

Cystic Fibrosis ***currents***

8th ACCP Central America CME Course
San Jose, Costa Rica
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Cystic Fibrosis

Learning Objectives

- 1. Become familiar with recent findings in the genetics of cystic fibrosis**
- 2. Gain appreciation of how CFTR gene mutations affect clinical phenotype**
- 3. Review interpretation of sweat chloride test**
- 4. Become informed about recent studies on ICS in CF**

MM – 17 yr old male

- presents with 2-yr history debilitating nausea**
- developed abdominal pain & nausea 27 mos ago**
- thought to have pancreatitis but still nauseous despite medical treatment incl. TPN x 3 mos**
- subsequent Dx eosinophilic gastroenteritis – Rx=restrictive diet**
- worse abdominal pain 12 mos ago – given Dx of acute on chronic appendicitis**
- pain resolved but his nausea persisted**

MM – 17 yr old male

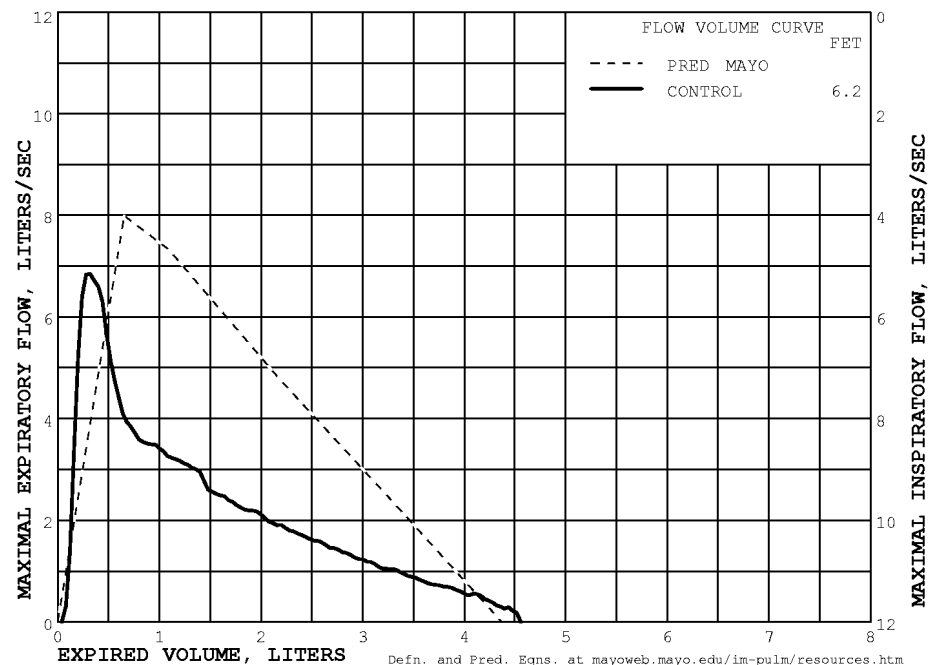
- **N-G & N-J tube feeding trials→unable to gain Wt**
- **had to restart his N-G feedings 16 mos ago because of nausea + weight loss**
- **Ht 20%ile. Wt 4%ile. BMI 18 (5%ile)**
- **Extensive GI workup (incl. scope) normal except decreased gastric accommodation on Nuc Med**
- **Past Dx of asthma...**

MM – 17 yr old male

17 y.o. Male Wt: 51.4 KG, BMI: 17.9 Ht: 169.6 cm
 Previous test: Desk:

