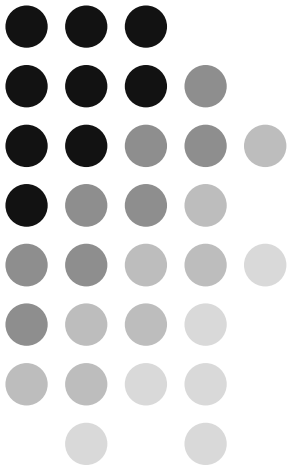
Overview of Cystic Fibrosis & Its Management



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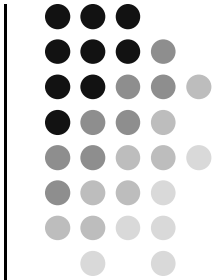
Disclosure/Disclaimer



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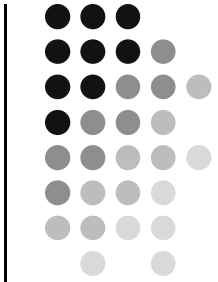
Learning Objectives



- Describe Cystic Fibrosis Epidemiology and Pathology
- Introduce CFTR and its classes of genetic defects
- List method(s) of CF diagnosis
- Discuss clinical CF features and symptoms
- Review common CF therapeutic agents
- Describe a typical CF exacerbation & management
- Introduce “new” CF therapy options

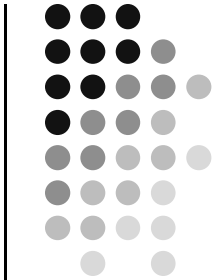
Epidemiology…

- Cystic Fibrosis (CF) is the second most common life shortening inherited disease in childhood, and is the most common among the Caucasian population
- Approximately 30,000 Americans have CF
- 1000 new cases identified annually
- More than 10 million Americans are unknowing, symptomless carriers of a mutated cystic fibrosis gene.

- ~50% identified via “Newborn Screen” by 2010
- 1: 2,500 Caucasians
- 1: 10,900 Native Americans
- 1: 13,500 Hispanics
- 1: 15,000 African Americans
- 1: 30,000 Asian Americans

Source: CDC. Cystic Fibrosis Clinical Validity. September 10, 2007
Lancet: 2003; 361-681
J. Ped. 1998; 132-255
American Lung Association State of Lung Disease in Diverse Communities 2010

New Born Screening



- All 50 states and the District of Columbia screen newborns for CF, but the method for screening may differ from state to state.
- Serum level of Immunoreactive trypsinogent, or IRT is identified
- In people who have CF, IRT levels tend to be high but IRT levels can also be high if a baby is premature or had a stressful delivery or for other reasons.
- Some states only test IRT levels on the first blood test. These are called IRT-only states. Other states conduct both an IRT and a DNA test. These are called IRT-DNA states.
- DNA testing is still only a "screen" for CF. It is not a diagnosis, which can only be confirmed with a sweat test.
- Sweat testing is required to either rule in or rule out a CF diagnosis.

Diagnosis…

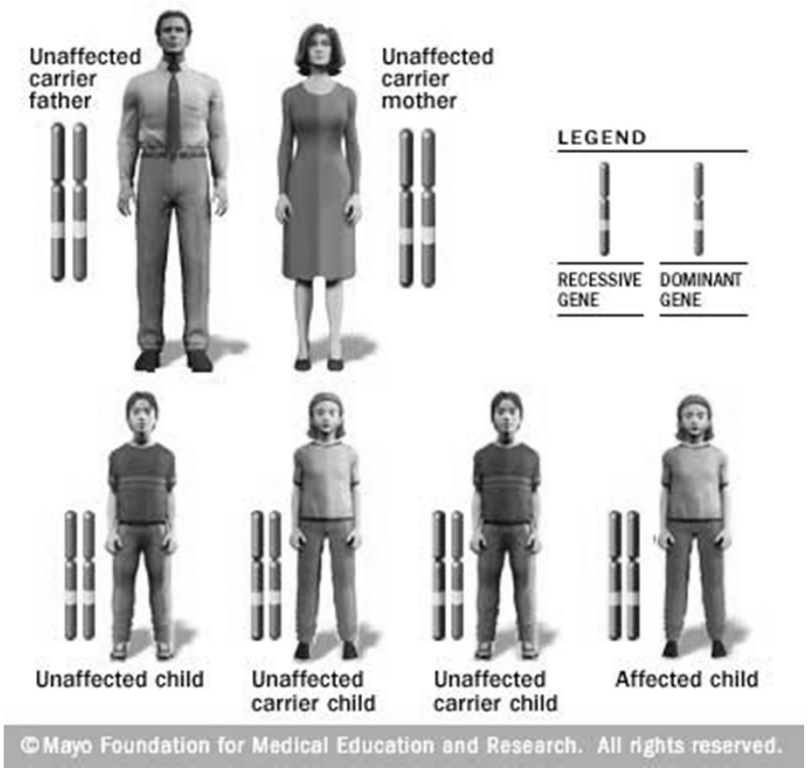
Criteria:

1. *Clinical symptoms consistent with CF in at least one organ system
2. Evidence of CFTR dysfunction via
   - *Elevated sweat chloride >60mmol/l (two tests)
   - Disease causing CFTR by genetic testing
     - Genetic mapping is not mandatory for diagnosis, but can help to confirm diagnosis and may assist in therapeutic options

