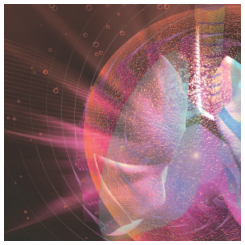

Advances in the Management of Cystic Fibrosis

CHEST 2013
October 26 - 31
Chicago, Illinois

MORNING
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Agenda

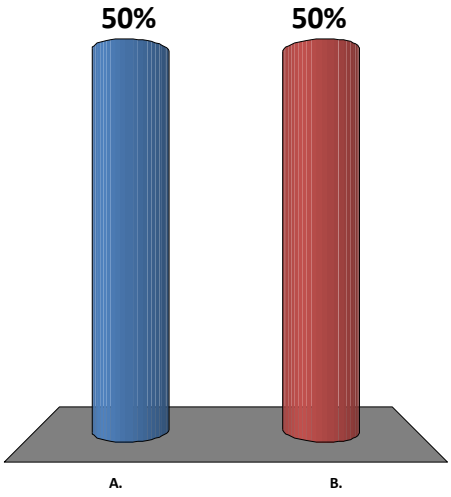
5:30–5:35 AM	**Welcome and Introduction** Paula J. Anderson, MD (Chair)
5:35–5:50 AM	**Review of Patient Case Presentation / Collection of Benchmark Outcomes Data** Paula J. Anderson, MD (Chair)
5:50–6:10 AM	**Updates on CF Mutations and their Role in Personalized Treatment** Paula J. Anderson, MD
6:10–6:30 AM	**Current and Emerging CF Treatments** Rubin Cohen, MD
6:30–6:50 AM	**Improving the Prevention and Treatment of Early and Chronic Airway Infections** Susanna McColley, MD
6:50–7:00 AM	**Re-Review of Patient Case Presentation / Collection of Post-Education Outcomes Data** Paula J. Anderson, MD (Chair)

Learning Objectives

- Discuss the latest information on CF mutations and the impact on personalized treatment of the disease
- Describe the safety and efficacy of currently available and emerging CF treatments
- Identify strategies to improve the prevention and treatment of early and chronic airway infections

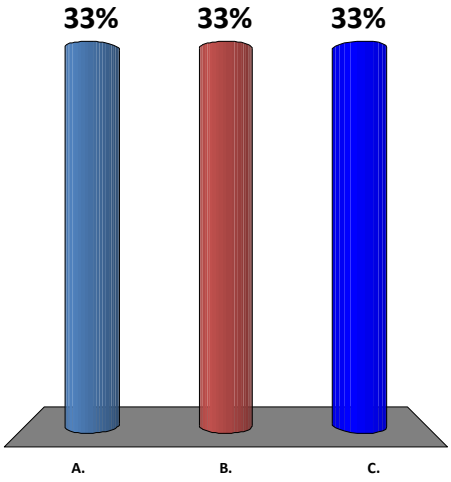
Do you actively care for patients with cystic fibrosis?

A. Yes
B. No

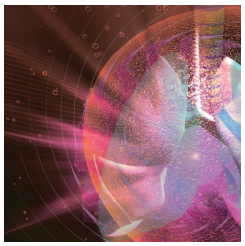


If you are actively caring for patients with cystic fibrosis, what type of patients do you see?

A. Pediatric
B. Adult
C. Both pediatric and adult



Advances in the Management of Cystic Fibrosis



Case:
29-year-old
Caucasian Male

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Case: 29-Year-Old Caucasian Male

History

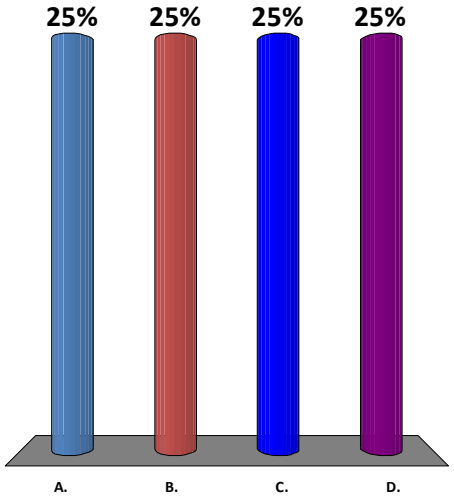
- Recurrent heat exhaustion since age 8–9
- IDDM diagnosed at age 22
- Frequent bronchitis; takes antibiotics every few months
- Pneumonia 2 years ago
- ¼ c brown sputum daily
- Salty powder on skin after sweating
- Found to be infertile 1 year ago; absent vas deferens
- Internet search–could this be CF?
- Requested testing for CF from local PCP
- Sweat chloride 70 mEq/L
- Genotyping: G551D; 2789+5G→A
- Parental genotyping confirms 1 mutation from each
- 1 stool daily (bulky, foul-smelling)
- Patient has maintained weight and denies sinus problems

Case: 29 Year-Old Caucasian Male

- **Physical**
  - Well appearing man; BMI 30
  - Significant only for purulent rhinorrhea and swollen turbinates
  - Lungs clear; No clubbing
- **Testing**
  - Spirometry: mild obstruction; FVC 82% predicted; FEV_1 72% predicted; FEV_1/FVC ratio 71%
  - CXR: fibronodular changes in both upper lobes
  - Sputum culture: *Mycobacterium avium-intracellulare*, *Aspergillus*, sensitive *S. aureus*
  - Labs: BMP normal, but glucose 260 mg/dL; HgbA1C 9.8; LFT normal; vitamins A, D, E low; INR 1.1; IgE 22

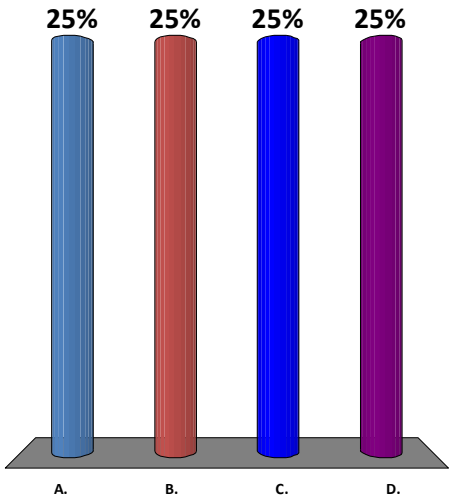
This clinical presentation and genotyping is consistent with a diagnosis of:

A. Chronic bronchitis
B. CFTR related metabolic syndrome
C. Nonclassic cystic fibrosis
D. Allergic bronchopulmonary aspergillosis



Indicated therapies for this patient would include:

A. rhDNAse (Pulmozyme®), airway clearance, TOBI®
B. rhDNAse (Pulmozyme®), Ivacaftor (Kalydeco®), airway clearance
C. Pancreatic enzymes, ADEK vitamins, TOBI®
D. Azithromycin, airway clearance, low-fat diet



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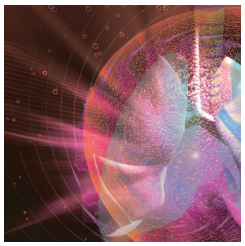

Updates on CF Mutations and Their Role in Personalized Treatment

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Sponsored by the American College of Chest Physicians.

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Speaker

Paula Anderson, MD, FCCP
University of Arkansas for
Medical Sciences
Little Rock, Arkansas

Faculty Disclosure

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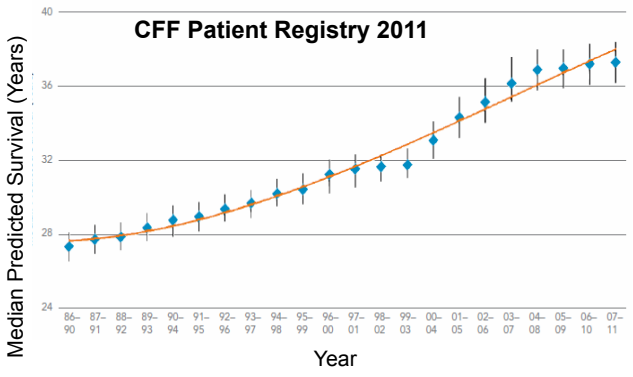
Paula Anderson, MD, FCCP
Grant monies (from sources other than industry): Cystic Fibrosis Foundation
Grant monies (from industry related sources): Kalobios, Mpex, Novartis

Learning Objective

- Discuss the latest information on CF mutations and the impact on personalized treatment of the disease

CF Survival Is Improving

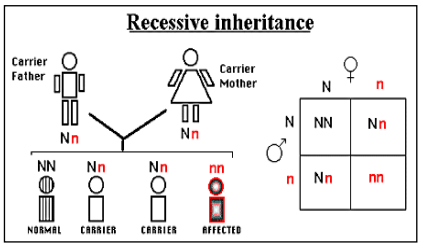
Median Predicted Survival Age, 1986-2011, Over 5-Year Bands



- 2011 median survival: 38 years
- 48% of patients are older than 18 years
- Newborn today may live to 5th or 6th decade
- Over 80% of deaths are from respiratory failure

CF Genetics

- One of the most common life-shortening inherited diseases in the US
- Autosomal recessive
- 1 in 30 Caucasians are carriers
- 1 in 3300 live births in Caucasians
- US ~30,000 affected individuals
- Other ethnicities - incidences in US
  - Hispanic: 1:9000
  - African American: 1:15,000
  - Asian: 1:32,000



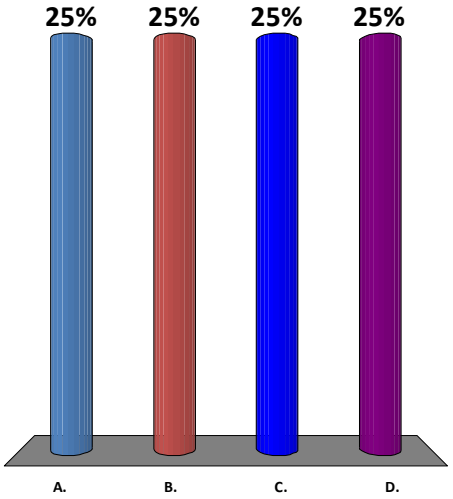
CFF.org. Accessed August 2013.
Rohlfs E, et al. *Clin Chem*. 2011;57:841-848.

CF Gene - 1989

Pearson H. *Nature*. 2009:460:164-169.

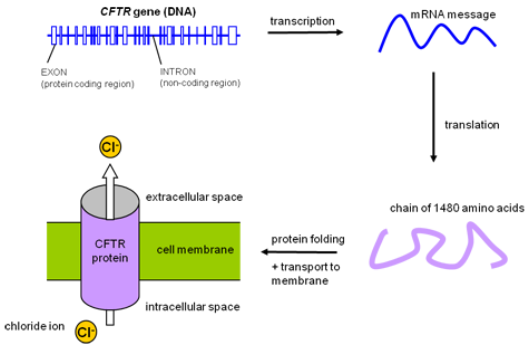
The gene responsible for causing CF encodes a protein that functions as:

A. A sodium channel
B. A sialic acid receptor
C. A chloride channel
D. An intracellular chaperone



CFTR Gene

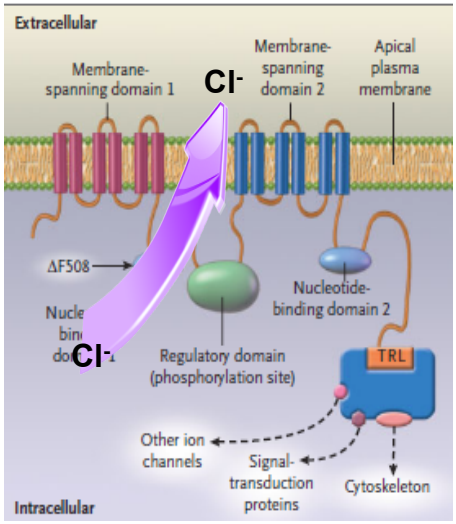
Cystic Fibrosis Transmembrane Conductance Regulator



- Long arm chr 7 (7q31.2)
- Large gene: 189 kilobases, 27 exons
- Transcribed into 6.5 kb mRNA
- Encodes 1480 amino acids

www.nchpeg.org. Accessed Aug 2013.
Tsui LC, Dorfman R. *Cold Spring Harb Prospect Med*. 2013;3:a009472.