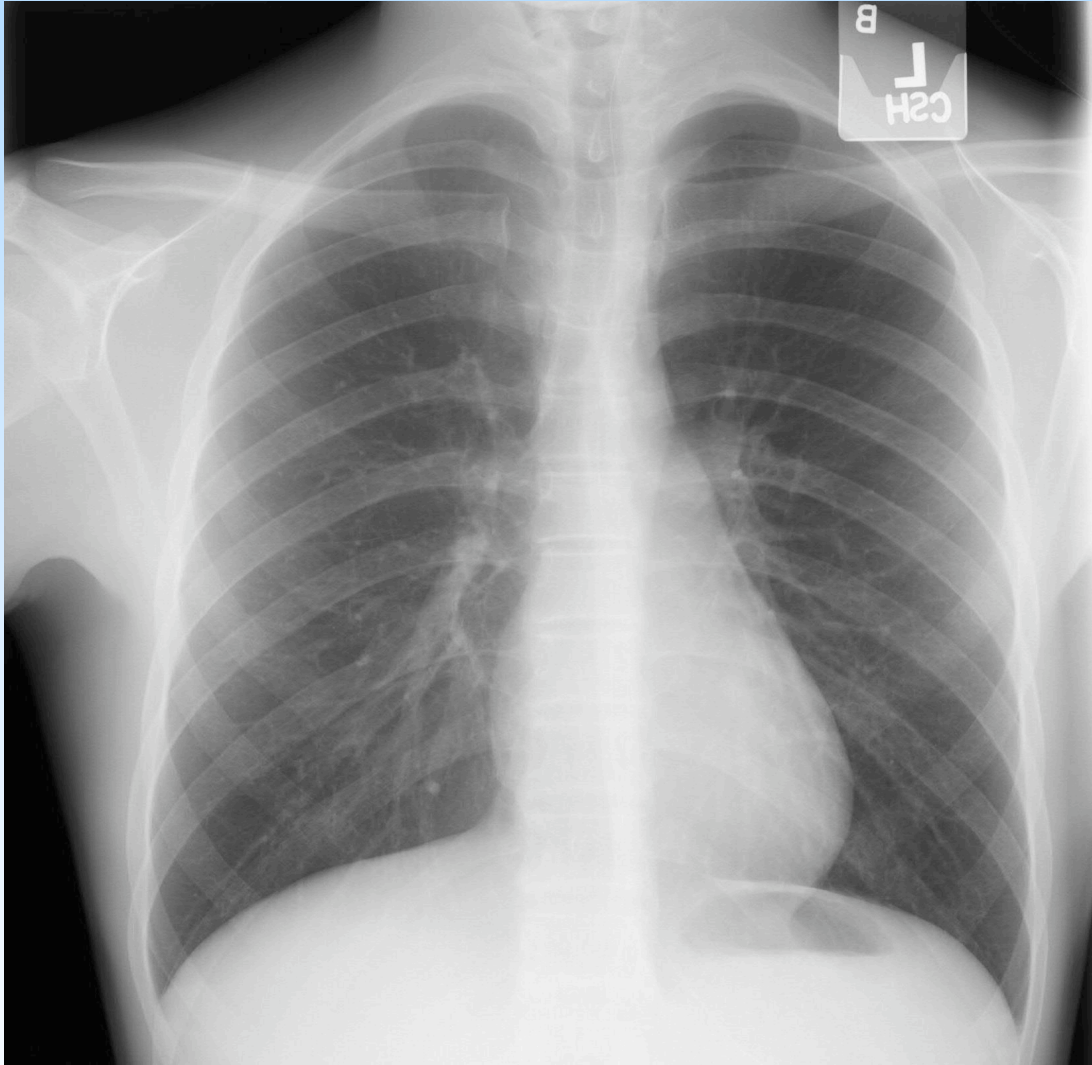
SPIROMETRY	PREDICTED		CONTROL	
	NORMAL	RANGE	FOUND	%PRED.
VC	4.37	>3.55	4.49	103%
FVC	4.37	>3.55	4.48	103%
FEV1	3.79	>2.95	2.69*	71%
FEV1/FVC	86.6	>73.4	59.9*	
FEF25-75	4.2	> 2.5	1.6*	38%
FEFmax	8.0	> 5.3	6.8	86%
MVV	151	> 106	90*	60%

*Outside normal range.