Cystic Fibrosis Foundation (www.cff.org)

Autosomal Recessive Genetics

Two carriers = 25% chance of CF in Child



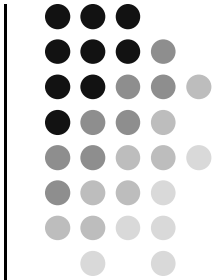
Mayo Foundation for Medical Education
Website visited: 10/18/12

1989:
Cystic Fibrosis Gene Identified,
The Human Genome Project begun

Researchers in CF (Dr. Francis Collins, et al) defined full human genome by 2003

Science. October, 1989

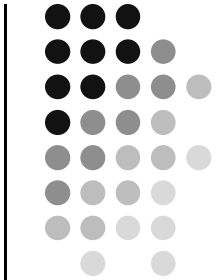
Evolution of Life expectancy:



- In the 1950s, few people with CF lived to go to elementary school.
- 1985, the median survival age was about 25 years. In 2007, the predicted survival age was 37.4 years.
- With earlier diagnosis, the age of survival for patients with CF continues to increase
- Impact of new “gene targeted” therapies?

Source: CDC. Cystic Fibrosis Clinical Validity. September 10, 2007
American Lung Association State of Lung Disease in Diverse Communities 2010

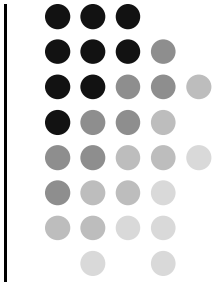
Pathology….



- CF is caused by mutations (≥1400+ described) on chromosome 7 encoding for a 1480 amino acid polypeptide that functions as a chloride channel
- Most common defective genotype, 2 copies: **del**F508 in Caucasian population (deletion of DNA bases coding for phenylalanine at position 508)
  - G542X
  - G551D
  - N1303K
  - W1282X
- Amino acid polypeptide common name: "CFTR"
  Cystic Fibrosis Transmembrane Conductance Regulator
- CFTR functions as a regulated chloride channel in epithelial membranes located in several organs
- Sodium & Bicarbonate channels also exist; all necessary for water, fluid, & pH balance
- Optimal cilia function depends on function of above channels

Lancet. 2003 681-689

Six classes of defective CFTR: genotype dependant



1. None synthesized
2. Defective processing*
3. Defective regulation
4. Defective conductance
5. Partly defective production or processing
6. Defective regulation of other channels

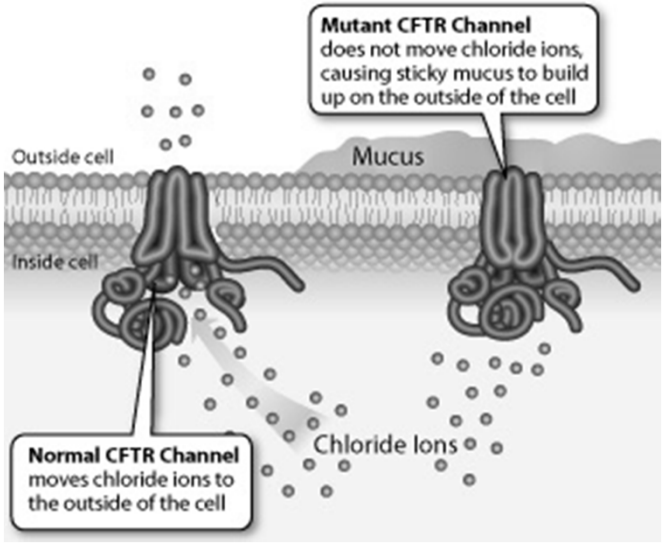
- Class 1, 2*, 3 most common (2* highest % worldwide)
- “Atypical CF” & symptoms do exist & may be associated with various mutation(s). Can be difficult to diagnose with current techniques

