Cystic Fibrosis
A Case Presentation
In a new era…

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Disclosure/Declarations

1. Decker declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, employment, gifts, stock holdings, and honoraria.
2. The patient case presented today, is NOT based on an actual patient.

The information within this presentation is for educational purposes only, and is not intended to substitute for the medical judgment of a patient's physician. Recommendations for use of any particular therapeutic agents or methods are based upon the best available scientific evidence and clinical guidelines. Reference in this activity to any specific commercial products, process, service, manufacturer, or company does not constitute its endorsement or recommendation.

Learning Objectives

- Define Cystic Fibrosis
- Introduce CFTR and its classes of genetic defects
- Describe Cystic Fibrosis Epidemiology and Pathology
- List CF diagnostic criteria
- Review clinical CF features and symptoms
- Discuss common CF therapeutic agents
- Introduce “new” therapies

What we are not diving into…

- Exacerbation management
- Pancreatic insufficiency
- CF-related sinus disease
- CF-related diabetes
- CF-related liver disease
- CF-related bone disease
- Vitamin D deficiency
- DIOS
- Infertility/CBAVD
- Mental health
  - depression/anxiety
- Cognitive Behavioral Therapy
- Managing a chronic illness
- Sustaining Daily Care
- Medical insurance issues

Patient Case

SL is a 32 yo woman with Cystic Fibrosis (CFTR gene mutation: F508del/2183delAA>G); average baseline FEV1pp of 55. Initiated E/T/I on 12/1/2019, with FEV1pp improvement to 70 within the first month. Her BMI increased to 23 after gaining ~ 15lbs. She has a h/o chronic scedosporium lung infection for which she had been taking itraconazole until starting E/T/I. She presents to clinic today for an unscheduled visit with a c/c: increasing sputum production, cough with limited volume hemoptysis x the past 3 days. Denies f/c/n/v; endorses social distancing and +mask wearing during pandemic.

PMH: pancreatic insufficiency, poly-arthropathies, sinonasal obstruction, DIOS.

SH: married with a 5 y.o son. Has comprehensive medical and Rx benefits and strong family support

After PE + sputum collection, it is suspected that scedosporium lung infection likely primary contributor to this CF exacerbation with bronchiectasis +hemoptysis. Re-starting antifungal therapy is considered.

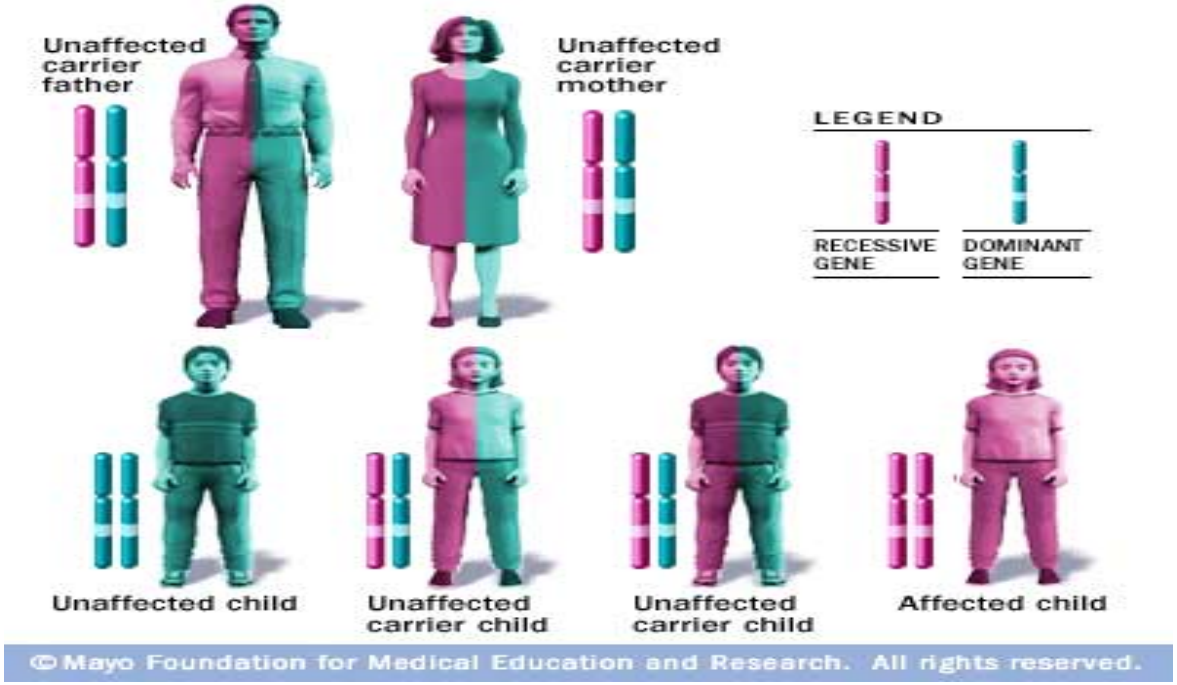
What antifungal therapy could the Pulmonary Clinical Pharmacist recommend at this point, along with what medication dose adjustment(s) if any?