CFTR Protein

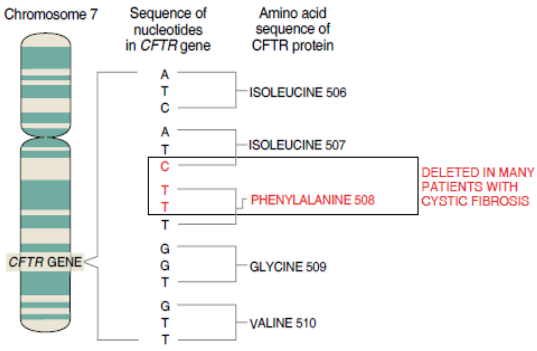


- Functions as a chloride channel
- Apical cell membrane
- Regulated by cAMP
- Other functions
  - Down-regulation of Na^+ transport
  - Regulates Ca^{++} activated Cl^- channels and K^+ channels
  - Affects expression of other proteins

Rowe SM, et al. *N Eng J Med*. 2005;352:1992-2001.

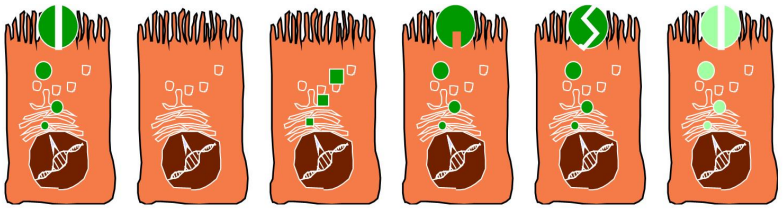
CFTR Mutations

- Over 1900 CFTR mutations
- F508del most common
  - Homozygous – 47%
  - Heterozygous – 40%
- Other mutations
  - G542X – 5%
  - G551D – 4%
  - R117H – 3%
  - N1303K – 2.5%
  - 2789+5G>A – 1.3%



CFF Patient Registry. www.cff.org. Accessed Aug 2013.

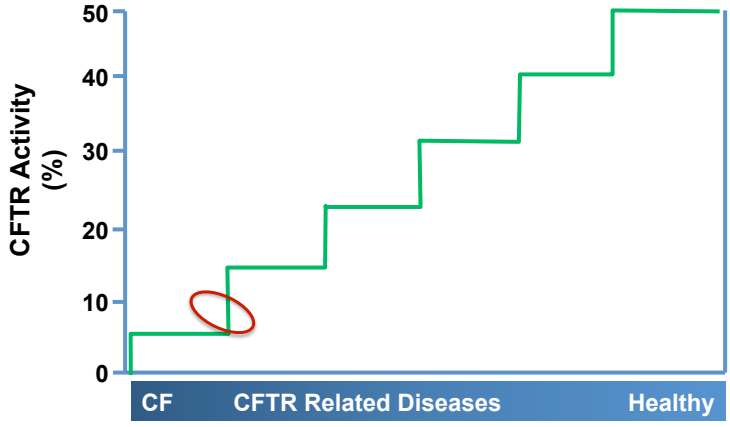
Classes of CFTR Mutations



Normal	I	II	III	IV	V
	No synthesis	Block in processing	Block in regulation	Altered conductance	Reduced synthesis
	G542X	F508del	G551D	R117H D1152H	3849+10kbC→T 5T A455E
Patients affected (%)	12%	87%	5%	5%	5%

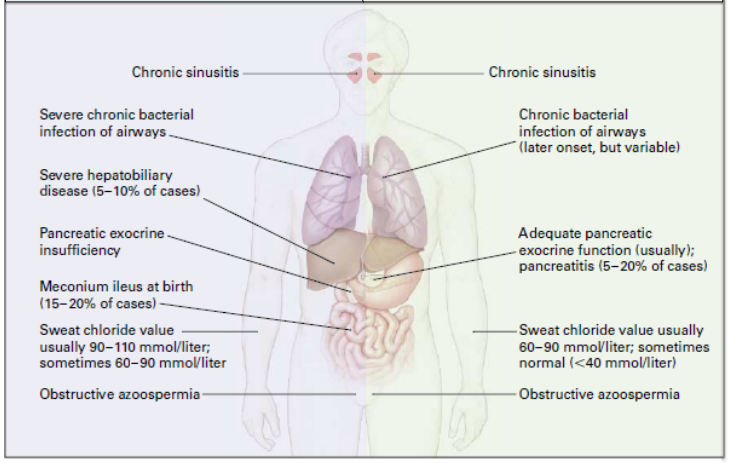
Scriver CF, et al. *The Metabolic and Molecular Bases of Inherited Disease*. 2001:5121-5188.

How Much Improvement Is Needed to Make a Clinical Difference?



Affected Organs

Classic Cystic Fibrosis (no functional CFTR protein)	Nonclassic Cystic Fibrosis (some functional CFTR protein, providing survival advantage)



Knowles M, Durie P. *N Eng J Med*. 2002;347:439-442.

CF Pathophysiology

CFTR gene defect

↓

Defective ion transport

↓

Airway surface liquid depletion

↓

Defective mucociliary clearance

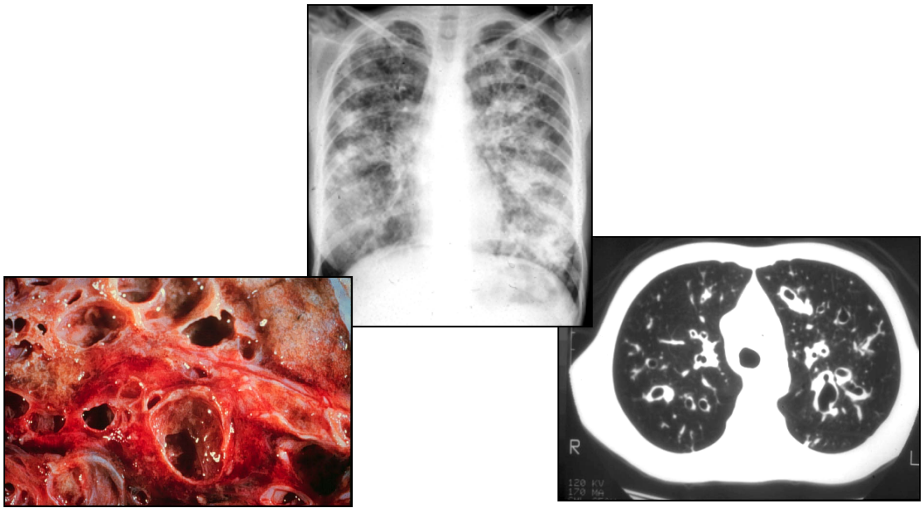
↓

Mucus obstruction

↙ ↘

Infection → Inflammation

Bronchiectasis



Question

An 18-year-old Caucasian woman is referred to you for bronchiectasis. She has recurrent bouts of bronchitis, chronic sinusitis and consistently grows *H. influenzae* from sputum cultures. She denies any GI issues and maintains a normal weight. Sweat chloride value is 80 mEq/L and genotyping reveals G551D and R117H. In addition to other treatments, she is started on ivacaftor (Kalydeco®). **Based on clinical trials, at her next visit you would expect to see:**

A. The same weight
B. Improved sweat chloride
C. Improved lung function
D. B and C
E. A and C

Think about your answer for a minute.

Keypad voting is on the next slide.

Based on clinical trials, at her next visit you would expect to see:

Now key in your response

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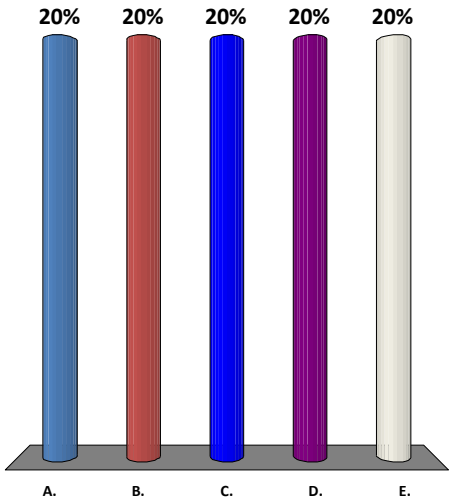


Can We Treat the Underlying Defect?

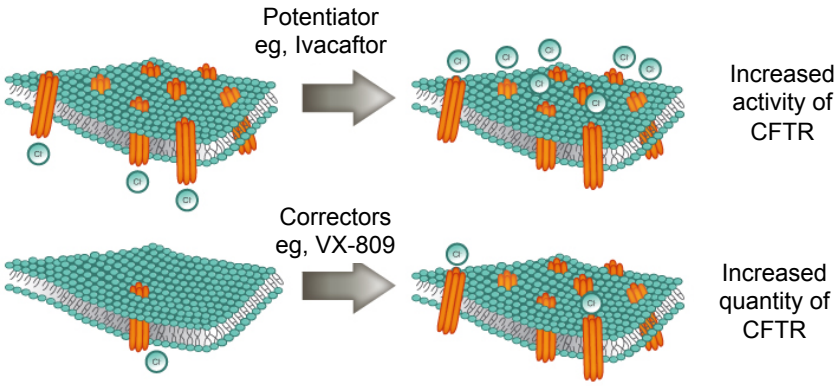
- Standard treatments
  - Airway clearance
  - Mucolytics (rhDNAse)
  - Mucous hydrators (HS)
  - Inhaled antibiotics (tobramycin–TOBI®; aztreonam–Cayston®)
  - Pancreatic enzymes and vitamins
  - Azithromycin
  - Lung transplant
- Novel approaches
  - Gene therapy
  - CFTR modulators

CFTR Modulation

- Addresses the underlying genetic defect
- Mutation specific – "personalized medicine"
- CF Foundation developed partnerships with biopharmaceutical industry in 1998 to discover new treatments
  - High throughput screening efforts
  - Discovery of small molecules that affect CFTR processing and function
    - Suppression of premature termination codons
    - Potentiators
    - Correctors

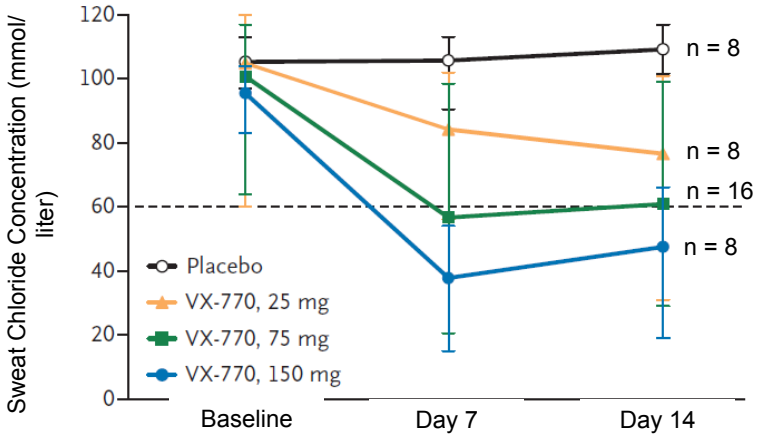
Rogan M, et al. *Chest*. 2011;139:1480-1490.

Potentiators and Correctors



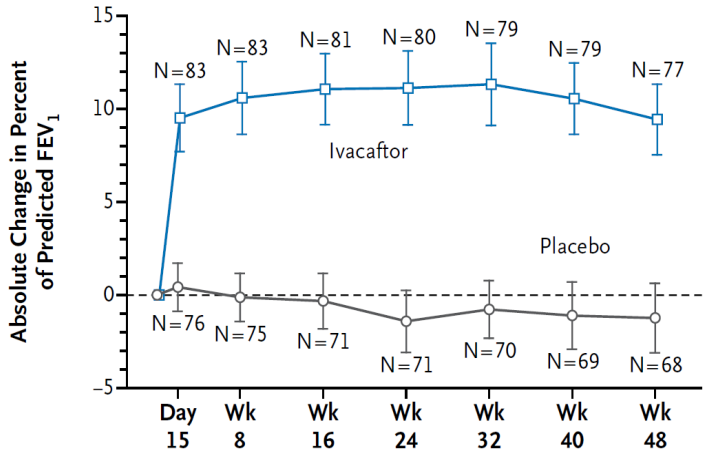
www.CFTR.info. Accessed August 2013.