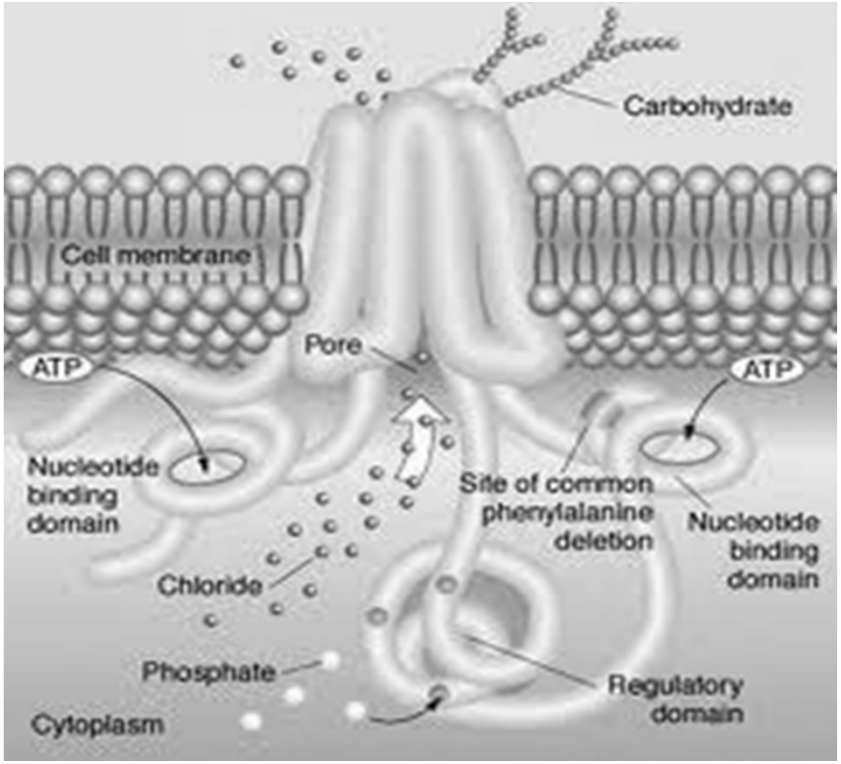
Lancet. 2003 681-689

CFTR…

Disease affects organs that express CFTR :

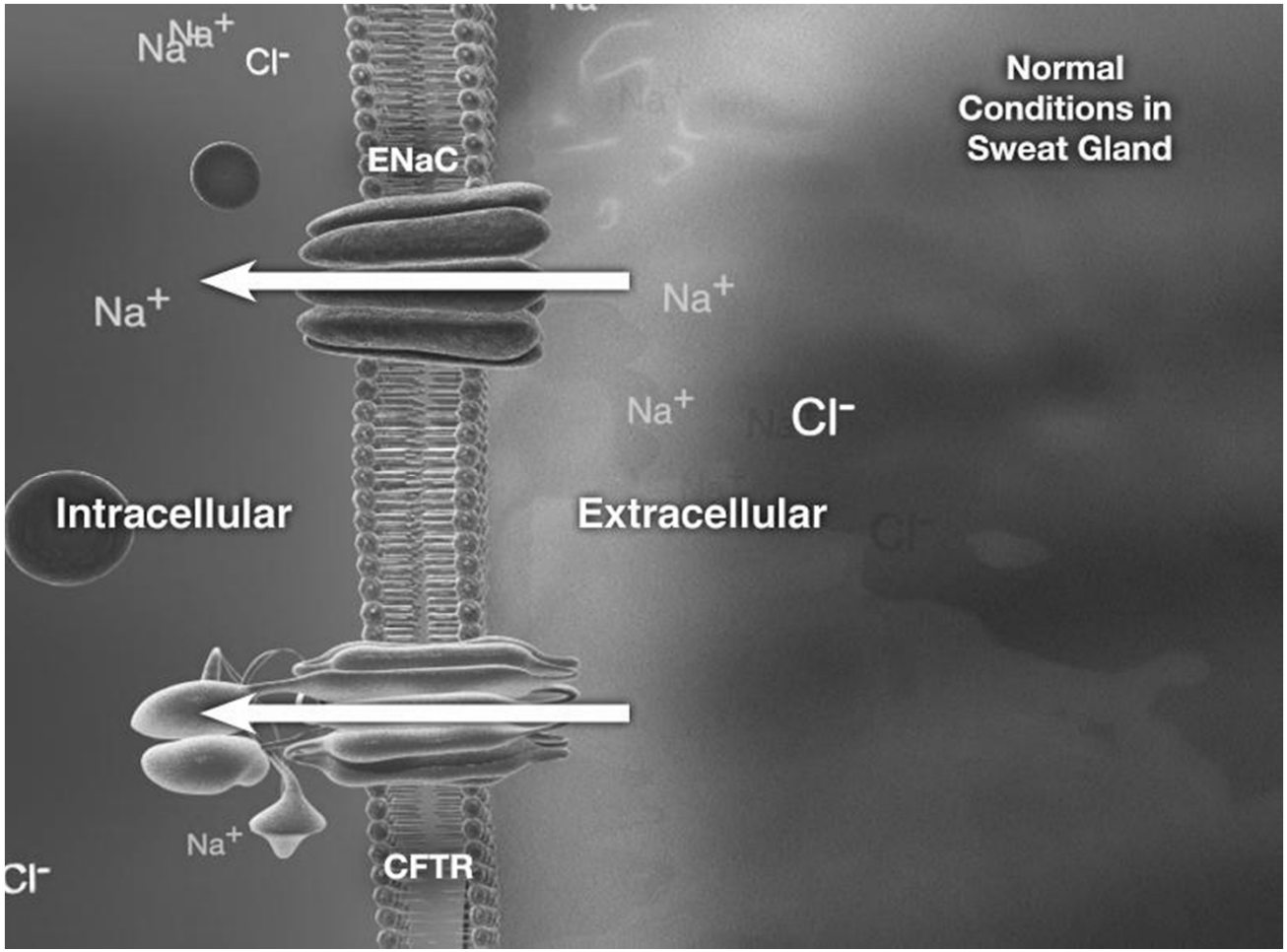
"Multisystem Disease"