Cystic Fibrosis

- Autosomal recessive disorder
- Gene mutations found on Chromosome 7
- The most common life shortening autosomal recessive disease among Caucasians
- Symptoms result from absent, insufficient, or ineffective CFTR protein
  - 5 Classes of gene mutations
- Primarily affects epithelial cells of the respiratory, GI, and reproductive tracts
- Can affect multiple organ systems

Autosomal Recessive Genetics

- CF caused by mutations in a single large gene on Chromosome 7 where CFTR protein is created
- Genetic databases list > 2000 possible disease causing recessive mutations to this gene
- Two carriers of one CFTR gene mutation = 25% chance of CF in their biologic child



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

Epidemiology…

- Approximately 30,000 Americans have CF & ~ 70,000 people worldwide
- ~1000 new cases identified annually
- More than 10 million Americans are unknowingly, symptomless carriers of one cystic fibrosis causing gene mutation

- ~60% identified via “Newborn Screen” by 2014; today this is higher

- 1: 2,500 Caucasians
- 1: 9000 Hispanics
- 1: 10,900 Native Americans
- 1: 15,000 African Americans
- 1: 30,000 Asian Americans

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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

Evolution of Life expectancy

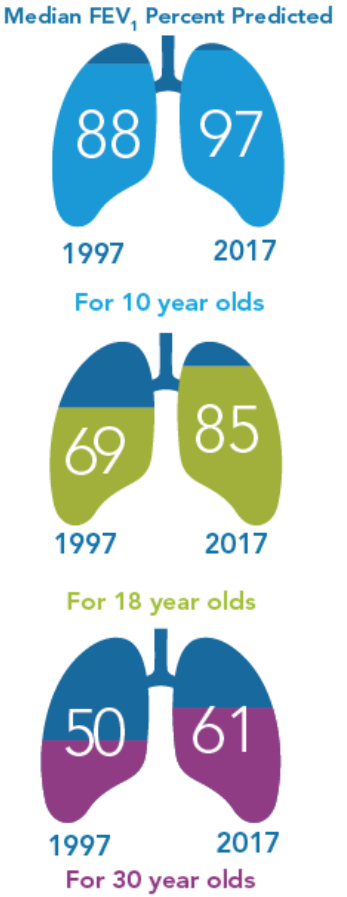
- In the 1950s, few children with CF lived to go to elementary school
- 1985, the median survival age: 25y.o.
- In 2007 ~ 37.4 y.o; in 2014 ~39 y.o; 2019 ~ 46 y.o
- With early diagnosis & highly effective therapies, the survival age continues to increase
- Impact of “gene-targeted” therapies?

Source: CDC. Cystic Fibrosis Clinical Validity. September 10, 2007
CFF Patient Registry Annual Data Report; 2014
American Lung Association State of Lung Disease in Diverse Comm 2010