VX-770 (Ivacaftor) Phase 2
G551D



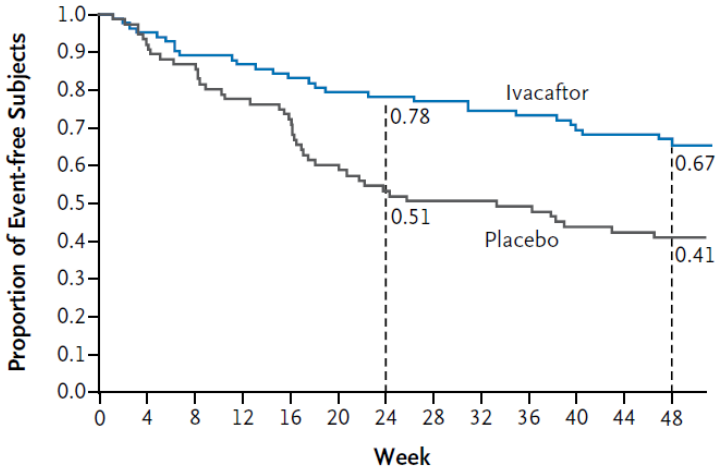
Accurso FJ, et al. *N Engl J Med*. 2010;363:1991-2003.

Ivacaftor Phase 3



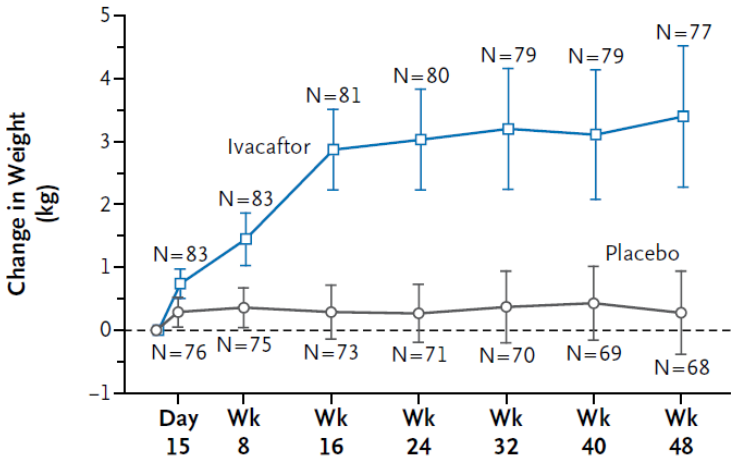
Ramsey BW, et al. *N Engl J Med*. 2011;365:1663-1672.

Exacerbation Rate



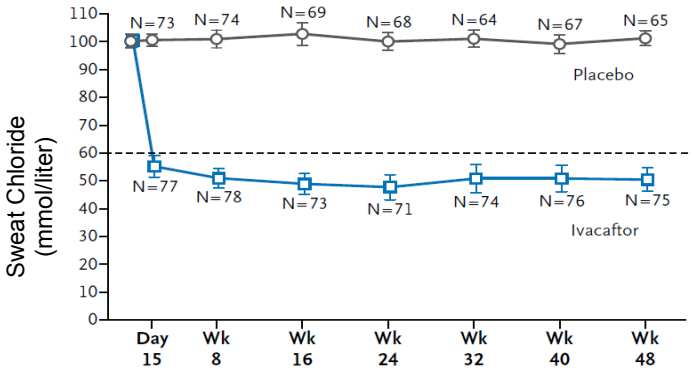
Ramsey BW, et al. *N Engl J Med*. 2011;365:1663-1672.

Weight Gain



Ramsey BW, et al. *N Engl J Med*. 2011;365:1663-1672.

Sweat Chloride Levels



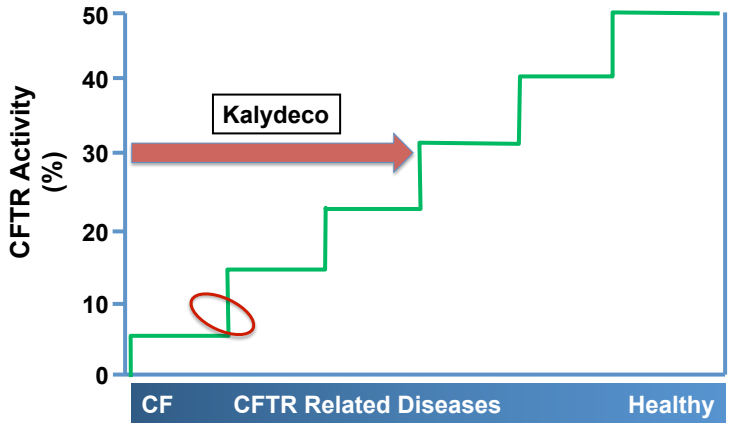
Safety

Incidence of AEs was similar with ivacaftor and placebo

Serious AEs: ivacaftor, 24%; placebo, 42%

Ramsey BW, et al. *N Engl J Med*. 2011;365:1663-1672.

How Much Improvement Is Needed to Make a Clinical Difference?



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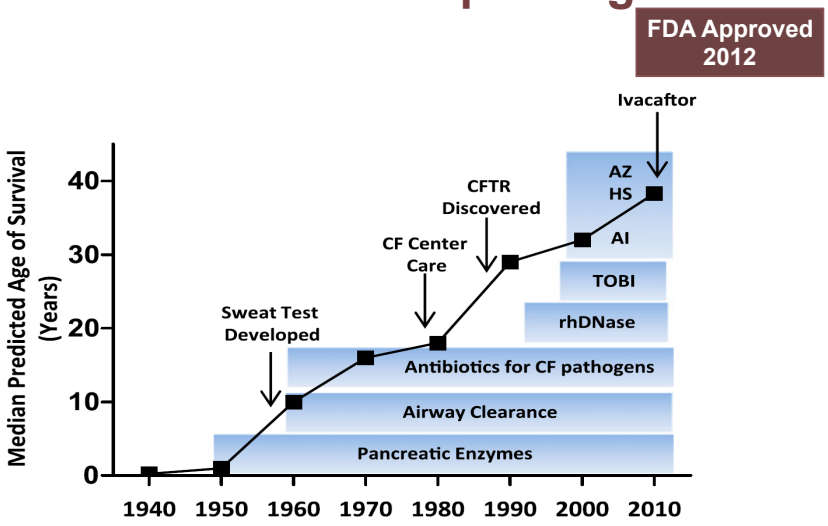


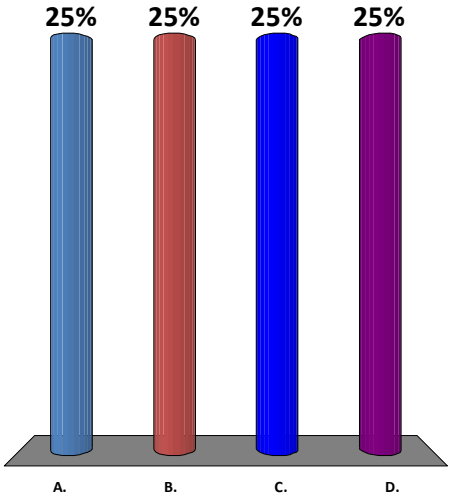
Clancy JP, Jain M. *Am J Resp Crit Care Med*. 2012;186:593-597.

Key Messages

- Cystic fibrosis is a common inherited disease that can present in adulthood
- The genetic defect causes abnormalities in the CFTR protein which functions as a chloride channel in epithelial cells
- Different mutations in the CFTR gene result in a variable effect on CFTR protein processing and functioning
- There are exciting new treatments available or in development that are specific for different types of CFTR mutations
  - We are entering an era of personalized medicine for CF

The gene responsible for causing CF encodes a protein that functions as:

A. A sodium channel
B. A sialic acid receptor
C. A chloride channel
D. An intracellular chaperone



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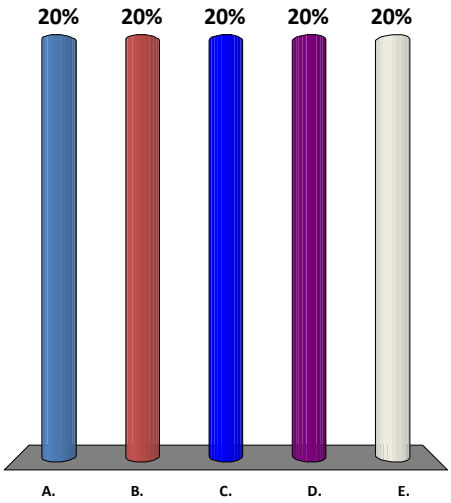
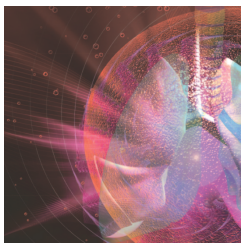


HOFSTRA NORTH SHORE-LIJ SCHOOL of MEDICINE AT HOFSTRA UNIVERSITY

North Shore LIJ
North Shore-Long Island Jewish Health System

Advances in the Management of Cystic Fibrosis



Current and Emerging Cystic Fibrosis Treatments

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Speaker

Rubin I. Cohen, MD, FACP, FCCP, FCCM
Adult CF and Bronchiectasis Center
Beth Thalheim Asthma Center

Hofstra North Shore-LIJ School of Medicine
Manhasset, New York

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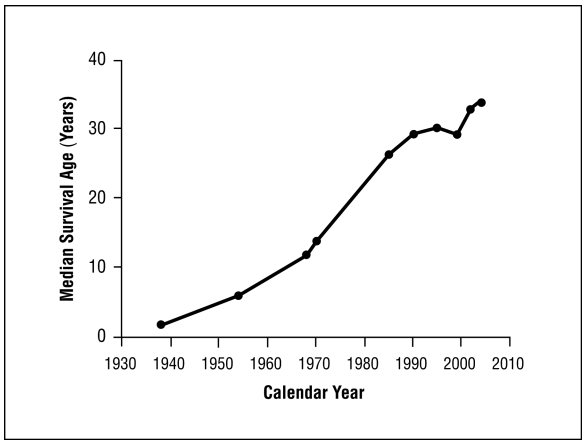
Rubin Cohen, MD, FACP, FCCP, FCCM
Principal Investigator: ALA-ACRC, CFFT TDN
Grant monies: CFF
Consultant fee, speaker bureau, advisory committee, etc: Gilead

Learning Objective

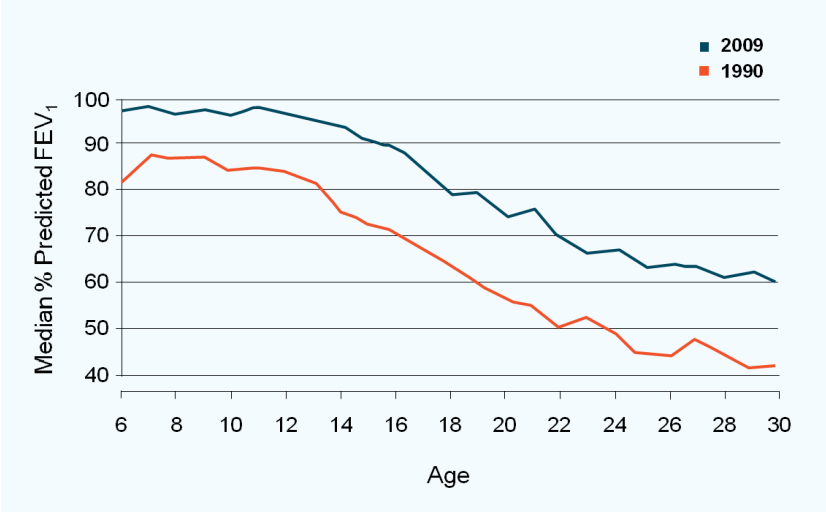
- Describe the safety and efficacy of currently available and emerging CF treatments

Survival Increased Over the Years



Davis PB. *Am J Respir Crit Care Med.* 2006;173:475-482.

