordered when albuterol is not well tolerated. Note the usual duration of effect of albuterol is 3-6 hours and Levalbuterol is 4-6 hours. Bronchodilators by MDI or dry-powder inhalers are not usually used for hospitalized CF patients. Remember beta-agonist agents may also increase ciliary activity.

3. **Hypertonic saline:** Hypertonic (7%) saline (HTS) - 4 ml nebulized 2 to 4 times daily; minimum of twice daily. Always administer a rapid onset-beta agonist prior to HTS. Exercise caution with the use of hypertonic saline in patients with asthma/ “reactive airways” as HTS may induce bronchospasm. May need to begin with 3.5% saline or “half-dose” (2-3 ml) 7% HTS. Some patients may only tolerate 3.5% saline.

4. **Dornase alfa (Pulmozyme®):** Normally we nebulize Dornase alfa 2.5 mg twice daily during hospitalizations. This should be nebulized after hypertonic saline. There is no evidence to support twice daily dosing for exacerbations. Pulmozyme® is FDA approved for both once and twice daily dosing.

5. **Mechanical CPT:** Order high frequency chest wall oscillation (HFCWO) Vest, manual CPT (by RT), and/or Acapella™ device four times a day. CPT usually follows nebulized treatments. Nebulized
treatments may be given during the 30 minute Vest sessions. Patients may benefit from a combination of several mechanical methods. Additional methods may be suggested by Respiratory Therapy.

6. **Hemoptysis**: If a patient is having significant hemoptysis, hold hypertonic saline and CPT until hemoptysis resolves. Dornase alfa and bronchodilators may be given.

7. **Supplemental oxygen**: Is indicated if resting pulse oxygen saturation at rest or when ambulating is ≤90%. Hypoxia requiring supplemental O2 should be confirmed with a room air ABG.

**TREATMENT of RESPIRATORY INFECTIONS**

1. **Bronchiectasis**: The most common type of pulmonary exacerbation in cystic fibrosis is an exacerbation of bronchiectasis. Bronchiectasis is a suppurative lung disease with upper zone predominance. Pneumonia with alveolar consolidation may occur, but is less common. Pleuritic pain is common, although parapneumonic effusion is not common. Parenteral antibiotics are always used when hospitalization is required.

2. **Sinusitis**: Acute sinusitis or exacerbation of chronic sinusitis frequently accompanies an exacerbation of bronchiectasis. Nasal polyps are frequently present and may contribute to sino-nasal obstruction.

3. **CF culture results**: Review results of sputum CF cultures for the past year. The most common pathogen is *Pseudomonas aeruginosa* (85% of adults at Tulane). *Pseudomonas aeruginosa* in the CF patient typically evolves into mucoid phenotypes. Mucoid strains grow in a biofilm which are inherently drug-resistant and essentially impossible to eradicate from the respiratory tract. Sixty-five percent of our patients have mucoid *Pseudomonas aeruginosa*. Frequently there are multiple strains of *Pseudomonas aeruginosa*, both mucoid and non-mucoid, isolated from several different sputum samples with differing susceptibility patterns. Occasionally other strains of *Pseudomonas* such as *P. fluorescens* will be isolated. Approximately 19% of *Pseudomonas* isolates will be multiderug-resistant. The next most common pathogen is *Staphylococcus aureus*, frequently MRSA. Approximately 20% of our patients will be coinfected with *Pseudomonas aeruginosa* and *Staph aureus*. Non-typeable *H. influenzae* infections occasionally may occur. Other less common pathogens are *Alcaligenes (Achromobacter) xylosoxidans* and *Stenotrophomonas maltophilia*. *Burkholderia cepacia* complex infections can be very serious, but are uncommon (<1% of all patients) at the Tulane CF Center. Remember that the results of sputum cultures in the CF patient may represent only be the “tip of the iceberg”.