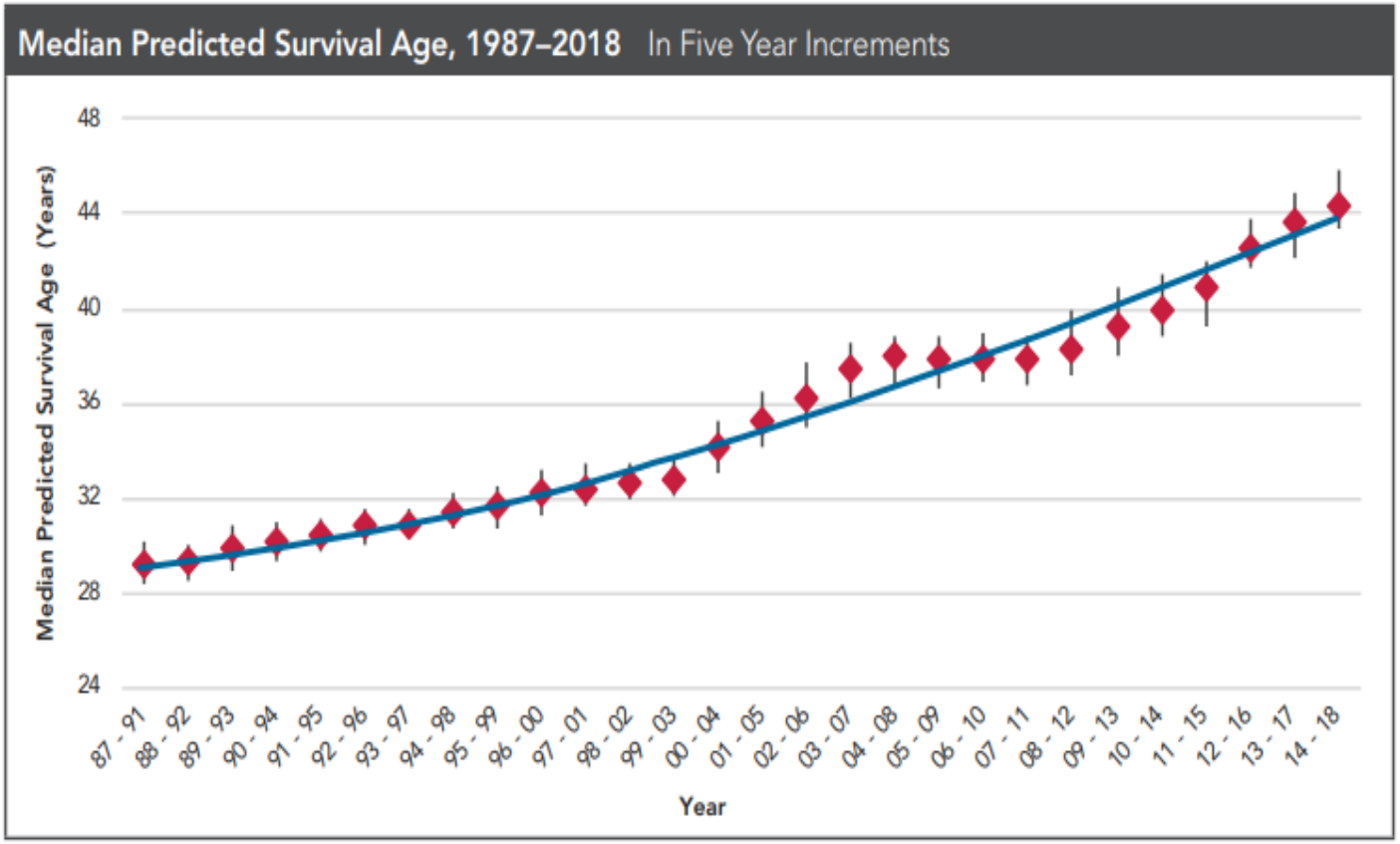
The Good News….

Survival continues to improve

LUNG FUNCTION



Lung function is a primary indicator of health and contributes to survival for people with CF.



*Using the currently recommended method for calculating median predicted survival. For more information about the methodology, please see the Technical Supplement available at cff.org.

Why the increase in survival?

- Airway Clearance medicines/techniques
  - dornase alfa & hypertonic saline
- Anti-*Pseudomonal* antibiotic therapies
- Pancreatic enzyme replacement therapy
- Inhaled antibiotics
  - Tobramycin, aztreonam, colistimethate
- Chronic Azithromycin (anti-inflammatory)
- Highly effective CFTR Modulators
- CF Care Center Network and Registry data collection

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Pathology…. What's CFTR?