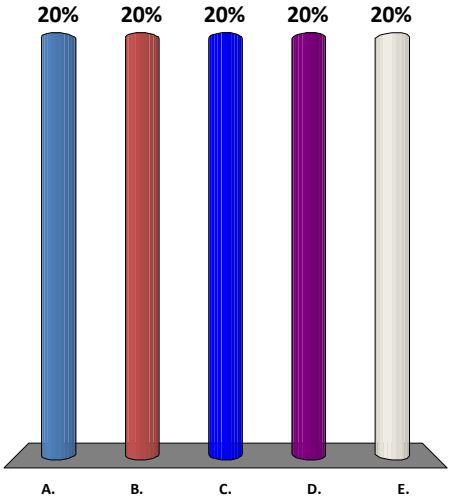
Epidemiology: CF Patients Lose an Average of 1.7% FEV_1 Lung Function Per Year



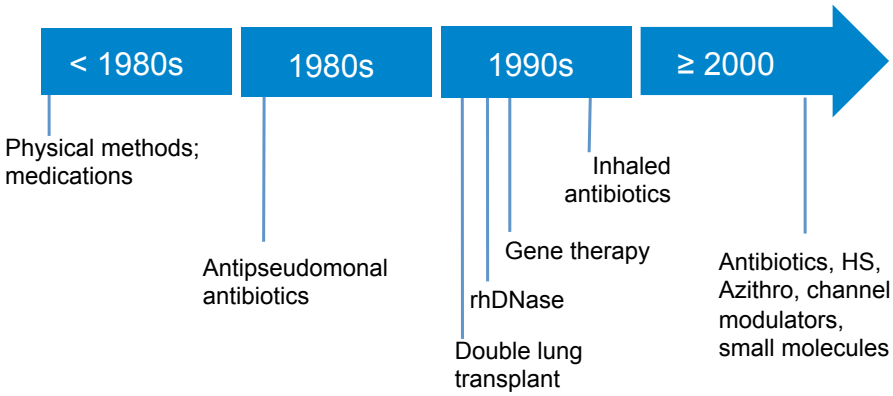
Cystic Fibrosis Foundation. Patient Registry Annual Data Report 2009. Bethesda, MD; 2011.

Which of the following agents has NOT been shown to be effective in CF?

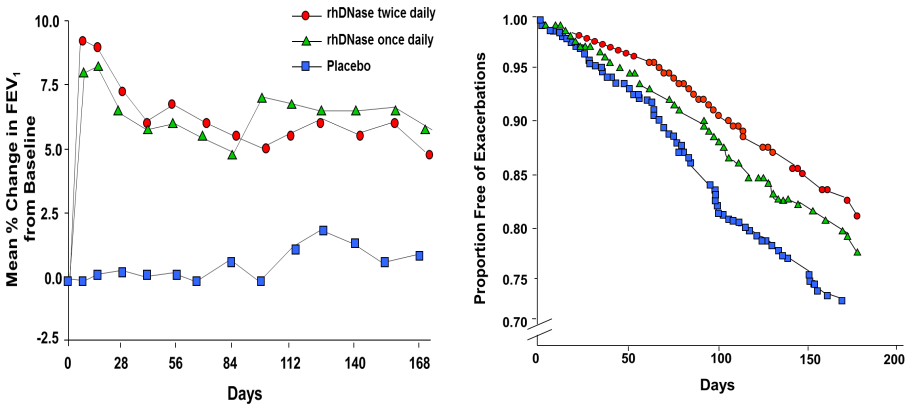
A. Hypertonic Saline
B. Acetylcysteine (Mucomyst)
C. Recombinant Human DNase (Pulmozyme)
D. Dry Powder Mannitol



Evolution of CF Treatment



Recombinant Human DNase or dornase-alfa: Pulmozyme®

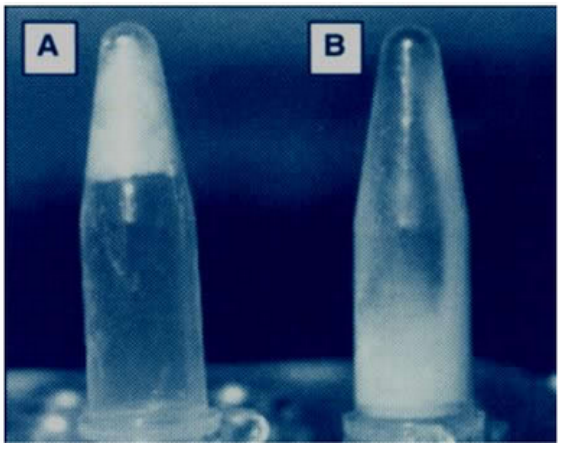


Safety: voice alteration, laryngitis; rarely severe; resolved within 21 days of onset

N = 968

Fuchs HJ, et al. *N Engl J Med*. 1994;331:637-642.

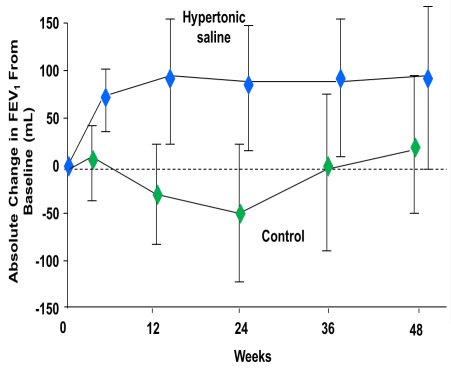
rhDNase Increases the Pourability of Cystic Fibrosis Sputum

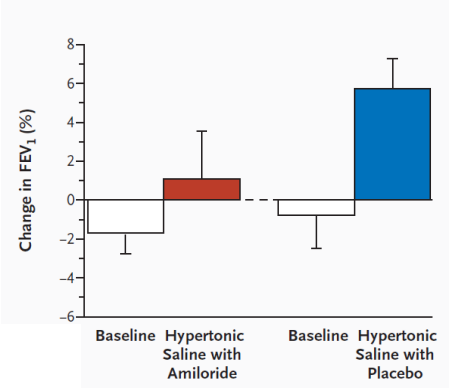


Shak S. *PNAS*. 1990;87:9188-9192.

Hypertonic Saline (HS)

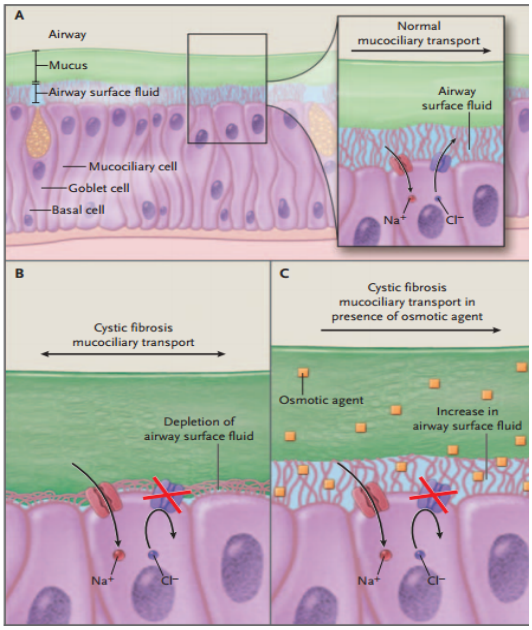
Hypertonic Saline (HS)





- *In-vitro* data further suggested that sustained hydration of airway surfaces was **the factor** that caused the improved mucociliary clearance

Elkins MR, et al. *N Engl J Med*. 2006;354:229-240.
Donaldson SH, et al. *N Engl J Med*. 2006;354:241-250.



Ratjen F. *N Engl J Med*. 2006;354:291-293.

Dry Powder Inhaled Mannitol

- Treated group had a mean improvement in FEV_1 of 105 ml (8.2% above baseline)
- The treated group (400 mg inhaled mannitol, twice daily) had a relative improvement in FEV_1 of 3.75% (P = 0.029) vs. control (50 mg)
- There were fewer exacerbations in the treated group (not significant), but exacerbation rates were low
- Conclusions: Inhaled mannitol, 400 mg twice a day, resulted in improved lung function over 26 weeks, which was sustained after an additional 26 weeks in the extension open-label phase

Aitken ML, et al. *Am J Resp Crit Care Med*. 2012;185:645-652.

Dry Powder Mannitol

- Uncertainty over safety and efficacy data: FDA advisory panel unanimously recommend against approval of dry powder formulation of mannitol in CF
- Issue eliciting most concern was higher rate of hemoptysis treatment group, particularly in children
- In two studies, rate of hemoptysis (not associated with an exacerbation), was almost 11% in adults on DPM, compared with about 8% of controls
- BUT in those aged 6-17 years, rate was almost 8% among those on DPM, compared with almost 2% among controls
- Tolerability with more patients on DPM stopping treatment because of adverse events (11% vs. 6%)
- Approved for age over 6 years in Australia and in adults in the EU

FDA. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM336995.pdf. Accessed Aug 2013.

Other Mucolytics

- There are no well-validated alternative mucolytic agents available at this time

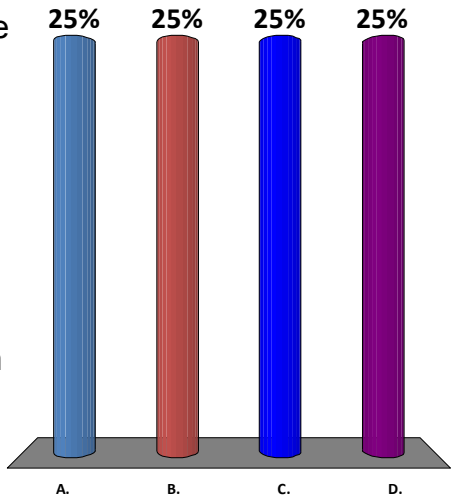
Anti-Inflammatory Agents Macrolides

- The precise mechanisms of action of macrolides are unclear
- Azithromycin reduces virulence factor production, decreases biofilm production, and has bactericidal effects on *P. aeruginosa* when it is growing in its stationary (biofilm) phase, interferes with colony signaling (so-called quorum sensing)
- Macrolides affect cytokine production by many cell types and alter polymorphonuclear cell function, making them effective anti-inflammatory agents

Hoffmann N, et al. *Antimicrob Agents Chemother*. 2007;51:3677-3687.
Yousef A, Jaffe A. *Pediatr Resp Rev*. 2010;11:108-114.

Corticosteroids in CF (correct statement):

A. Should not be used systemically due to their side effect profile
B. Inhaled corticosteroids are effective without the side effects of systemic therapy
C. Systemic corticosteroids in CF may be effective as short-term therapy
D. The role of corticosteroids in CF remains unclear as a randomized trial has not yet been conducted

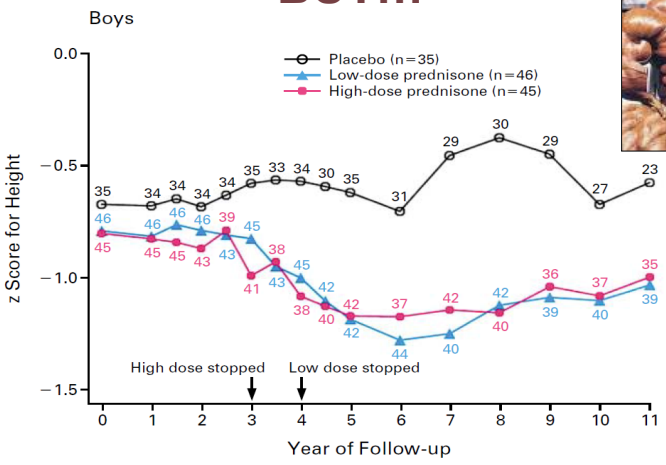


Corticosteroids

- Promising initial results led to a large multicenter randomized trial comparing alternate-day therapy with prednisone at 2 mg/kg and 1 mg/kg to placebo
- Enrolled only children and adolescents with CF
- The higher dose group was discontinued because of an unexpectedly high incidence of cataracts, glucose intolerance, and growth retardation
- The 1 mg/kg and placebo groups continued to the end of the 4-year trial
- The steroid-treated group showed benefit with respect to pulmonary function, particularly the subset of patients chronically infected with *Pseudomonas*

Eigen H, et al. *J Pediatr*. 1995;126:515-523.

BUT…



In summary: Corticosteroids have a beneficial effect but at significant cost. Long-term oral corticosteroid therapy, even in an alternate-day regimen, should be avoided if at all possible.
These studies do suggest that anti-inflammatory agents work.

Lai HC, et al. *N Engl J Med*. 2000;342:851-859.

Inhaled Corticosteroids

- A multicenter, randomized, controlled trial of ICS withdrawal concluded that it is safe to consider stopping ICS in CF thereby reducing drug burden and possible adverse effects

Balfour-Lynn IM, et al. *Am J Resp Crit Care Med*. 2006;173:1356-1362.