Defn. and Pred. Eqns. at mayoweb.mayo.edu/im-pulm/resources.htm

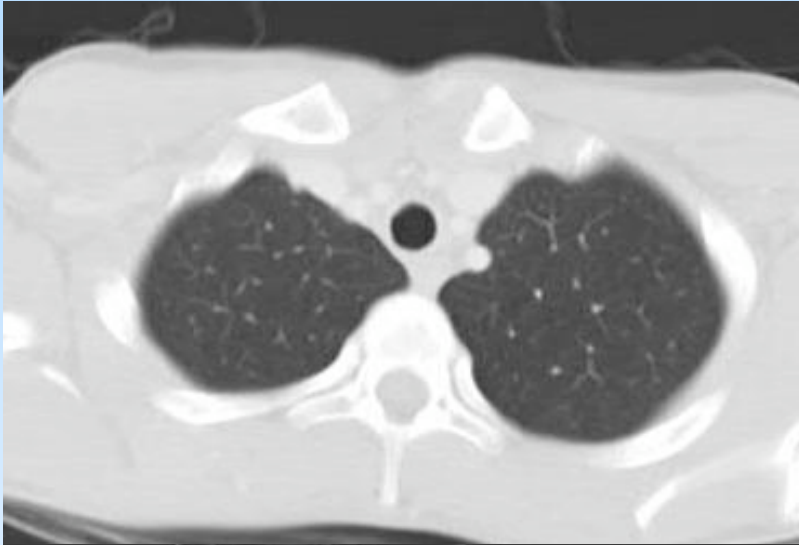
MM – 17 yr old male



MM – 17 yr old male

- **Since age 6 mos, frequent episodes "asthmatic bronchitis", i.e. tachypnea, cough & wheeze.**
- **Normal sweat Cl⁻ when Dx asthma made at ~2 yr**
- **Breathing issues settled when started school**
- **Year before Mayo Clinic, c/o cough & tight chest**
- **Often felt phlegm in throat but expectorated nil**
- **Denied exertional dyspnea before abdo Sx began**
- **Fam Hx: uncle with "fertility" problem**

MM – 17 yr old male



MM – 17 yr old male

- **Sweat Cl 30 & 34 mEq/L with >300 mg collected**
- CFTR gene sequence detected deletion @Exon 10
DNA change: 1677_1678delTA
- Predicted to result in premature protein truncation
- These results indicate that this individual is at least a CF carrier & increases probability that pancreatic disease related to abnormal CFTR function

PS – patient had vas deferens...& a small varicocele

MM – 17 yr old male

So what does one do?

OCCASIONAL REVIEW

Cystic fibrosis: terminology and diagnostic algorithms

K De Boeck, M Wilschanski, C Castellani, C Taylor, H Cuppens, J Dodge,
M Sinaasappel, on behalf of the Diagnostic Working Group