- CFTR: **Cystic Fibrosis Transmembrane Conductance Regulator: a protein that functions as a chloride channel. Must be present, folded correctly and operational to be effective.**
- Most common defective CFTR gene mutations = 2 copies: **del**F508 in Caucasians (deletion of DNA bases coding for phenylalanine at position 508). Others include:
  - G542X
  - G551D
  - R117H
- Sodium & Bicarbonate channels also exist; all necessary for fluid & pH balance
- Optimal cilia function requires functioning channels and fluid balance

Lancet. 2003 681-689

Pathology…. What's CFTR?

- Complex Protein
- Expressed in several organ systems
- Production, location, function are key
- Primary function
  - chloride ion channel
- Secondary functions
  - Influences bicarbonate secretion
  - regulates eNaC
- Gene mutations may alter function

5 classes of CFTR gene mutations

Class I. No functional CFTR is created: 22%

Class II. CFTR is created; misfolded; not at cell surface: 88%

Class III. CFTR @ cell surface; gating function faulty: 6%

Class IV. CFTR @ cell surface; channel function faulty: 6%

Class V. CFTR @ cell surface in insufficient quantities: 5%

- **Class I & II mutations most common**
- **"Classic" or "atypical CF" phenotypes exist & may be associated with various gene mutation(s).**

Lancet. 2003 681-689
J Pediatrics 2008; 153:S4

Diagnosis

1. Clinical symptoms consistent with CF in at least one organ system
2. Evidence of CFTR dysfunction via ANY:

- Sweat chloride test >60mmol/l (often using two tests)
- Abnormal nasal potential difference
- Disease causing CFTR mutation(s) by genetic testing
  - Newborn screening
  - Genetic mapping is not mandatory for diagnosis, yet is now standard of care within CF Centers, can confirm diagnosis and assist with therapeutic options

Organs involved?
Any that express CFTR protein

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

* Most common cause of morbidity/mortality

Clinical Features

Impaired or absent transport of chloride, sodium and bicarbonate in organs expressing CFTR protein **leads to thick, viscous secretions, poor or absent cilia function and increased salt concentrations in sweat gland secretions.**

CF Pulmonary Disease
A Key Biomarker

- **$ppFEV_1$ is the single best predictor of mortality in CF patients**

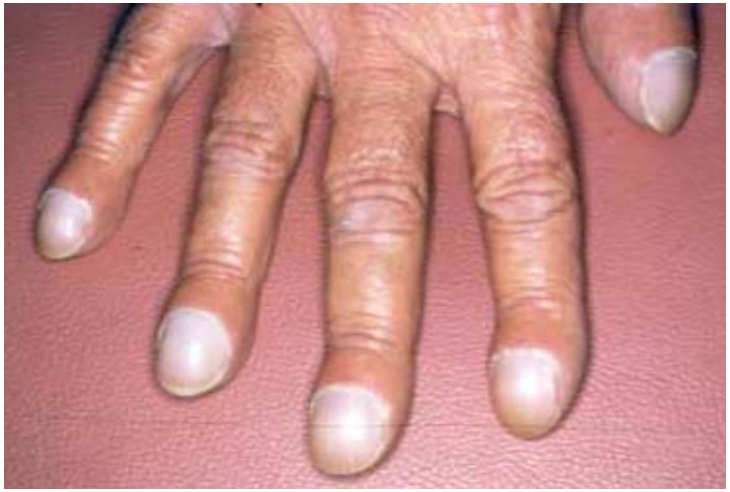
- **Progressive loss of lung function**
  - **"Classically": mean decrease in $ppFEV_1$ 2-4% per year**
  - **"Modern":**
    - Typically well maintained in childhood
    - Vulnerability exists between 18-25 years
    - The importance of adherence/ability to "sustain daily care"
    - Role of emerging pathogens
    - The era of CFTR modulators likely to modify the survival curve