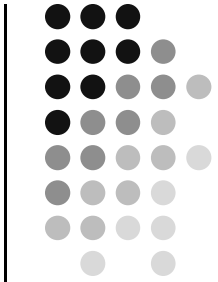
Mass Genomics.org
Website visit: 8/4/12

CFTR effects
Other channels too…



MassGenomics.org
Website visit: 8/4/12

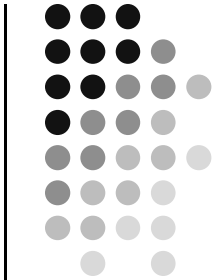
Organs effected:
Any that express CFTR



- Lungs*
- Secretory cells (exocrine)
- Sinuses
- Pancreas
- Intestines
- Liver
- Reproductive Tract

- Most striking changes observed in lungs and GI tract early in life.
- Airway Inflammation is well documented even in neonates with CF

Clinical Features…

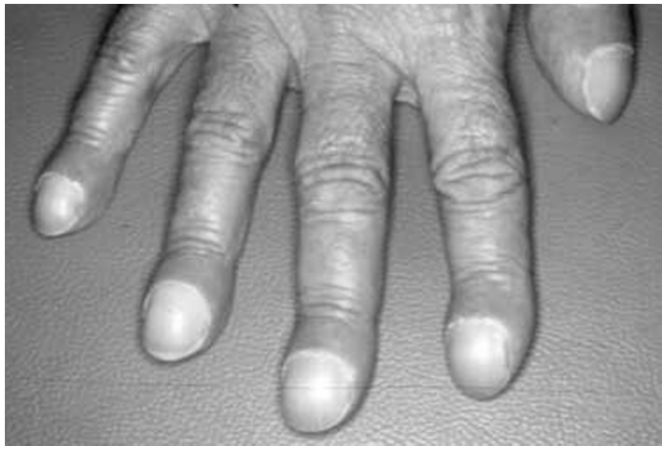


Impaired or absent transport of chloride, sodium, and bicarbonate leads to thick, viscous secretions in the effected organs and increased salt content in sweat gland secretions

Clinical Symptoms…

Respiratory:

- Cough, hyperinflation, PFT's consistent with obstructive airway disease, bronchiectasis, increased sputum production
- S.Aureus, H. Influenza, P. Aeruginosa infections common
- Digital clubbing seen:
- Periods of clinical stability followed by exacerbation



Clinical Symptoms…

Sinuses:

- Panopacification of paranasal sinuses in 90 to 100% of CF patients > 8 mos old
- Nasal polyposis in 10 to 35% of CF patients
- Chronic rhinosinusitis may be noted in patients with only one CFTR mutation
- Nasal surgery for polyp removal common in CF management

Clinical Symptoms…

Pancreas:

- Many with insufficient pancreatic exocrine function at birth; others may move from pancreatic sufficiency to insufficiency
- Malabsorption of fat (steatorrhea) and protein
- Malabsorption of fat soluble vitamins: ADEK
- Failure to thrive may be a presenting sign w/o newborn screening
- Pancreatic insufficient patients require oral pancreatic enzyme replacement
  - Fecal fat test can be completed to document fat loss and malabsorption
- Pancreatic endocrine dysfunction may occur:
  - Decreased or destroyed function of islet cells
  - CFRD
  - Insulin use for management (no oral hypoglycemic therpies)

Clinical Symptoms…

Gastrointestinal:

- Meconium Ileus in 10% to 20% of newborns with CF
- Steatorrhea
- Failure to thrive (weight loss)
- Small bowel obstructions: “DIOS” or “meconium ileus equivalent” occurs in 15% of adults with CF and those with advanced disease
- Bowel evacuation often necessary
- Surgery may be indicated

Clinical Symptoms…

Biliary:

- Biliary cirrhosis due to thick bile in ducts
- Elevations of serum alkaline phosphatase
- Hepatomegaly (enlarged liver)
- Cholelithiasis (gallstones)
- Few CF patients develop periportal fibrosis, portal hypertension & variceal bleeding
- Cholecystectomy & Liver transplantation does occasionally occur in CF; not common

Clinical Symptoms…

Fertility:

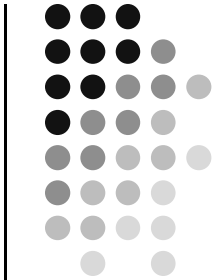
- Males: 95% or more with CF are infertile
  - Spermatogenesis may be normal
  - Defects in sperm transport
  - Incomplete development of, or absent vans deferens
  - Rare, but possible to have ~normal lung function and absent vans deferens; infertility becomes presenting symptom prior to diagnosis
    - Occurrence primarily before newborn screening

Clinical Symptoms…

Fertility (Cont):

- Female infertility: ~ 50%
- Related to amenorrhea (may be secondary to malnutrition)
- Related to viscous cervical mucus
- With increased life expectancy and improved nutritional status; pregnancy in CF has become a newer clinical focus
- Pharmacists are consulted re: daily medication options & therapies safe in exacerbations

Clinical Symptoms…



Musculoskeletal:

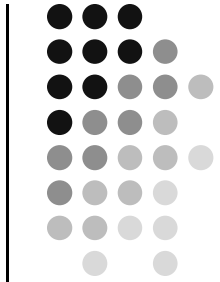
- CF causes reduced bone mineral content
- Accelerated bone loss and decreased bone density: often seen in homozygous delF508
- Poor to no absorption of Vitamin D may contribute to osteoporosis
- Arthropathy occurs in 2% to 10% of CF patients
- Chest wall pain is a common adult symptom