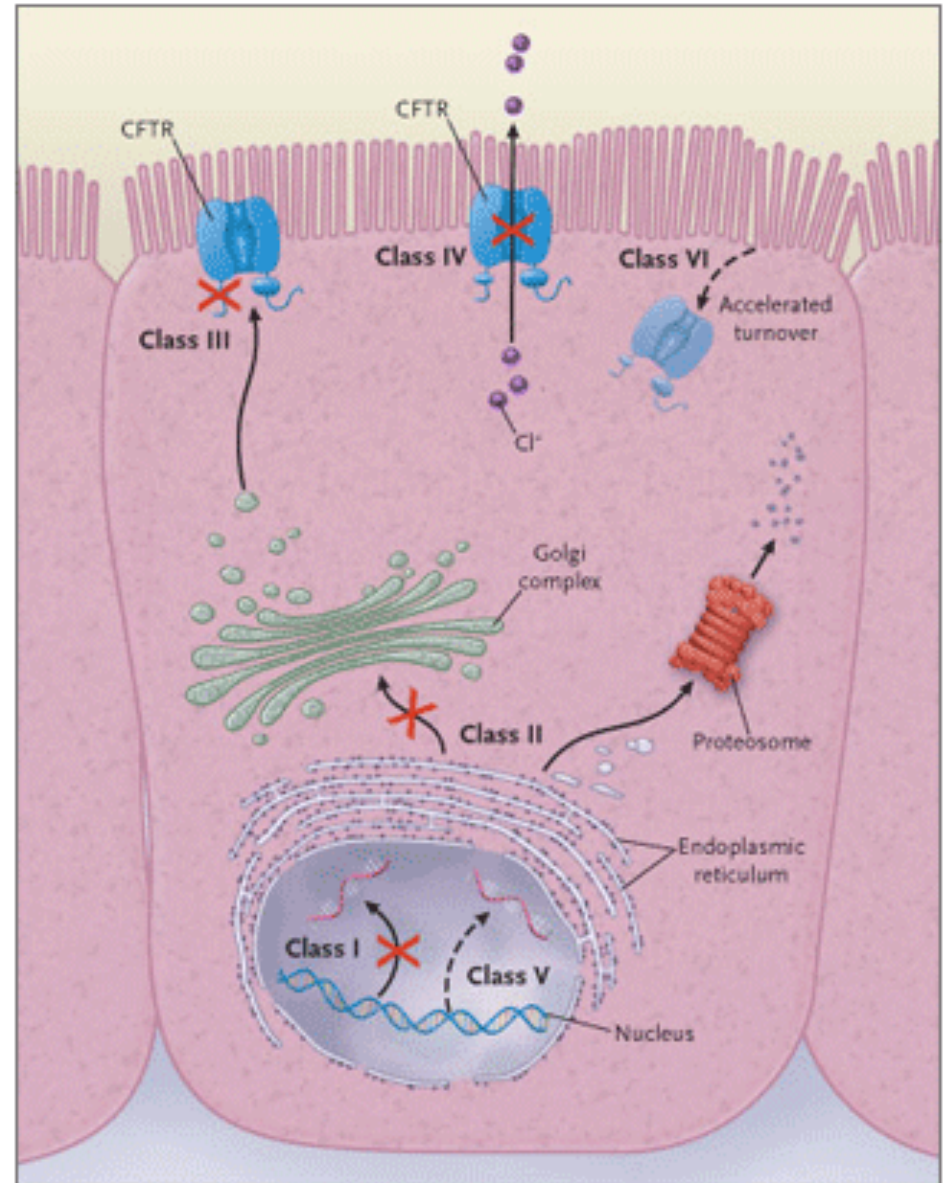
.....
Thorax 2006;**61**:627–635. doi: 10.1136/thx.2005.043539

What is CFTR ?

- **Channel for Cl⁻ ion**
- **Regulates activity of another Cl⁻ channel**
- **Regulates activity of amiloride sensitive Na⁺ channel**
- **Net result ⇒ increased transepithelial potential difference pathognomonic for CF**

6 types of CFTR gene mutation associated with defective product

- absence of synthesis (class I)
- defective protein maturation & premature degradation (class II) eg. $\Delta F508$
- disordered regulation, such as diminished ATP binding and hydrolysis (class III)
- defective chloride conductance or channel gating (class IV)
- reduced number of CFTR transcripts due to a promoter or splicing abnormality (class V)
- accelerated turnover from the cell surface (class VI)



Rowe et al. Cystic Fibrosis. *NEJM* 2005;352:1992.

How is CFTR related to disease?

- Ion transport abnormalities result in abnormal salt concentration & water content in airway lining fluid (“low-volume” model)
- Retained secretions and bronchial casts in infants diagnosed by newborn screen indicate early impairment of mucociliary clearance
- **Homozygosity or compound hetero for class I-II-III mutations results in more severe disease**

Clinical Manifestations suggesting CF

Highly suggestive

Suggestive but less specific

GI Manifestations

Meconium ileus

Exocrine pancreatic insufficiency children

Failure to thrive

Hypoalbuminemia

Fat-soluble vitamin deficiency

Distal intestinal obstruction syndr

Rectal prolapse

Portal hypertension

Cholelithiasis in child w/o hemol. disorder

Primary sclerosing cholangitis

Exocrine pancreatic insufficiency adult

Clinical Manifestations suggesting CF

Highly suggestive

Suggestive but less specific

Sinopulmonary Manifestations

Persistent infection with mucoid *Ps aeruginosa*

Bronchiectasis in both upper lobes

Persistent infection with mucoid *B cepacia*

Nasal polyps children

Persistent/recurrent infection with *S aureus*, *Ps aeruginosa*, *Hem Influenzae*, or *A xylosoxidans*