[1] Kerem E *NEJM* 1992; 326(18) [2] Ramsey BW *J Pediatr* 1994; 124

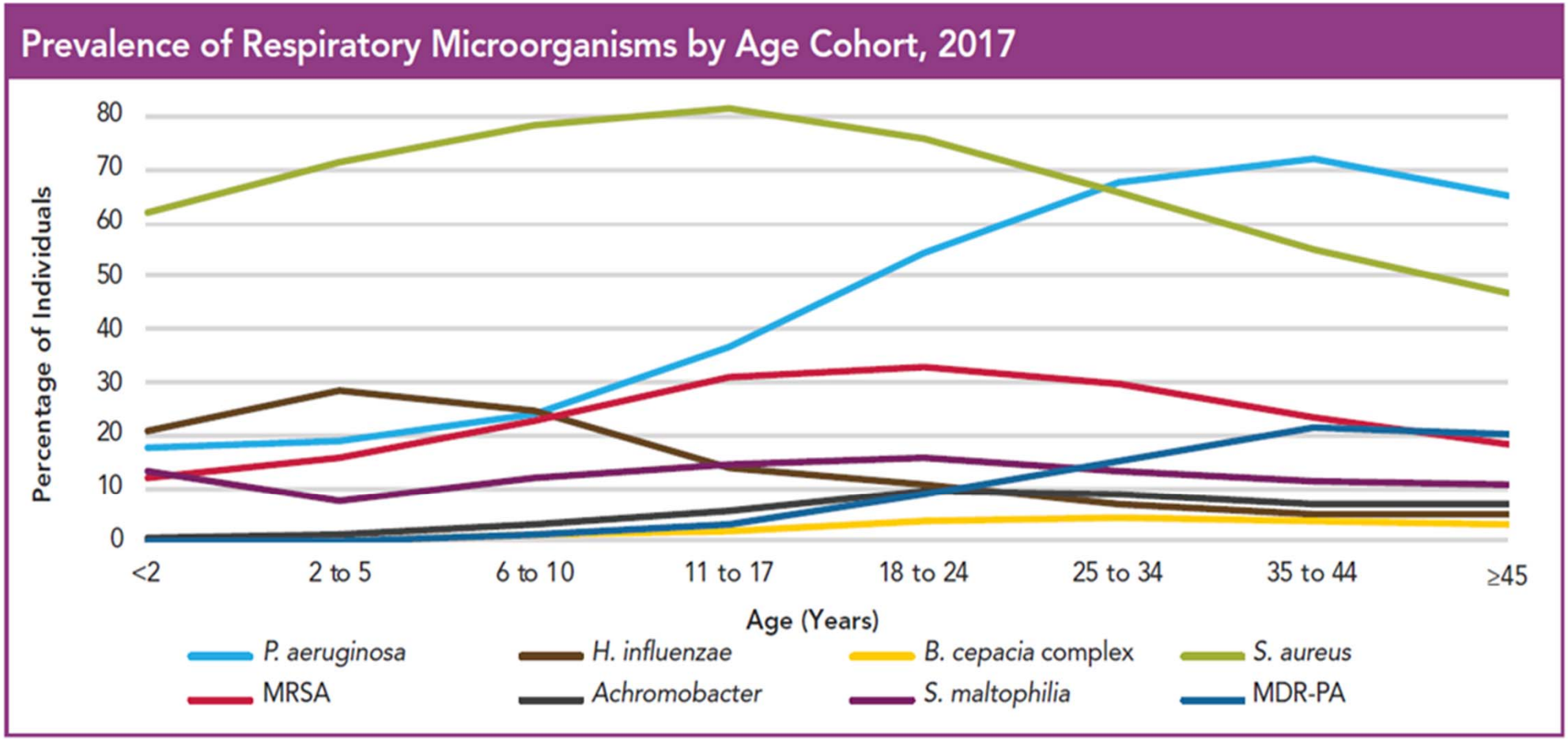
*Clinical Features

Pulmonary:

- Cough, chest hyperinflation, PFT's demonstrating obstructive airway disease, bronchiectasis, increased sputum production
- S. Aureus, H. influenza, P. aeruginosa infections common;
  - Less common: fungal
- Digital clubbing common
- Periods of clinical stability followed by exacerbations



Respiratory Microbiome: Changes over a Lifetime



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*Clinical Features

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 one CFTR mutation
- Sinus infections can trigger CF exacerbations
  - Similar microbiology in upper and lower airways
- Nasal surgery for polyp removal common in CF management

*Clinical Features

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
- Chronic pancreatitis may develop in pancreatic sufficient patients
- 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 is the current recommended therapy to date

*Clinical Features

Gastrointestinal:

- 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 Features

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 occur in CF; not common

*Clinical Features

Fertility:

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

*Clinical Features

Fertility (Cont):

- **Females:** infertility “higher in CF”
- Related to amenorrhea (may be secondary to malnutrition) & viscous cervical mucus
- With increased life expectancy & improved nutritional status; pregnancy in CF has become a newer clinical focus
- Assume a female with CF can conceive
- Pharmacists often consulted re: safe medication options for daily use and in exacerbations

*Clinical Features

Musculoskeletal:

- Reduced bone mineral density
- Accelerated bone loss
- Poor to no absorption of Vitamin D may contribute to osteopenia / osteoporosis
- Arthropathy occurs in 2% to 10% of patients
- Chest wall pain is a common adult symptom

Therapeutic Categories

- **Routine/daily Therapy**
  - Remains primary focus of care; may change w/ CFTR modulators
  - Has helped to significantly increase life expectancy
  - Rigorous daily oral, inhaled & airway clearance regimens can be burdensome and adherence is difficult
  - Includes quarterly CF-Center clinic visits w/ PFT
- **Exacerbation Therapy**
  - Currently without ONE clear definition of a CF exacerbation
  - Provided within In-Patient or Out-Patient settings
  - Often includes IV antibiotics
  - Optimal length of IV therapy may depend on initial response
  - Not a focus of today's discussion

Routine/Daily Therapy

Respiratory

- Focus is to “sustain daily care” in attempt to limit exacerbations
- Purpose had been on expectoration of viscous sputum that obstructs airways and provides environment for bacterial overgrowth and bronchiectasis
- Chest Physiotherapy & huff cough: no studies completed to prove effect on course of disease (percussion, VEST®, vigorous exercise)
- Studies underway to evaluate whether daily pulmonary regimens remain as beneficial in era of highly effective CFTR modulators.

Thorax 1990; Vol 45: 881-884
Port CF

Routine/Daily Therapy

Respiratory

- P. aeruginosa is considered a major pathogen in adults.
  S. aureus and H. influenzae also significant.
- Initial colonization period with non-mucoid strains of P.aeruginosa often followed by chronic infection with mucoid strains.
- Mucoid strains generally difficult to eradicate with poor penetration of antibiotics into anaerobic mucoid layer (biofilms)
- Rapid mutator strains of bacteria form with increased resistance patterns

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

Choice of Antimicrobial

Respiratory

- Pseudomonas: *MDR era*

  A: Aminoglycoside
  - Tobramycin (Inh or IV)

  B: anti-PsA beta lactam
  - Ceftazidime
  - Cefepime
  - Pipercillin/tazobactam
  - Aztreonam
  - Carbapenem: Mero/Imi/Dori
  - Colistimethate (substitute for tobramycin)
  - SAVE FLUORQUINOLONES for outpatient use

- MSSA/MRSA:
  - Bactrim DS 1-2 tabs PO BID
  - Doxycycline/minocycline
  - Clindamycin
  - Vancomycin IV
  - Linezolid 600mg po BID
- Stenotrophomonas:
  - Often a colonizer
  - Bactrim DS 2 tabs PO BID

Other CF respiratory concerns

- NTM (MAC, M.Abscessus)
- B.cepacia, acromobacter
- ABPA ~ Serum IgE: ≥ 500 IU/mL
- "Emerging pathogens"
  - Molds and Fungi
    - aspergillus, scedosporium, candida
    - antifungal therapies can have significant DDI
  - Difficult to clear
- Therapies associated w DDI and/or toxicities
  - TDM involved
- Hemoptysis

Fungi and Mold Therapies

- Amphotericin
- Fluconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Isavuconazonium sulfate

- CYP3A4 inhibitors may decrease metabolism & **increase serum concentrations of CYP3A4 substrates (Ivacaftor)**
- Substrate dose adjustments may be necessary

Routine/daily ACT Therapy

- **SABA** (MDI and/or nebulized solution):
  - Often used prior to mucolytic therapies
  - As needed for wheeze and shortness of breath (SOB)
  - Albuterol
  - Levalbuterol

Routine/daily Therapy

Mucolytics (Decrease sputum viscosity, improve lung function, decrease exacerbations):

- 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 for airway "wetting".
- Deoxyriboneuclease (Dornase or Pulmozyme®): inhale 2.5mg/2.5mls via nebulizer once daily to decrease sputum viscosity.