Clinical Symptoms…

Recurrent venous thrombosis:

- CF is a risk factor for venous thrombosis
- Most venous thrombotic events (VTE) occurred in the setting of a central venous catheter; “provoked” (often placed for IV antibiotic use during exacerbations).
- Monitor for signs/symptoms of line induced VTE: use D-dimer; Doppler ultrasound
- Remove line if possible, anticoagulate per guidelines
- Pharmacists often consulted regarding LMWH, NOAC and/or warfarin therapies and dosing

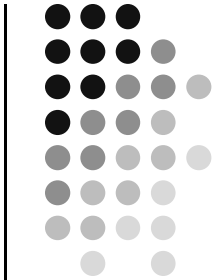
Symptom Monitoring…



Respiratory System: a primary focus with progression of decline primarily associated with CF morbidity/mortality

- Cough frequency
- Sputum production
- Chest pain
- Dyspnea
- Exercise Tolerance
- 6MWT used to identify need for supplemental 02
- Spirometry (%FEV1)
  - Monitors lung function over time
  - Guides lung transplant discussion

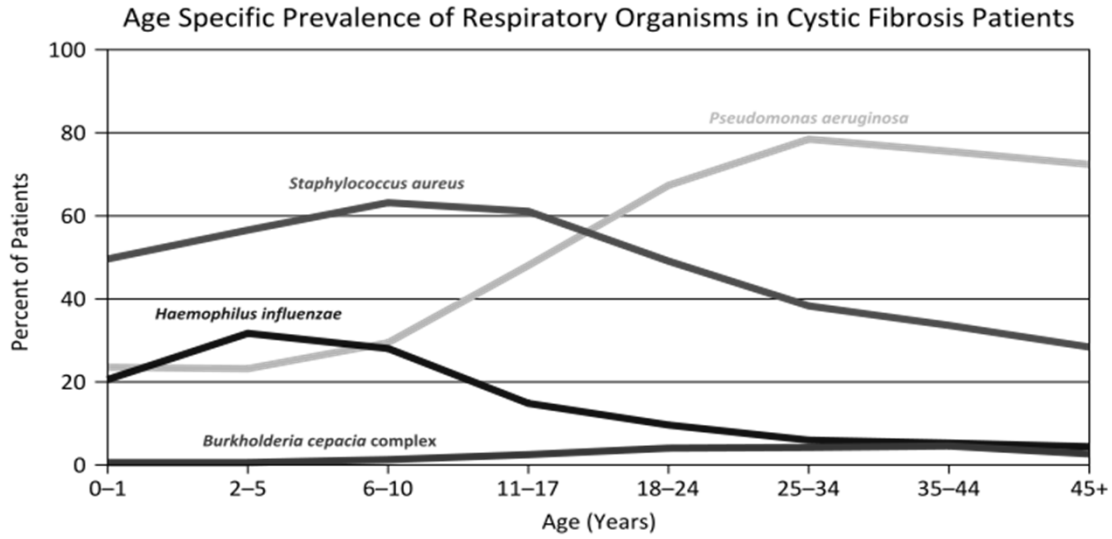
Treatments…Two Catagories



- Symptomatic Treatments
  - Remains primary form/category of therapy at this time
  - Has significantly increased life expectancy; primarily through antimicrobials (oral, IV, inhaled)
  - Rigorous daily oral, inhaled & airway clearance regimens
- Causative Treatments
  - Restores partial/full CFTR production & function
    - Depending on gene mutation(s)
  - Gene Therapy
    - Kalydeco® (Ivacaftor)
    - Orkambi® (Ivacaftor + lumicaftor)
  - Research & Development on-going: CFF website

Symptomatic Treatment…

- Chest Physiotherapy (“airway clearance”): judged as routine; no studies completed to prove effect on course of disease (chest percussion, acapella, VEST®, vigorous exercise, hypertonic saline)
- Prevention of bacterial lung infection transmission via controlled hygiene measures and separation (isolation) guidelines



Thorax 1990; Vol 45: 881-884
Port CF

Symptomatic Treatment…

- P.aeruginosa is considered a major pathogen.
  S. aureus and H. influenzae also significant.
- Initial colonization period with non-mucoid strains of P.aeruginosa are followed by chronic infection with mucoid strains.
- Mucoid strains generally cannot be eradicated likely due to poor penetration of antibiotics into anaerobic sputum plugs and into mucoid layer (biofilms)
- Rapid mutator strains of bacteria form with increased resistance
- Adaptive resistance patterns occur

J.Clin Invest 1999; 103: 1113-1117
J. Antimicrob Chemo 1996; 37: 1155-64

Symptomatic Treatment…

- Inhaled therapy with anti-pseudomonas agents have had positive clinical impact. Sputum Culture/ Sensitivities guide but do not dictate choice:
  - Tobramycin neb suspension: 300mg/5mls or 300mg/4mls inhaled BID x 28 days on/ 28 days off then repeat cycle
  - TOBI® Podhaler: 112mg (28mg/cap) inhaled BID
  - Colistimethate: 75mg to 150mg inhaled BID x 28 days on/28 days off then repeat cycle. Reconstitution required
  - Aztreonam: 75mg inhaled three times daily x 28 days on/ 28 days off then repeat cycle