Evidence of bronchiectasis, atelectasis, hyperinflation, or persistent opacities on CXR

Hemoptysis assoc. with diffuse disease other than TB, vasculitis

Chronic and/or productive cough

ABPA

Nasal polyps in adults

Chronic pansinusitis on CT

Clinical Manifestations suggesting CF

Highly suggestive

Suggestive but less specific

Other (neither GI nor respiratory)

**Hypochloremic
alkalosis w/o vomiting**

**Congenital bilateral
absence vas deferens
(CBAVD)**

Osteopenia/osteoporosis age<40

Atypical diabetes

Digital clubbing

Cystic Fibrosis

- **CF phenotype has become continuum of Sx that defies def'n into distinct categories**
- **Clinically useful to distinguish between classic and non-classic (atypical) CF**
- **Sweat Cl^- remains gold standard for making this distinction**
- **Single organ involvement, and class IV-VI mutations more likely, in patients with non-classic CF**

Table 1 WHO diagnostic list for single organ disease phenotypes associated with *CFTR* mutations²

Isolated obstructive azoospermia*
Chronic pancreatitis*
Allergic bronchopulmonary aspergillosis*
Disseminated bronchiectasis*
Diffuse panbronchiolitis*
Sclerosing cholangitis*
Neonatal hypertrypsinogenaemia

*At least one *CFTR* mutation identified.

It is likely that this classification will need further revision in the future as our knowledge and understanding of these conditions increase.²

So how should one interpret sweat Cl^- values?

- **Non-CF individuals very rarely have $\text{Cl}^- > 60$**
- **Classic CF phenotype, with or without pancreatic insufficiency, has $\text{Cl}^- > 60$**
- **Very rare to have CF phenotype with $\text{Cl}^- < 30$ (exception 3849+10kbC>T)**
- **Vast majority of CF, classic or otherwise, have $\text{Cl}^- > 40$**
- **~4% tests have Cl^- results in 30-60 range, of whom ~1/4 patients will have 2 CFTR mutatⁿ**

Cystic Fibrosis

So how should one make CF diagnosis?

1. **Rosenstein & Cutting for US CFF, *J Ped* 1998**

- **One or more of classical phenotypic features**
- **Hx of CF in sib or positive newborn screen**
plus
- **Laboratory evidence of CFTR abnormality**
 - **Elevated sweat Cl**
 - **Known mutations in each CFTR gene**
in vivo abnormality ion transport

Cystic Fibrosis

Rosenstein & Cutting for US CFF, *J Ped* 1998

CFTR mutation defined as gene alteration that fulfills one of the following criteria:

- 1. changes AA sequence that severely affects synthesis or function**
- 2. causes early termination signal**
- 3. alters invariant nucleotides of intron splice**
- 4. causes novel AA sequence that does not occur in normal CFTR genes from ≥ 100 carriers from patient's ethnic group**

Cystic Fibrosis

- **US CFF data indicates ~2-2.5% of patients have no identifiable CFTR mutation**
- **Number of known mutations approaches 2K**
- **Altered DNA sequence alone not enough... involvement in disease must be established**
- **Today's polymorphism could be tomorrow's mutation**