Ibuprofen

- High-dose oral ibuprofen studied in two large, long-term, placebo-controlled trials
- In a single-centre study, Konstan and colleagues showed a decrease in the rate of loss of lung function over 4 years after ibuprofen treatment compared with placebo. Largest benefit seen in younger patients (5–13 years)
- Multicentre Canadian trial enrolled 6–18 years of age with mild lung disease. There was no significant effect of ibuprofen on the primary endpoint, FEV_1, compared with placebo
- BUT, ibuprofen-treated group spent fewer days in the hospital than patients in the placebo group (1·8 days vs. 4·1 days per year)

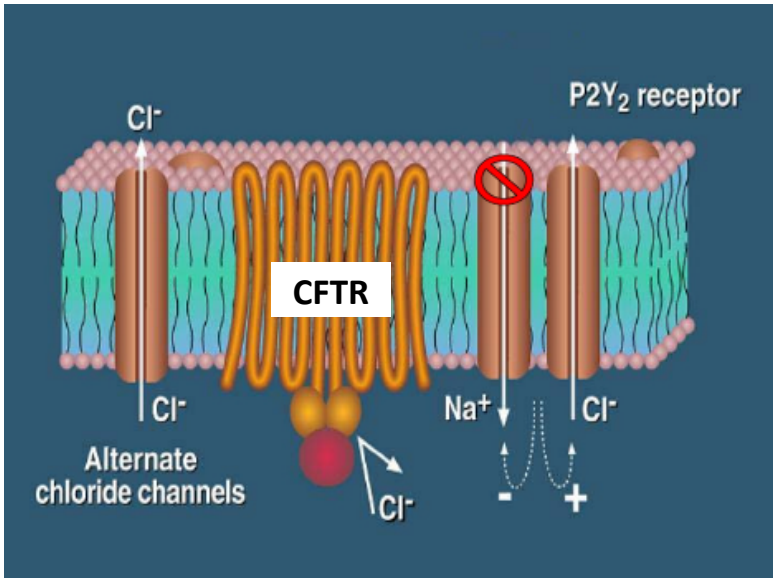
Konstan M, et al. *Am J Respir Crit Care Med*. 2007;176:1084-1089.
Lands LC, et al. *J Pediatr*. 2007;15:249-254.

Ibuprofen

- No significant adverse events were reported in either of these studies
- However, a retrospective report from another institution showed that many patients treated with high-dose ibuprofen discontinued treatment, often because of GI side effects
- Ibuprofen treatment, if used, seems most beneficial when started before the development of severe inflammation and pathological changes in the lung

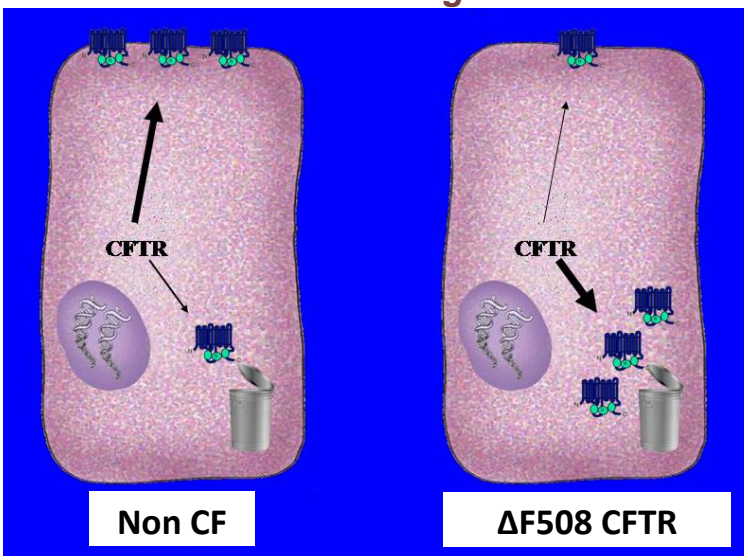
Konstan M, et al. *Am J Respir Crit Care Med*. 2007;176:1084-1089.
Lands LC, et al. *J Pediatr*. 2007;15:249-254.
Fennel PB, et al. *J Cyst Fibros*. 2007;6:153-158.

Ion Channel Modulators

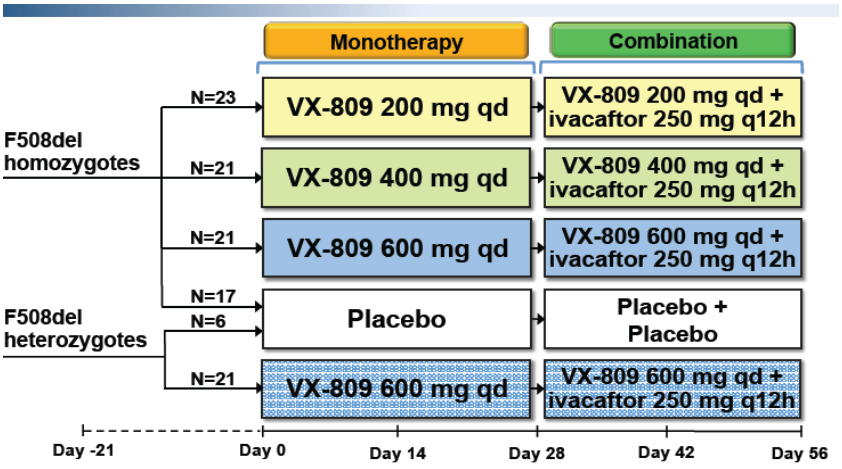


ΔF508 CFTR

Too Little at the Right Place

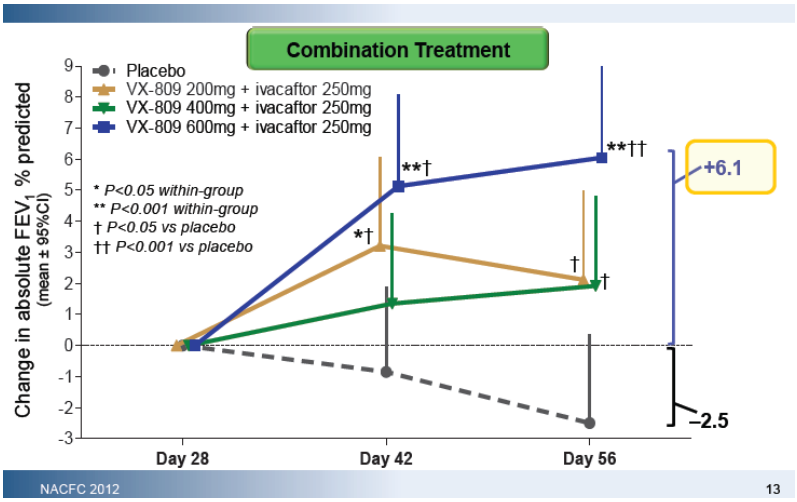


Clinical Evaluation of VX-809 and Ivacaftor Combination: Cohort 2 Study Design



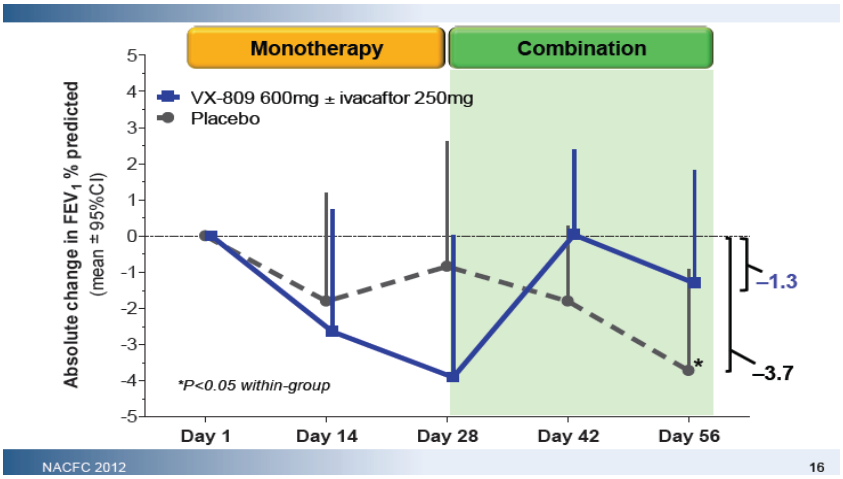
Boyle M, et al. *Pediatr Pulmonol*. 2012;47(S35):315.

Change in Absolute FEV_1 % Predicted in F508del Homozygous Patients



Boyle M, et al. *Pediatr Pulmonol*. 2012;47(S35):315.

Change in Absolute FEV_1 % Predicted in Patients Heterozygous for F508del

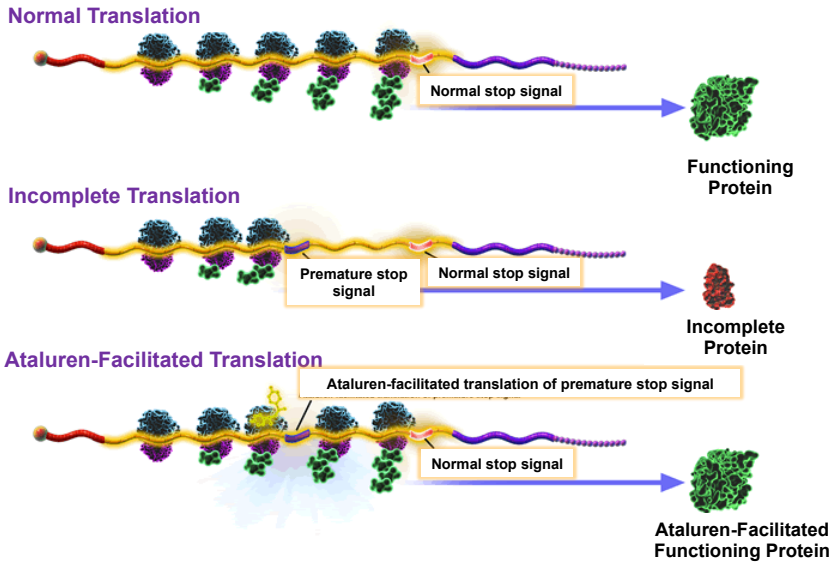


Boyle M, et al. *Pediatr Pulmonol*. 2012;47(S35):315.

Small Molecules in CF Therapy
CLASS I

- **Class I** includes premature termination codons (PTCs) or nonsense codons
- Nonsense mutation: single point alteration in DNA resulting in *inappropriate presence* of UAA, UAG, or UGA **STOP CODON** in the protein coding region of messenger RNA (mRNA) transcript
- Such a stop codon causes *premature cessation* of translation, with protein truncation leading to loss of function and consequent disease
- Nonsense mutations are responsible for 11% of CF cases worldwide
- In Israel, nonsense mutations are the #1 cause of CF
- Nonsense mutations produce little functional CFTR, these patients have severe CF

Ataluren Mechanism of Action



The Phase 3 Trial Ataluren vs. Placebo

- FEV_1 40 to 90% predicted
- 48 weeks
- Primary endpoint: improvement in FEV_1 % predicted from baseline
- Secondary: pulmonary exacerbations
- Tertiary: nasal potential difference
- 238 subjects randomized, intent to treat
  - 116 ataluren (10, 10, 20 mg/kg; morning, midday, evening doses)
  - 116 placebo (TID)

ClinicalTrials.gov. http://www.clinicaltrials.gov/ct2/show/NCT00803205. Accessed Aug 2013.

Results

- No significant changes vs. placebo in any parameters measured
- FEV_1 % predicted -2.5% ataluren; -5.5% placebo ($P = 0.124$)
- Among the *a priori* stratifications: the interaction of treatment with chronic inhaled antibiotic was significant
- In those ***not*** being treated with chronic nebulized antibiotics, FEV_1 % predicted was 6.7% in favor of ataluren
- Safety: pulmonary exacerbation, cough, upper respiratory tract infections similar frequencies for ataluren and placebo groups

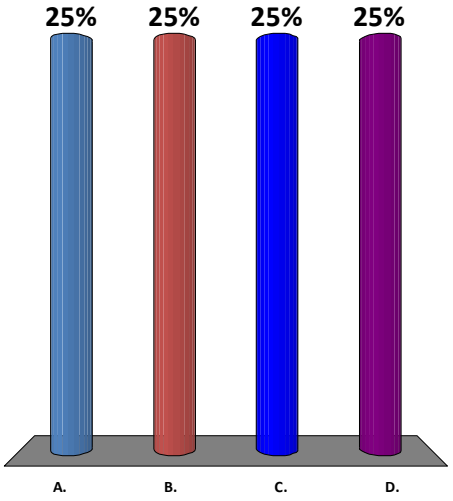
Konstan M, et al. 35th European Cystic Fibrosis Conference. Dublin, Ireland June 2012.
Aditya S, et al. *J Biomed Pharm Res*. 2013;2:21-25.