Ped Pulm 1989; Vol 6: 91-98
J Antimicrob Chemother 1987; Vol 19: 831-838
NEJM 1999; 340: 23-30

Symptomatic Treatment…

Daily Antibiotic therapy

- Chronic azithromycin:
  - 250mg po once daily or 500mg po 3 x per week
  - Standard anti-bacterial properties
  - Indirect anti-inflammatory properties
  - Managing CF related bronchiectasis- airway inflammation secondary to persistent infection
  - Sputum culture x 3 prior to initiation to r/o NTM

ERJ November 1, 2004; Vol 24 834-838
Treatments in Resp Med, 2004; Vol 4 117-122

Symptomatic Treatment…

Mucolytics (Decreases sputum viscosity, improves lung function, decreases exacerbations):

- Deoxyriboneuclease (Dnase or Dornase®): inhale 2.5mg/2.5mls via nebulizer once daily.
- Hypertonic Saline (HyperSal®) 3% or 7%: inhale 4mls via nebulizer once to twice daily (albuterol use prior). FDA approved as a device vs a drug.

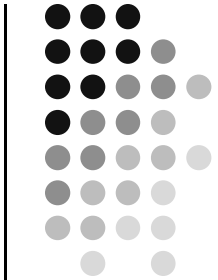
* Clinically, patients encouraged to use during airway clearance with VEST® or other chest percussion devices

Lancet 2001; 358; 1316-1321

Symptomatic Treatment…

- SABA (MDI and/or nebulized solution):
  - Often used daily prior to mucolytic therapies
  - As needed for wheeze and shortness of breath (SOB)
  - Albuterol
  - Pirbuterol (no longer available on US market)
  - Levalbuterol (one isomer of albuterol; non-inferior data available (but not superior); more expensive

Symptomatic Treatment…



Nutrition

- Fat, protein and fat-soluble vitamin absorption is reduced or absent in pancreatic insufficiency
- Oral Enzyme Replacement Therapy is necessary to control steatorrhea and encourage nutritional health
- Nutritional status is closely correlated with lung function
- BMI & growth rate is closely monitored
- Weight loss is one sign of CF exacerbation
- Inter-patient variability/preference exists among enzyme replacement products

Symptomatic Treatment…

Nutrition

- Oral enzyme replacement therapy dosed using units of lipase/kg/meal:

  Maximum: 2,500 units lipase/kg/meal or snack

  Each capsule contains: lipase, amylase, protease

  Capsules can be opened and contents placed in or on food

  Powder also exists for use in formula
- Total daily dose (capsules/powder) is titrated by patient/caregiver based on content of fat or protein in meals and snacks
- Titration also based on bowel movements (number per day, and fat content)
- Creon®, Zenpep®, Pancreaze®, Pertzye®, Viokase®, generics
- Antacids (PPI or H2-blockers) often prescribed for daily use

Symptomatic Treatment…

Nutrition

- Fat soluble vitamin replacement is often required (ABDEK)
- Traditional OTC multivitamins are generally not interchangeable for CF vitamin on a one-to-one basis.
- Can use separate A,D,E,K if needed ($)
- Monitor serum vitamin levels; bone density

Symptomatic Treatment…

Nutrition

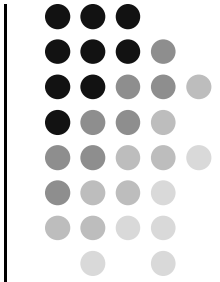
- OGTT to monitor for CFRD
  - Once annually to every other year
- Insulin is the only appropriate therapy in CFRD
- Typically, Glargine used once to twice daily
- Lispro used per sliding scale and/or per gram of carbohydrate intake
- Diabetes clinic referral: Diabetes Education helpful
- Nutritional consultation varies widely from non-CFRD: high calorie/high protein/high fat diets

Symptomatic Treatment…

Liver Disease

- Not present in majority of patients with CF
- If elevated liver enzymes are noted, therapy with Ursodiol 20mg/kg/day can improve biochemical indices of liver function
- When present, generally considered a negative prognostic indicator

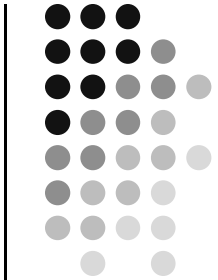
Symptomatic Treatment…



Pain:

- Chronic chest pain is frequent in adults
- Clinicians may initiate management with APAP or NSAIDs: monitor for renal function with other renally toxic medications
  - avoid NSAIDs during exacerbations treated with aminoglycosides
- Advancement to opioids is common: monitor for effect on lung and bowel function; psychosocial issues may arise

Symptomatic Treatment…



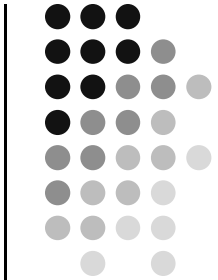
- Oral prednisone (1 to 2 mg/kg every other day):
  improved lung function & reduced frequency of exacerbation x 2 years only. Generally used w/ antimicrobial therapies. Risks may outweigh benefits
- ICS +/- LABA:
  Insufficient evidence to establish whether ICS +/- LABA is beneficial in CF maintenance. CFF guidelines discourage use w/o clear asthma diagnosis
- LABA alone: may be used in patients without associated asthma diagnosis