* Clinically, patients encouraged to use VEST® or other chest percussion during nebulized airway clearance therapies.

Lancet 2001; 358; 1316-1321

Routine/daily Therapy

- Cyclic inhaled therapies with anti-pseudomonal 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

Routine/daily Therapy

- Chronic azithromycin:
  - 250mg po once daily or 500mg po 3 x per week
  - Standard anti-bacterial properties
  - Also with anti-inflammatory properties
  - Managing CF related bronchiectasis- airway inflammation secondary to persistent infection

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

Routine/Daily Therapy

Nutrition

- Fat, protein and fat-soluble vitamin absorption is reduced or absent in pancreatic insufficiency
- Pancreatic Enzyme Replacement Therapy (PERT) is necessary to control steatorrhea and promote nutritional health; typically patients are strongly adherent.
  - Lipase, amylase, protease
- Nutritional status is closely correlated with lung function
- Weight loss is one sign of CF exacerbation
- Inter-patient variability/preference exists among enzyme replacement products
- Adherence tends to be strong

Routine/Daily Therapy

Nutrition

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

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

  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

Routine/Daily Therapy

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

Routine/Daily Therapy

Nutrition

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

Routine/daily Therapy

Pain

- Chronic pain (arthritic or chest) is frequent in adults
- Clinicians may initiate management with hydroxychloroquine, NSAIDs or APAP
  - avoid NSAIDs during exacerbations treated with aminoglycosides to decrease r/o renal toxicity
- Advancement to opioids had been common, seems to be decreasing recently: monitor for effect on lung and bowel function; psychosocial issues may arise

Routine/daily Therapy

Psychosocial

- Significant social & medical impact
  - Developmental and emotional issues; depression common
  - School/work performance
  - Participation in age-appropriate activities
  - Adherence to complex medication regimens
  - Financial impact
  - Vocational training-preparing for adult life
  - Family planning (medication use & genetic testing)
  - Diagnosis, treatment for depression & on-going monitoring
  - Social Work and Mental Health care is important

CFTR Modifying Agents

- Restore at least some CFTR migration and function
  - Depending on Class of gene mutation(s)
  - May improve the underlying pathology
- Names:
  - **Kalydeco®** (Ivacaftor**): 1/2012**; G551D x 1 then expanded
  - **Orkambi®** (Ivacaftor + lumicaftor): **9/2016**; F508del x 2
  - **Symdeko®** (Ivacaftor + tezacaftor): **6/2019**; F508del x2
  - **Trikafta®** (Ivacaftor + tezacaftor + elexacaftor)
    - **10/2019**; at least F508del x 1 + "other"
    - **Highly effective CFTR modulator** (replacing most previously)
- Research & Development on-going: CFF website
- Became a part of "Routine Therapy" overnight.