Key Messages

- Improved understanding of CF pathophysiology has increased survival
- Treatment protocols thus far are geared toward treating consequences of the disease (mucus, infection, inflammation)
- For the first time, we have potential therapy that may treat the underlying protein defect

Which of the following agents has NOT been shown to be effective in CF?

A. Hypertonic Saline
B. Acetylcysteine (Mucomyst)
C. Recombinant Human DNase (Pulmozyme)
D. Dry Powder Mannitol



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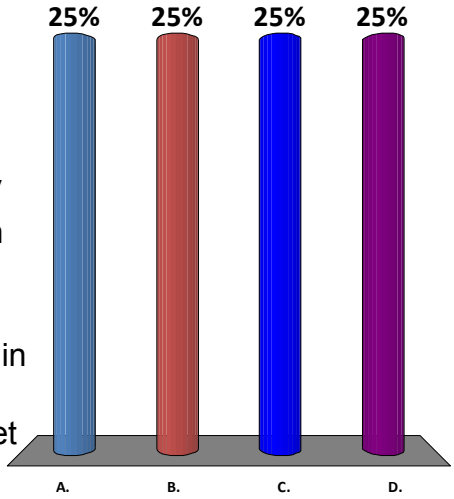
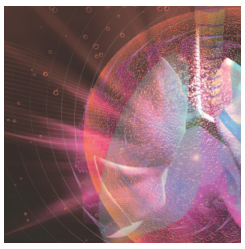


Advances in the Management of Cystic Fibrosis



Improving the Prevention and Treatment of Early and Chronic Airway Infections

CHEST 2013
October 26 - 31
Chicago, Illinois

MORNING
EDUCATIONAL
SYMPOSIUM

Educational Support

Sponsored by the American College of Chest Physicians.

This educational activity is supported by an educational grant from Gilead Sciences, Inc.

This educational activity is supported by an educational grant from Novartis.

Speaker

Susanna A. McColley, MD, FCCP
Anne & Robert H. Lurie Children's Hospital of Chicago
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Faculty Disclosure

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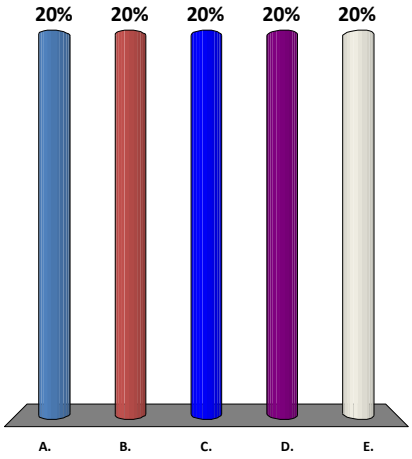
Susanna A. McColley, MD, FCCP
Grant monies: Cystic Fibrosis Foundation; National Heart, Lung, and Blood Institute; Agency for Healthcare Research and Quality
Consultant fee, speaker bureau, advisory committee, etc: American Board of Pediatrics; American Academy of Pediatrics; Vertex Pharmaceuticals

Learning Objective

- Identify strategies to improve the prevention and treatment of early and chronic airway infections

Based on improvements in FEV_1 and sputum *Pseudomonas aeruginosa* density demonstrated in clinical trials, which of the following would be a reasonable treatment choice for an 18-year-old patient with CF and chronic *P. aeruginosa* infection?

A. Aztreonam lysine for inhalation
B. Tobramycin inhalation solution
C. Tobramycin inhalation powder
D. All of the above
E. A and B



Improving the Prevention and Treatment of Early and Chronic Airway Infections

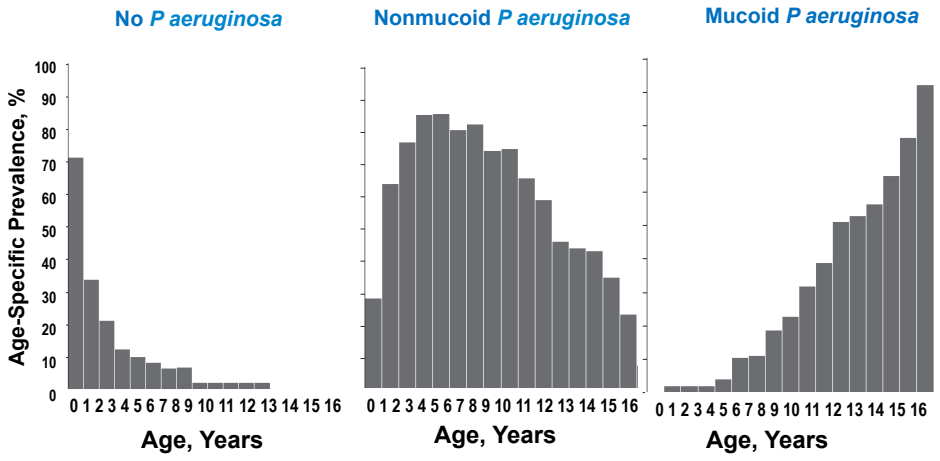
- Why inhaled antibiotics?
  - Rationale and review
- *P aeruginosa* eradication
  - Why and how
- Available therapies: what for whom?
  - Tobramycin inhalation solution
  - Tobramycin inhalation powder
  - Aztreonam lysine
- Unanswered questions

Why Inhaled Antibiotics?

- Chronic airway infection with *Pseudomonas aeruginosa* is common and is associated with worse clinical outcomes

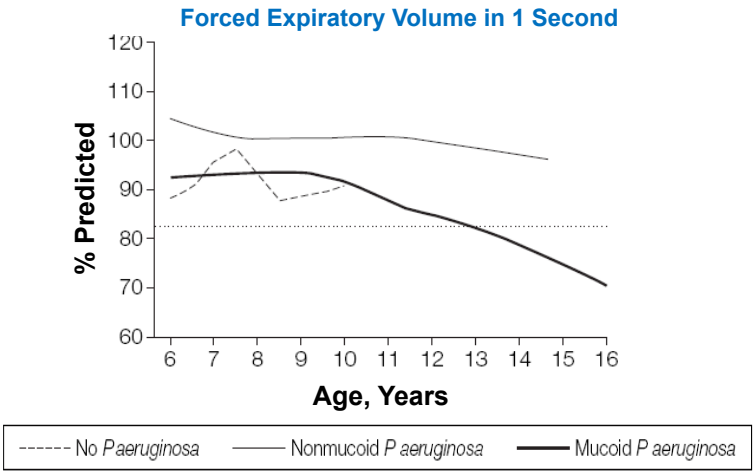
Li Z, et al. *JAMA*. 2005;293(5):581-588.

Why Inhaled Antibiotics?



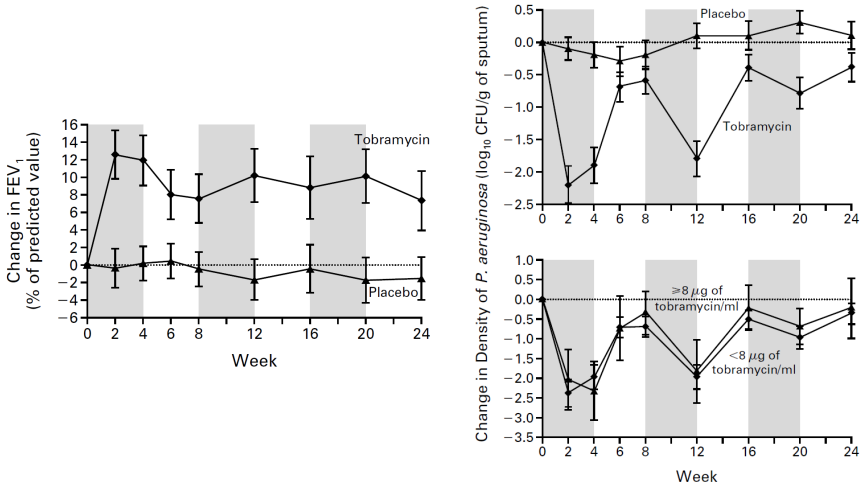
Li Z, et al. *JAMA*. 2005;293(5):581-588.

Mucoidy Is Associated With Chronic Infection and Lung Function Decline



Li Z, et al. *JAMA*. 2005;293(5):581-588.

Suppressing *P. aeruginosa* Improves FEV_1



This is associated with decreased PA bacterial sputum density

Ramsey B, et al. *N Engl J Med*. 1999;340(1):23-30.

Tobramycin Solution for Inhalation Chronic Airway Infection

Patient Survival

	Mortality rate without TSI	Mortality rate with TSI	Increase in the predicted % of patients surviving
2 years	2.1%	1.3%	0.8%
5 years	8%	5.2%	2.8%
10 years	15%	9.9%	5.1%

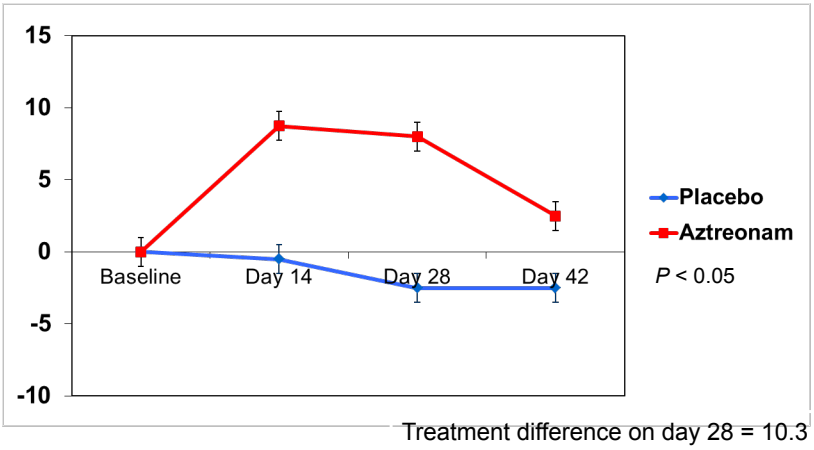
TSI use was associated with a 21% reduction in the odds of subsequent year mortality ($P < 0.001$)

Sawicki GS, et al. *Pediatr Pulmonol*. 2012;47(1):44-52.

AZLI for Chronic Airway Infection

AIR-CF-1 Clinical Trial

Change in FEV_1 (% of Predicted Value) from Baseline

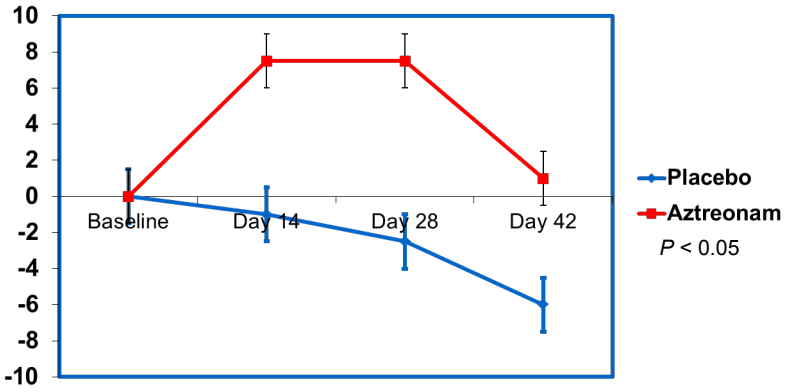


Treatment difference on day 28 = 10.3 %

Retsch-Bogart GZ, et al. *Chest*. 2009;135(5):1223-1232.

AZLI for Chronic Airway Infection
AIR-CF-1 Clinical Trial

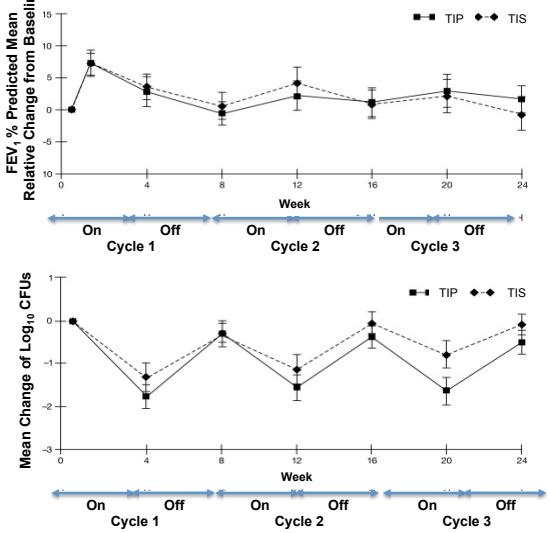
Change in CFQ-R Respiratory Score from Baseline



Treatment difference on day 28 = 9.7 points

Retsch-Bogart GZ, et al. *Chest*. 2009;135(5):1223-1232.