Growth rate can be affected in pediatric population

Use of ICS in CF patients with asthma co-morbidity is acceptable

The Cochrane Library; June 16 2010

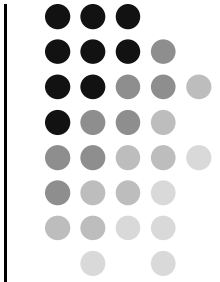
Symptomatic Treatment…



Psychosocial

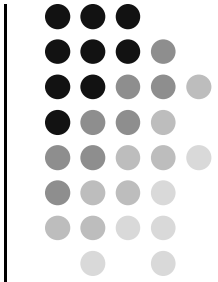
- Significant social impact
  - Developmental and emotional issues; depression common
  - Diagnosis and treatment for depression (screen annually)
  - School/work performance
  - Participation in age-appropriate activities
  - Adherence to complex medication regimens
  - Financial impact
  - Vocational/educational training-preparing for adult life
  - Family planning (medication use & genetic testing)
  - Chronic narcotic use is common in adults

Causative Therapies: New & Future…



- Kalydeco® (Ivacaftor):
- **FDA approved, 2012 for CF patients with G551D**
- **150mg orally BID**
- **February 21, 2014 the FDA approved the expanded use for G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D mutations**
- **Potentiates function of chloride-ion channel**
- **Counseling Points:**
  - Take with fat-containing foods
  - Monitor Liver Enzymes
  - Several DDI: Decrease dose with Inhibitors of CYP3A (ie, clarithromycin or fluconazole)
  - Do not use with inducers of CYP3A (ie, rifampin)
  - May require less enzyme replacement therapy

Causative Therapies: New & Future…



- Orkambi®: (Lumicaftor + Ivacaftor)
  - **FDA approved July 1st, 2015**
  - **Both entities in each tablet (200mg/125mg/tab)**
  - **Two tablets (400mg/250mg) orally BID**
  - **CF patients with 2 copies of Δ F508 only**
  - **Corrects & potentiates function of chloride-ion channel**
  - **Counseling points:**

    -Take with fat-containing foods (nuts, eggs, avacodo)

    -Monitor Liver Enzymes

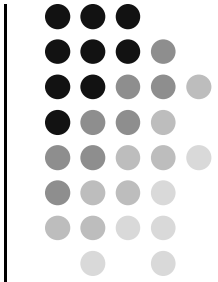
    - Baseline and periodic eye exam (pediatric recommendation)

    -Several DDI: Decrease dose with Inhibitors of CYP3A (ie, clarithromycin or fluconazole)

    -Do not use with inducers of CYP4503A (ie, rifampin)

    - May decrease efficacy of oral contraceptives; recommend 2 forms

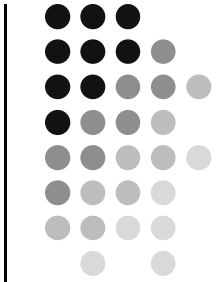
Causative Therapies: New & Future…



Repairing the defective **ΔF508** protein is particularly challenging. In this mutation, a series of problems prevents the protein from reaching the surface of the cell.

Lumacaftor exposure moves the **ΔF508** CFTR protein to the cell surface where Ivacaftor can improve its function helping to increase the flow of chloride and ultimately water in and out of the cell.

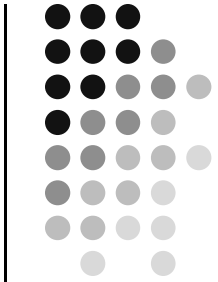
Causative Therapies: New & Future…



VX661 + Kalydeco®

- VX-661 is a “corrector”, designed to work with Ivacaftor to move defective CFTR protein to the proper place in the airway cell membrane and improve its function as a chloride channel
- In Phase 3 trials for CF patients with two copies of delF508 (most common genotype)

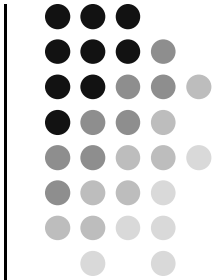
Causative Therapies: New & Future…



- Ataluren
- Non-sense mutation(s)
- In Phase 3 trial

  A novel, small molecule compound that promotes the read-through of premature truncation codons in the CFTR mRNA.