3. **Antibiotic selection**:

   a. **Pseudomonas aeruginosa**: Two IV antipseudomonal agents are the standard of care for broad coverage and possible synergistic effect. A typical regimen would include one agent from the beta-lactam class, e.g. piperacillin/ tazobactam (Zosyn®), ceftazidime, or meropenem, plus a second agent, either an aminoglycoside or a fluoroquinolone. Meropenem should not be used as the anti-pseudomonal drug of “first choice”. Doripenem is not recommended for lower respiratory tract infections. Review the results of susceptibility testing over the prior 6-12 months. Choose antimicrobial agents based on previous these results. You may have to make a judgment based on multiple previous isolates with variable susceptibility patterns. Susceptibility for the mucoid strains is probably more critical than the non-mucoid strains. Antimicrobial regimens are usually based on the last course of treatment, unless there was a suboptimal response to the previous antibiotic regimen. The CF Foundation Guidelines and Up-to-Date both recommend two agents for *Pseudomonas*. There is no evidence-based data to support the CFF Consensus, but this is the standard approach in North America, the UK, and Europe. If the severity of disease is judged to be “moderate” (clinical judgment call), monotherapy with an IV beta-lactam agent may be an option.

   b. **Methicillin/ oxacillin-susceptible Staphylococcus aureus**: For patients infected with only MSSA use nafcillin or a first or second generation cephalosporin (e.g. cefazolin). For infections with MSSA plus *Pseudomonas* the 2-drug regimens used for *Pseudomonas* should provide adequate coverage for MSSA.

   d. **Methicillin/ oxacillin-resistant Staphylococcus aureus**: Infection with MRSA is an increasing problem. Use IV vancomycin, linezolid, or sulfamethoxazole – trimethoprim (SMX /TMP). (Note that IV
SMX/TMP has been on a national back-order for the past year.) Many patients do not tolerate IV vancomycin due to adverse effects (“redman” syndrome). If MRSA is considered a less important cause of the pulmonary infection, may consider oral linezolid, high-dose oral SMX/TMP, or oral minocycline/doxycycline.

e. **Non-typeable H. influenzae**: Non-typeable *H. influenzae* infections may occur concurrently with *Pseudomonas* and/or *Staph*. This organism is susceptible to a wide variety of antibiotics, including 2nd generation cephalosporins, penicillin/beta-lactamase inhibitor combinations, carbapenems, and fluoroquinolones.

f. **Polymicrobial infections**: Infections due to multiple organisms, e.g. *Pseudomonas aeruginosa*, *Staphylococcus aureus* and/or another gram negative bacillus may require combinations of 3 antibiotic agents to provide adequate coverage.

g. **Stenotrophomonas maltophilia**: This organism is an increasing problem in the CF population, occurring in 12% of US CF patients. *S. maltophilia* is frequently multiply-drug resistant and can develop resistance during treatment. It is typically resistant to the beta-lactam class and aminoglycosides. Sulfamethoxazole - Trimethoprim (SMX/TMP) is generally considered the antibiotic of choice. Some authorities recommend utilizing combinations of SMX/TMP with Ticarcillin/Clavulanate (Timentin®) or levofloxacin. Many strains have been reported as being susceptible in-vitro to the tetracyclines (doxycycline and minocycline) and the quinolones, especially newer quinolones such as moxifloxacin (Avelox).

h. **Alcaligenes (Achromobacter) xylosoxidans**: *A. xylosoxidans* is also an increasing problem in the CF population with current incidence of eight percent. It is now being recognized as a cause of deterioration of lung function. It is typically fairly drug resistant, but is usually susceptible to SMX/TMP. Some authorities recommend utilizing multi-drug combinations of IV minocycline, ciprofloxacin, and imipenem/meropenem. It also may be susceptible to Levofloxacin, Timentin® and/or Augmentin®. If use oral Augmentin XR®, the suggested dose is 2000 mg twice a day.

i. **Burkholderia cepacia complex**: Members of the *B. cepacia* complex class may be multi-drug resistant and some have been associated with a fatal invasive infection (“Cepacia syndrome”). *B. cenocepacia* is the most problematic species for CF patients. These infections are uncommon at TMC.