Tobramycin Inhalation Powder: EAGER Trial



- No difference in FEV_1 or PA sputum density
- Patients preferred TIP

Konstan MW, et al. *J Cyst Fibros*. 2011;10(1):54-61.

TSI versus AZLI

- Assael et al: Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: comparative efficacy trial
- Result
  - AZLI superior
  - However, most enrollees were on long term TSI prior to randomization

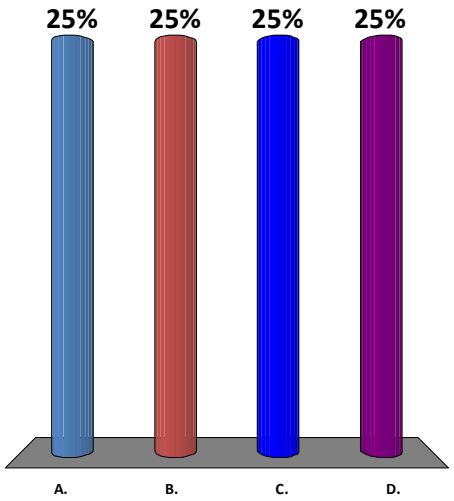
Assael BM, et al. *J Cyst Fibros*. 2012;12:130-140.

Summary of Suppression Data

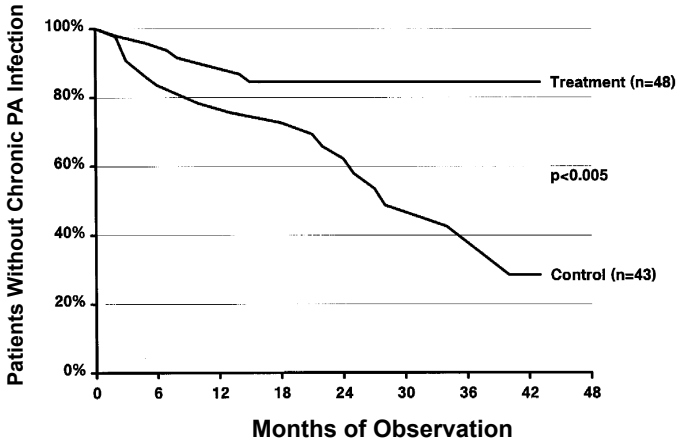
- Suppression of chronic *Pseudomonas aeruginosa* infection is associated with improved pulmonary function, quality of life, and survival
- Best approach remains to be defined
  - Close monitoring of effectiveness in individual patients is essential

Treating an asymptomatic CF patient with first isolation of *Pseudomonas aeruginosa* is likely to:

A. Have no clinical benefit
B. Be most successful in eradicating *P. aeruginosa* if tobramycin inhalation solution is combined with oral ciprofloxacin
C. Delay chronic infection
D. Cause intolerable side effects

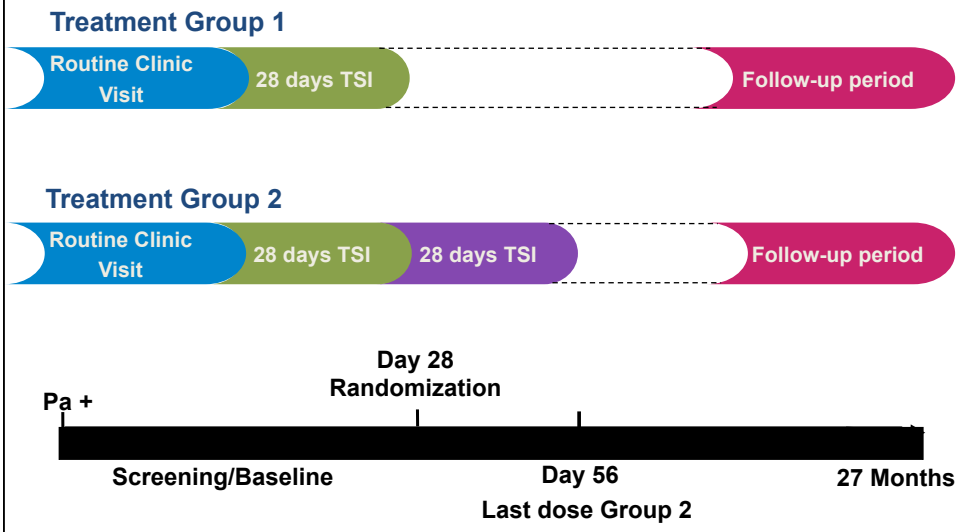


Eradication of *P aeruginosa:* Historical Data

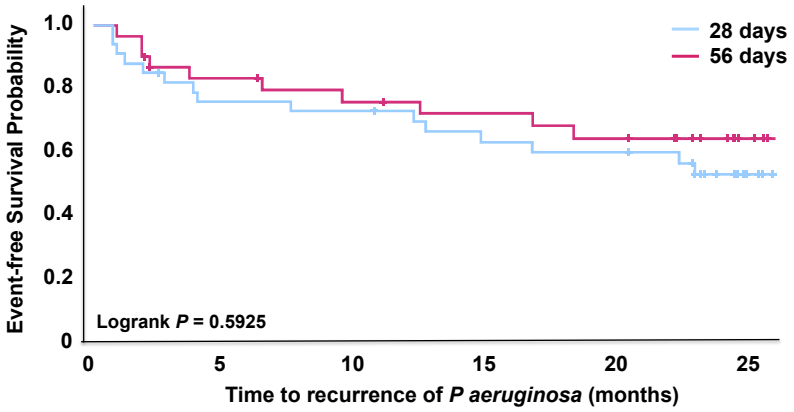


Frederiksen B, et al. *Pediatr Pulmonol.* 1997;23(5):330-335.

ELITE Study Design

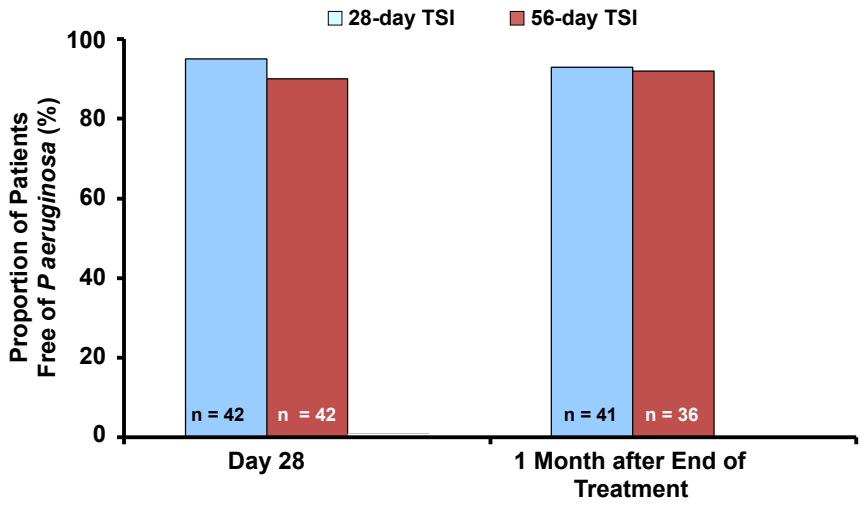


Median Time to Recurrence of *P aeruginosa* Infection (Any Samples)



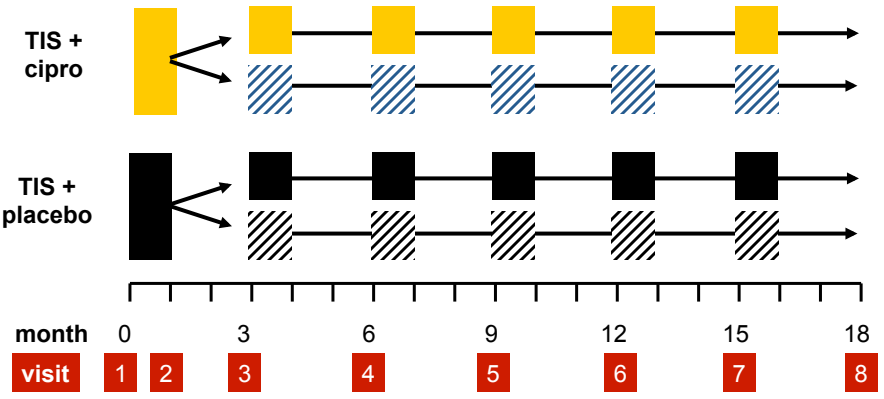
Ratjen F, et al. *Thorax*. 2010;65(4):286-291.

ELITE: Short Term Efficacy



Ratjen F, et al. *Thorax*. 2010;65(4):286-291.

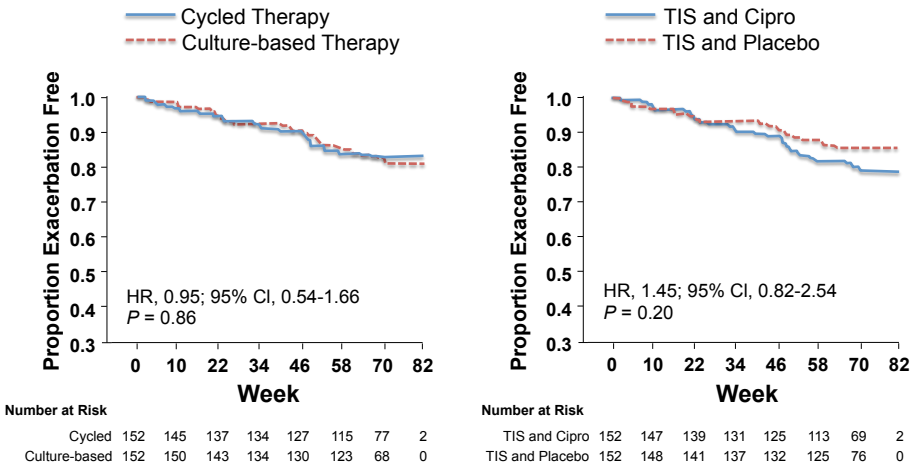
EPIC Study Design (at first *Pseudomonas* detection)



Solid blocks – chronic intermittent treatment

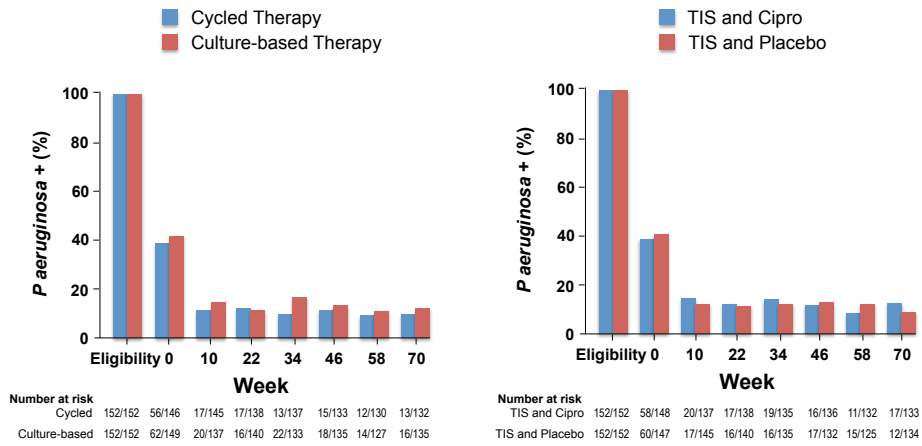
Striped blocks – treatment *only* when culture positive

EPIC Study: Results



Treggiari MM, et al. *Arch Pediatr Adolesc Med*. 2011;165:847-856.

EPIC Study: Results



Treggiari MM, et al. *Arch Pediatr Adolesc Med*. 2011;165:847-856.

ALPINE Study

- Open-Label Phase 2 Trial to Evaluate the Safety and Efficacy of Aztreonam for Inhalation Solution (AZLI) in Pediatric Patients With CF and New Onset Lower Respiratory Tract Culture Positive for *Pseudomonas Aeruginosa*
- CF patients age 3 mos to < 18 years and newly detected PA pulmonary colonization/infection
- Primary outcome: proportion of patients with PA-negative cultures at all time points during a 6-month monitoring period (after cessation of AZLI) treatment; cultures at baseline, days 28 (end of AZLI treatment), 56, 112, 196
- Trial completed; analysis under way

http://clinicaltrials.gov/show/NCT01375049. Accessed August 2013.