Common Daily Regimen*:



Acetaminophen 500mg/tab: 1-2 tablets q6hr prn

Albuterol MDI: 2 puffs q 4 to 6 hours prn Albuterol 2.5mg/3ml solution: Inhale 3mls by neb q 4 to 6 hours as needed (when not using MDI)

Azithromycin 250mg/tab: 1 tablet daily

Aztreonam 75mg/ml: Inhale 75mg by neb TID x 28 days on, then 28 days off, then repeat cycle (alternate cycles with TOBI)

Fluticasone Propionate NS: 50mcg in EN BID

Citalopram 20mg/tab: 1 tab daily

Cholecalciferol 5000 i.u/tab: 1 tablet daily

Dornase Alpha 1mg/ml: Inhale 2.5mg/2.5mls by neb daily

Insulin Glargine: 10 units SC once daily; Insulin Lispro: 2 units SC per SS

Lactobacillus: 2 capsules BID

CF Multivitamin (AquaADEKs): 2 capsules daily (with or without additional VitD)

Mupirocin 2% ointment: Apply to nares BID prn

Omeprazole 20mg/capsule: 1 capsule daily

Oxycodone 5mg/tab: 1 to 3 tablets every 6 hours as needed for pain

Creon 24,000: 4 to 5 capsules with meals; 2 to 3 capsules with snacks

Sinucleanse Squeeze Nasal Rinse: Mix and rinse sinuses once daily

Tobramycin: 300mg/5ml inhalation suspension: 300mg/5mls by neb BID x 28 days on/ 28 days off; then repeat cycle (alternate with Aztreonam)

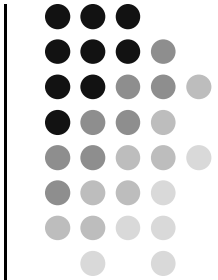
HyperSal 7% inhalation solution: Inhale 4 mls by neb once to twice daily with VEST

Zolpidem 5mg/tablet: 1 tablet at HS prn

+/- Kalydeco or Orkambi BID

*Doesn't include time to use devices such as VEST twice daily. Patients will not use two inhaled antibiotics in the same month

CF Exacerbations…

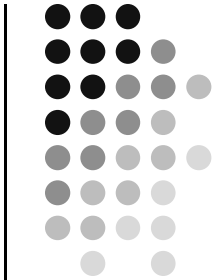


Definition:

"If it walks like a duck, looks like a duck, sounds like a duck…it might be a duck"

- No one, clear definition, however, you'll know it when you see it…
- CF community could use a clear definition

CF Exacerbation…



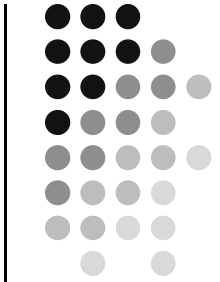
- Increased Sputum production
- Change in Sputum Color (yellowish to med/dark green)
- Increased cough frequency
- Hemoptysis may occur
- Decreased energy level (malaise)
- Decreased Appetite
- Weight loss
- Decrease in Spirometry measures (%FEV1)

Managing CF Exacerbations…

Treatment:

- Continue most daily medications
- Consider Inhaled antibiotic therapy initiation or change in dosing
- Consider oral prednisone burst (10mg/day x ~10 days)
- Add: At-home or In-Patient oral or IV therapy x 14 days
  (dual IV antibiotic regimens are common; inhaled antibiotics discontinued most often)
- Sputum Culture/Sensitivity to guide choice; does not dictate choice
- May require PICC line or can consider placing Hickman Catheter
- Often 1 anti-pseudomonas agent (Tobramycin) and 2nd broad spectrum agent:
  - Tobramycin 5-10mg/kg/dose (q 12 hours versus q 24 hours)
  - Ciprofloxacin: 600mg IV Q12 hours
  - Piperacillin/Tazobactam: 4.5 Gram IV Q 6 hours
  - Cefepime: 1 Gram IV Q 8 hours or Q 12 hours
  - Meropenem: 2 Gram IV Q 8 hours
- Monitoring of Peak/Trough levels of Tobramycin necessary, SCr, HCG
- Increase airway clearance frequency

CF Exacerbations…



- Obtain baseline SCr and HCG
- Discontinue oral NSAID's & inhaled TOBI:
  - if using other renally toxic medications
- Increase Airway Clearance Frequency
  - VEST or Percussion
  - Use Dornase Alpha QD & HyperSal 7% BID
- Monitor for efficacy: *%FEV1 improvement
- Monitor for stool frequency (C-Diff)
- Monitor for appetite & weight gain

CF Exacerbations…

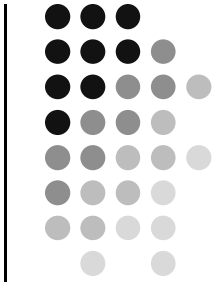
Special Populations:

- Pregnant women
- Patients with %FEV1 $\leq$ 30 %predicted
- + MRSA patients
- NTM (non-tubercular mycobacterium) infections
- MDR pathogens in sputum
- Renal function compromise
- Patients with multiple drug allergies and/or intolerances
- Line-related DVT and anticoagulation

Transplantation in CF…

- Considered when %FEV1 $\leq$ 30 % predicted
- Typically “Double-Lung” versus “Single-Lung”
- Patient still has “CF”
- Several daily medications remain post-op
- Several new medications begin post-op
- Average life expectancy post-op: ~5 years
- Vaccinate completely prior to transplantation

The Pharmacist's Role in CF…



- Listen to patient; focus on patient's description of symptoms: CF exacerbation?
- Review CFF website/guidelines with patients
- Assess adherence; identify barriers
- Offer medication education/support
- Review lab results and monitor for DDI
- Assist with device techniques (many different devices being used)
- Assist with insurance coverage issues
- Offer general support
- Communicate with MD, NP, PA-C, RD, SW, RN

Be A Part of the Solution!

For more information, visit:

www.cff.org