j. **Other gram-negative bacilli**: Other less common gram-negative bacilli that are isolated may also be important as pathogens, e.g. non-aeruginosa strains of *Pseudomonas*, *Acinetobacter* species, *Ralstonia* species and *Pandoraea* species. Select antibiotics based on most recent susceptibility tests. ID Consult may be appropriate for these cases.

k. **Anaerobic bacteria**: There are recent studies suggesting that anaerobes may be important respiratory pathogens in CF patients. Their isolation requires specialized culture techniques. The most commonly identified species are *Prevotella*, *Veillonella*, *Propionibacterium*, and *Actinomyces*. In general any patient with poor or only fair oral hygiene is at increased risk of anaerobic pulmonary infections. A tip-off to an anaerobic infection may be foul-smelling (putrid) sputum. These are generally susceptible to meropenem and Zosyn®.

4. **History of Prior Antibiotics**: Assess previous parenteral antibiotic therapy and any past occurrence of adverse effects (AE). Use of an agent from a class to which the patient has had prior allergic reactions may require desensitization. Consult the Allergy Service ASAP. Exercise caution with the use of nephrotoxic agents if a patient has evidence of a decrease in GFR over time, e.g. an increase in serum creatinine or calculated GFR <60 ml/min, or has proteinuria.

5. **Monitoring for Renal, Hepatic and/or Hematologic Adverse Effects (AE)**: All antibiotics have the potential for renal, hepatic and/or hematologic AE. A key to avoidance of nephrotoxicity from aminoglycosides is maintaining appropriate trough levels. See the ANTIBIOTIC DOSES, SCHEDULES, & NOTES for ADULTS with CYSTIC FIBROSIS (attached) for details re drug levels and recommended labs. Hypomagnesaemia and urine microalbuminuria are early indicators of renal injury and may precede an increase in serum creatinine. If there is a significant increase in serum creatinine (≥0.4 mg/dl) during therapy, obtain urinalysis and random urine microalbumin/creatinine ratio. If proteinuria is detected, obtain random urine protein/creatinine ratio. Nafcillin, carbapenems and quinolones have been associated with
drug-induced liver injury. Penicillins and cephalosporin have been associated with anaphylaxis and hematologic adverse effects. Meropenem is associated with elevated AST and ALT of uncertain significance. Significant eosinophilia is occasionally encountered. An absolute eosinophil count (AEC) of ≥1500 is considered toxic. Drug fever may occur with a number of antibiotics, typically occurring in the second to third week, or even after completion. Drug fever will necessitate cessation of the offending drug.