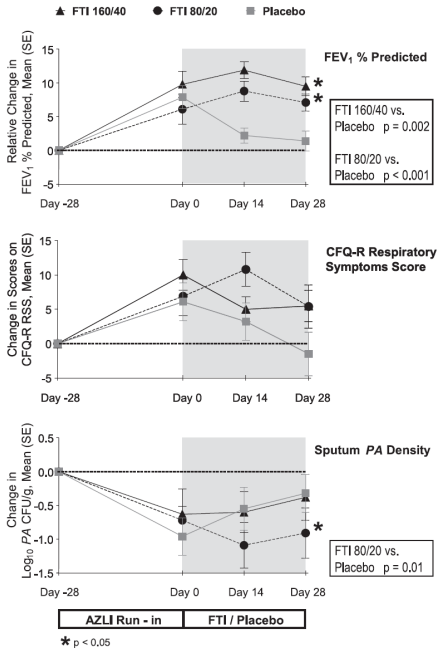
Summary of Eradication Data

- A single month of inhaled tobramycin inhalation solution, 300 mg BID, works as well as a longer course or cycled therapy in the setting of a negative culture
- Other antibiotic approaches may be helpful; awaiting ALPINE results

Unanswered Questions

- Should continuous, alternating inhaled antibiotics be used for patients with chronic PA infection?
- What is the best approach for patients who "fail" initial PA eradication?
- What about other CF-related organisms?

AZLI Alternating With Tobramycin/ Fosfomycin



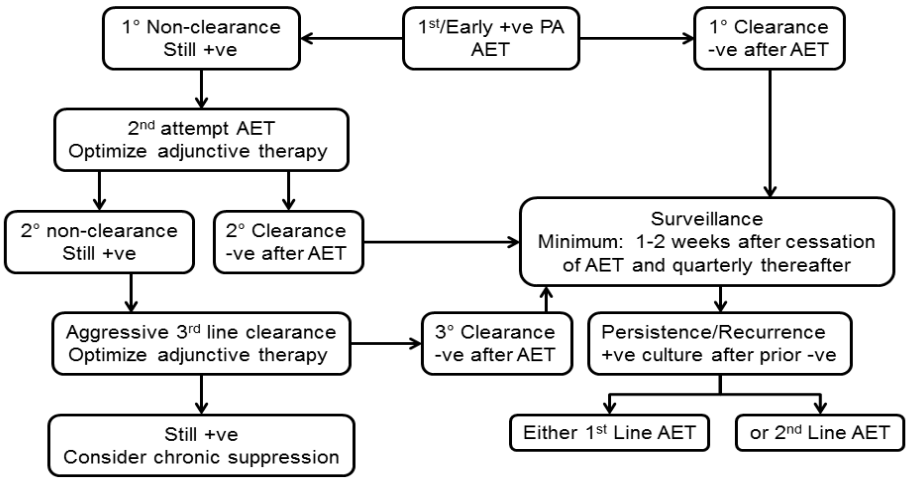
Trapnell BC, et al. *Am J Respir Crit Care Med*. 2012;185(2):171-178.

Alternating Antibiotic Therapy for Chronic Airway Infection

- Study design
  - **Continuous, alternating antibiotic therapy**
  - Prospective, observational, cohort study
  - N = 30
  - Treatment groups
    - AZLI every other month
    - TSI every other month
    - AZLI and TSI alternating months
  - Study endpoints – antibiotic resistance profiles, microbial response, pulmonary function, CFQ-R respiratory symptoms

www.clinicaltrials.gov/ct2/show/NCT01319253. Accessed August 2013.

Artimino Algorithm for Antibiotic Eradication Therapy (ECFS)



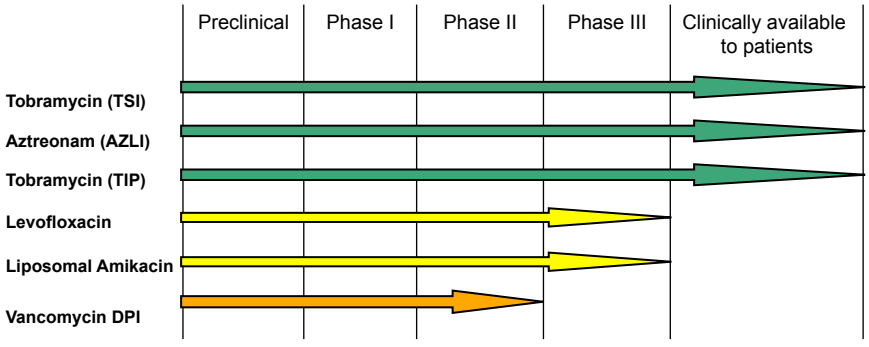
Döring G, et al; Consensus Study Group. *J Cyst Fibros*. 2012;11(6):461-479.

Other Organisms Associated With Increased Mortality

- Historically, most “feared” CF infection is *Burkholderia cepacia* complex
- *Mycobacterium abscessus* associated with more rapid decline of lung function
- Risk-adjusted mortality rate for CF patients with *MRSA*: 27.7:1000 vs. 18.3:1000 in patients without *MRSA*
- Reports of epidemic strains/severe disease with a number of organisms including *Achromobacter xylosoxidans* and *Pandoraea apista*
- Approaches to therapy are not yet defined

Dasenbrook EC, et al. *JAMA.* 2010;303(23):2386-2392.

Aerosolized Antibiotic Development Pipeline



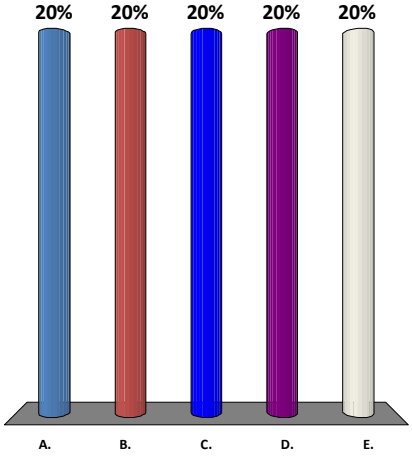
http://www.cff.org/research/drugdevelopmentpipeline/. Accessed August 2013.

Key Messages

- Chronic airway infection with *Pseudomonas aeruginosa* is an important clinical problem in children and adults with CF
- Suppression of chronic PA has clear benefits; several treatment options are available
- Eradication of new PA is an accepted and widely used strategy; optimal strategy is still evolving

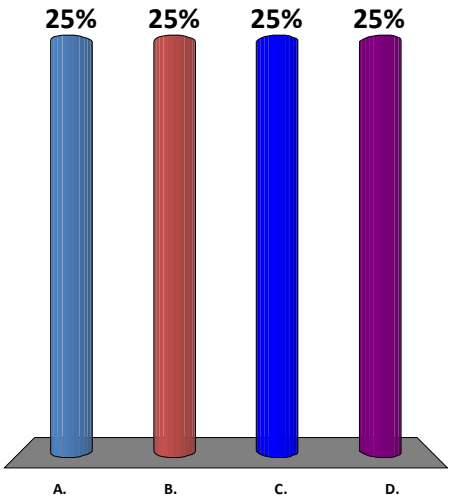
Based on improvements in FEV_1 and sputum *Pseudomonas aeruginosa* density demonstrated in clinical trials, which of the following would be a reasonable treatment choice for an 18-year-old patient with CF and chronic *P. aeruginosa* infection?

A. Aztreonam lysine for inhalation
B. Tobramycin inhalation solution
C. Tobramycin inhalation powder
D. All of the above
E. A and B



Treating an asymptomatic CF patient with first isolation of *Pseudomonas aeruginosa* is likely to:

A. Have no clinical benefit
B. Be most successful in eradicating *P. aeruginosa* if tobramycin inhalation solution is combined with oral ciprofloxacin
C. Delay chronic infection
D. Cause intolerable side effects



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  - LiPuma JJ. The changing microbial epidemiology in cystic fibrosis. *Clin Microbiol Rev.* 2010;23:299-323.

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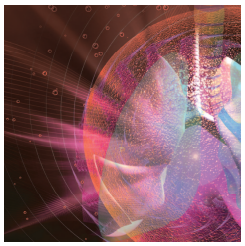
Advances in the Management of Cystic Fibrosis



Case:
29-year-old
Caucasian Male

Case: 29-Year-Old Caucasian Male

History

- Recurrent heat exhaustion since age 8–9
- IDDM diagnosed at age 22
- Frequent bronchitis; takes antibiotics every few months
- Pneumonia 2 years ago
- ¼ c brown sputum daily
- Salty powder on skin after sweating
- Found to be infertile 1 year ago; absent vas deferens
- Internet search–could this be CF?
- Requested testing for CF from local PCP
- Sweat chloride 70 mEq/L
- Genotyping: G551D; 2789+5G→A
- Parental genotyping confirms 1 mutation from each
- 1 stool daily (bulky, foul-smelling)
- Patient has maintained weight and denies sinus problems

Case: 29 Year-Old Caucasian Male

- **Physical**
  - Well appearing man; BMI 30
  - Significant only for purulent rhinorrhea and swollen turbinates
  - Lungs clear; No clubbing
- **Testing**
  - Spirometry: mild obstruction; FVC 82% predicted; FEV_1 72% predicted; FEV_1/FVC ratio 71%
  - CXR: fibronodular changes in both upper lobes
  - Sputum culture: *Mycobacterium avium-intracellulare*, *Aspergillus*, sensitive *S. aureus*
  - Labs: BMP normal, but glucose 260 mg/dL; HgbA1C 9.8; LFT normal; vitamins A, D, E low; INR 1.1; IgE 22

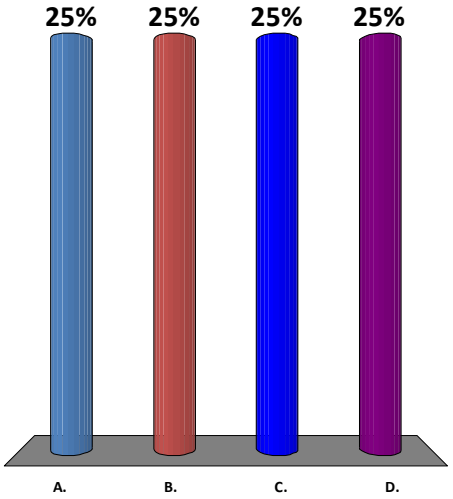
This clinical presentation and genotyping is consistent with a diagnosis of:

A. Chronic bronchitis

B. CFTR related metabolic syndrome

C. Nonclassic cystic fibrosis

D. Allergic bronchopulmonary aspergillosis



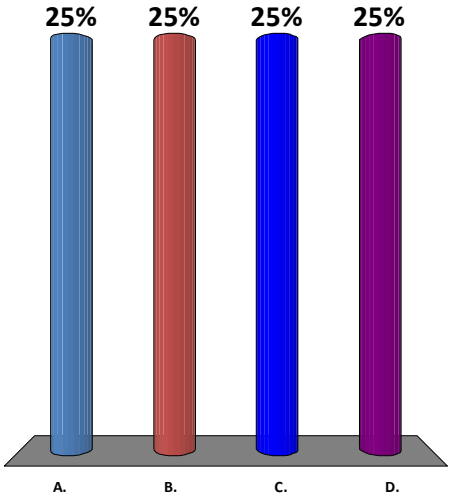
Indicated therapies for this patient would include:

A. rhDNAse (Pulmozyme®), airway clearance, TOBI®

B. rhDNAse (Pulmozyme®), Ivacaftor (Kalydeco®), airway clearance

C. Pancreatic enzymes, ADEK vitamins, TOBI®

D. Azithromycin, airway clearance, low-fat diet



Case Follow-up

- **Treatment Approach**
  - Airway clearance with the Vest
  - Inhaled rhDNase (Pulmozyme®) and albuterol
  - Low dose of pancreatic enzyme replacement and ADEK vitamins
  - Prescribed ivacaftor (Kalydeco®)
- **Follow-up Clinic Visit**
  - Feeling much better
  - Minimal cough and sputum
  - No abdominal symptoms
  - No salt collecting on his skin
  - Repeat spirometry
    - FVC 84% predicted
    - FEV_1 85%
    - FEV_1/FVC ratio 77%
  - Endocrinology will assist with optimization of glucose control