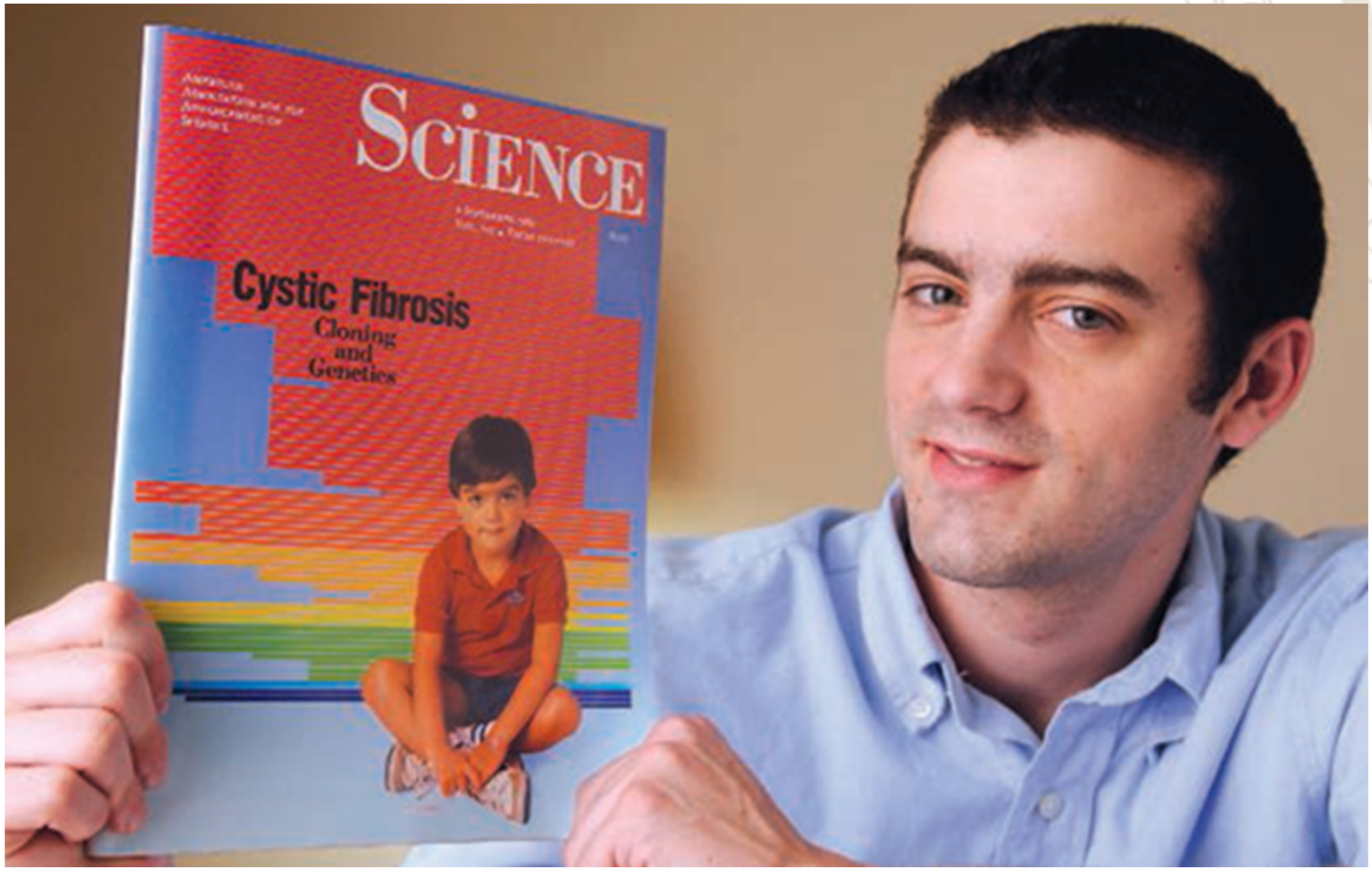
CFTR Modifying Agents
A Total Game Changer

- **Trikafta®**: (elexacaftor +tezacafor+ Ivacaftor)
  - FDA approved October, 2019; "Highly Effective CFTR Modulator"
  - THREE entities in each ORANGE tab and Ivacaftor 150mg in each BLUE tab
  - 100mg elexacaftor; 50mg tezacaftor; 75mg ivacaftor per ORANGE tablet
  - Take 2 ORANGE tabs in am; and 1 BLUE tab 12 hours later
  - CF patients with at least ONE copy of F508del…could have ANY other mutation
  - Ivacaftor: Potentiates "channel-opening probability or gating"
  - Tezacaftor: Facilitates processing & trafficking of normal & mutant CFTR to cell surface
  - Elexacaftor: Improved processing & trafficking of CFTR to cell surface
  - **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 and other "azole" antifungal therapies)
    - Do not use with inducers of CYP3A (ie, rifampin, St. Johns Wort)

Back to our patient, SL

- On-going studies are needed to determine Trikafta effect on pulmonary microbiome- pre and post improvement in CFTR function
- If sputum cultures remain +, then treat to decrease particular organism burden contributing to symptoms and FEV1pp decline
- Regularly screen and monitor for possible DDI
- Consider voriconazole to manage scedosporium
  - (trough > 1 mcg/ml)
- Adjust Trikafta dose: 2 orange tablets ONCE daily M,W,F (no ivacaftor monotherapy in evenings); may need to HOLD CFTR modulator until ID goal(s) met, then restart.

THANK YOU



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