6. Details for Parenteral Antibiotic Therapy:
   a. The IV route is considered preferable for treatment of CF pulmonary exacerbations.
   b. Venous access: Request PICC line placement for patient without an implanted venous access device (VAD). PICC line placement is available at TMC 24/7. Access an implanted VAD/Port with ½” or ¾” Huber needle per TMC Protocol.
   c. Antibiotic doses: Doses of antimicrobial agents for CF patients are higher than for non-CF patients. Do not use “The Sanford Guide”. Dose to the MAX! CF patients have unique pharmacokinetics of most antibiotics, with an increased volume of distribution and/or increased clearance that necessitate higher than usual doses. Refer to the ANTIBIOTIC DOSES, SCHEDULES, & NOTES for ADULTS with CYSTIC FIBROSIS (attached). *Pseudomonas aeruginosa* in the CF patient may be multi-drug resistant. *Pseudomonas* strains in CF are frequently mucoid phenotype and grow in a biofilm which limits penetration by antibiotics. Bronchiectasis, a suppurative lung disease, requires higher doses of antibiotics and prolonged courses of treatment. Renal insufficiency may necessitate adjustment of antibiotic doses.
   d. Dosing schedules: For practical purposes a multi-drug regimen for *Pseudomonas* infections can only be done with a Q 6 or Q 8 hour dosing schedule. The beta-lactams and monobactams must be dosed Q 6 or Q 8 hours when treating *Pseudomonas* infections. Q 12 hour regimens of beta-lactam antibiotics are unacceptable for treatment of *Pseudomonas* infections. Colistin and ciprofloxacin can be dosed every 8 or 12 hours. Tobramycin is typically dosed utilizing extended interval (i.e. once daily) schedules. **Use a combination of antibiotic schedules that are easily synchronized.** For example a Q 6 hour schedule plus a Q 12 hour schedule is OK; but Q 8 hours plus Q 6 hours is not OK. For outpatient therapy, IV antibiotics which can be administered Q 8 or Q 24 hours are more “patient friendly”. Adjust administration times for convenience at home, no 2 am doses.
   e. Tobramycin extended interval dosing: Once daily dosing is now the standard practice with tobramycin. When tobramycin is ordered once daily the preferred administration time is 2:00 pm. If the initial dose is given at a non-standard administration time, the 2nd dose may be given ≥12 hours after the first dose and the 3rd dose at 2 pm the following day. With normal renal function a random level obtained 12-16 hours after the first dose will be within the target trough range. If CCR <70 ml/min, 2nd dose should be given 24 hours after the first dose, and the 3rd dose at 2 pm the next day. A random level should be obtained 20 hours after the first 2 pm dose. This level should be ≤ 2.0 mcg/ml. The 2 pm time facilitates obtaining periodic trough levels, especially as an outpatient.
   f. Duration of antibiotic therapy: The total duration of parenteral antibiotic therapy is typically 21 days and occasionally 28 days (in-hospital and out-patient therapy combined). Courses of 14 days may be appropriate for patients with relatively mild CF lung disease (FEV1 ≥ 70% predicted). These shorter courses are not commonly used at this Center with adult patients. Longer durations (5 – 6 weeks) may be necessary if there has been a suboptimal clinical response or early recurrence of an exacerbation. A suboptimal response may necessitate a change in the antibiotic regimen. Consideration of a longer duration or a change in antibiotic regimen should be discussed with one of the Adult CF Team physicians. All anti-pseudomonal antibiotics should be continued for the same duration.
   g. For detailed information re specific antibiotic dosing and monitoring see ANTIBIOTIC DOSES, SCHEDULES, & NOTES for ADULTS with CYSTIC FIBROSIS (attached).

7. Nebulized Antibiotics:
   a. Nebulized antibiotics such as tobramycin (TOBI® or compounded tobramycin), Cayston®, or compounded colistin/colistimethate are not routinely used in the hospital setting. They may be
considered in certain clinical situations, e.g. severe exacerbation or very drug resistant infection. They may be administered concomitant with IV aminoglycosides. Note that nebulized tobramycin is partially absorbed and may affect tobramycin serum levels and could increase the risk of nephrotoxicity.

**ACTIVITY AND PULMONARY REHABILITATION**

1. Patients should be encouraged to ambulate as tolerated.

2. Patients who are not too ill or too dyspneic should be scheduled for pulmonary rehab sessions (low tolerance exercise) daily, Monday thru Friday. Schedule with the Pulmonary Diagnostic Lab (988-8630)

**IMMUNIZATIONS**

1. If a patient is not up-to-date for pneumococcal vaccine, influenza vaccine, and/or pertussis (Tdap) vaccine, these vaccines should be given prior to discharge.

**DISCHARGE PLANNING**

1. Most hospitalizations will not exceed 1 week. Some patients admitted for “tune-ups” may only be hospitalized for 1 - 2 days. Length of stay will depend on severity of illness, comorbidities (e.g. CFRD), need for intensive ACT and low tolerance pulmonary rehab, slow response to therapy, lack of in-hospital problems or complications, and feasibility of safe at-home IV antibiotic therapy. Note that some patients requiring “tune-ups” with out-patient IV antibiotic therapy may not be hospitalized. Their treatment will be instituted on an outpatient basis. This decision will be made by the patient’s CF Physician.

2. The decision to discharge to out-patient care with IV antibiotics requires assessment of the severity of disease, initial response to therapy, appropriate home situation for IV antibiotics, and anticipated patient compliance. The problem(s) that necessitated hospitalization must be improving. Generally there should be a caregiver available to assist the patient at home. Patients with a history of non-compliance with home treatments and required follow-up visits and labs, or a history of line complications (e.g. infection, thrombosis, etc.) are not good candidates for out-patient parenteral antibiotic therapy.

3. The Pulmonary Diseases Section’s Nurse Practitioner, Jennifer Greenheck (pager 544-3509), should be contacted regarding patients being considered/planned for out-patient IV antibiotics therapy. The Nurse Practitioner generally will follow all CF patients while they are receiving out-patient IV antibiotics. They will typically be seen every 7 – 10 days.

3. Discharge plans must be reviewed with one of the CF Team Physicians prior to discharge.

4. The CF Center Social Worker and/ or Hospital Case Management will assist with arranging out-patient IV antibiotic therapy and care. Planning for discharge should begin 24 - 48 hours before the anticipated discharge. A minimum of 24 hours is normally required for arranging appropriate out-patient care. An order indicating planned discharge should be written the day prior to the anticipated date of discharge. This alerts the floor nurses. For week-end discharges arrangements should be completed on Friday.

***Out-patient Parenteral Antibiotic Therapy (OPAT) and Home Health Care***

1. The Social Worker/ Case Manager will contact the appropriate home health agency and/or infusion service agency. The infusion service agency may assist with the initial assessment and training for out-patient IV antibiotic therapy prior to discharge.

2. Specific orders are needed for out-patient care and OPAT. Remember the patient is actually being admitted to a different site and level of care, out-patient. Orders should include the specific antibiotic(s), doses, and number of days of therapy with the antibiotic completion date. ALL anti-pseudomonal antibiotics should be given for the same duration with the same stop date.

3. Orders for out-patient care should include orders for PICC or implanted venous access care (periodic cleaning of insertion site, dressing changes, flushes, etc.) and weekly labs. For some patients this may be done at an out-patient infusion center. There should be specific orders for weekly labs to include CBC
with diff, CMP, Mg, urine microalbumin/creatinine ratio, and random aminoglycoside level (patients receiving an aminoglycoside). For patients not receiving an aminoglycoside or colistin the Mg and URMICROA are omitted. A HSCRP should be ordered at “end-of-care”.

4. Follow-up care by the Adult CF Program Nurse Practitioner during OPAT is mandatory. The NP will monitor out-patient labs obtained during OPAT and will see patients in the Tulane Lung Center Clinic every 7 - 10 days. In some cases the patient may be seen by their CF Physician. PFTs will be obtained at each OV and at the completion of OPAT. Decisions regarding extending duration of OPAT will be made based on assessment at the follow-up visits. There should be a follow-up NP or MD visit at the completion of OPAT or within 7-10 days of completion. It is very important that there be documentation of response to therapy at the completion of IV antibiotics. Emphasize to the patient the importance of follow-up visits during OPAT. A patient’s non-compliance with follow-up visits could preclude future OPAT. The NP should arrange the follow-up appointment prior to discharge. All patients also should be seen by their physician in CF Clinic within 4-6 weeks of completing IV antibiotics for a pulmonary exacerbation. This follow-up should not be delayed for three months. Remember that the CF Foundation recommends routine CF Clinic follow-up visits every three months.

5. New prescriptions for a patient’s routine home medicines are not usually necessary. If new prescriptions other than the IV antibiotics are needed, it is preferable to generate these in eCW using a new “Telephone Encounter”.

6. A copy of the Discharge Orders/ Home Health - Infusion orders must be faxed to the Tulane Lung Center at 988-8629.

7. Dictate “E-sig” Discharge Summary. The Discharge Summary should include specific information regarding hospital course and discharge orders, including antibiotic doses with start and stop dates. The Discharge Summary should be dictated the day of discharge.

Prepared by Dean B. Ellithorpe, M.D.
Director, Tulane Adult Cystic Fibrosis Program
Tulane University Health Sciences Center
New Orleans, LA