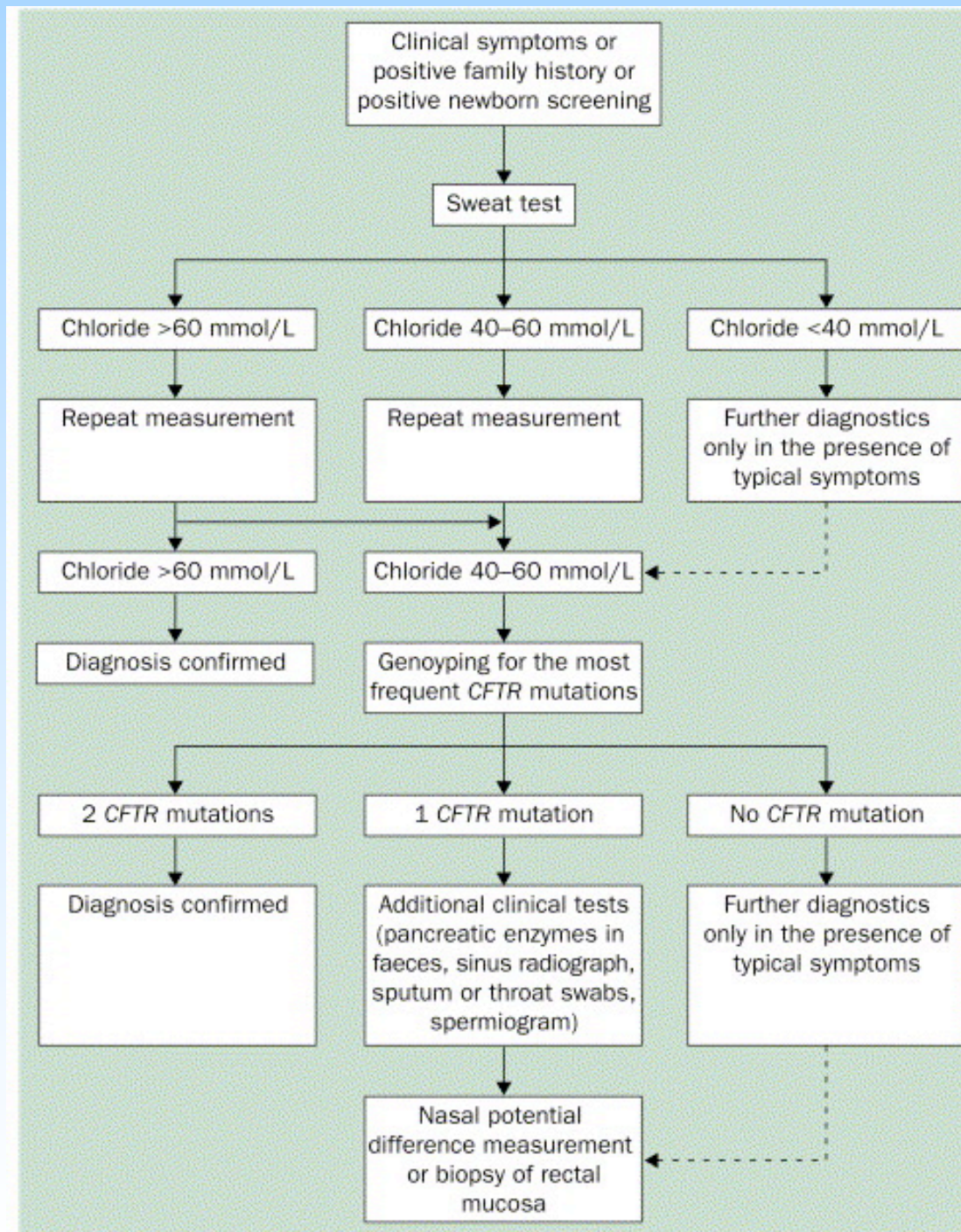
Workup for indeterminate sweat Cl⁻ (30-60 mEq/L)

If no CFTR mutations found

- Humoral immunodeficiency
- GER
- Allergy testing
- Ciliary dyskinesia

If 1 CFTR mutation found

- Proceed to CFTR gene sequencing



CFTR-related disease

**Most importantly, follow these patients
at least annually**

Do not discharge!

Control of airway inflammation in CF

Multicenter Randomized Controlled Trial of Withdrawal of ICS in CF

Balfour-Lynn, AJRCCM 2006; 173: 1356-1362

- **Multicenter randomized double-blind placebo-controlled trial in 18 pediatric & adult UK centers**
- **During the 2-mo run-in period, all patients received fluticasone; they then took either fluticasone or placebo for 6 mo.**
- **FP group: n = 84, median age 14.6 yr, mean (SD) FEV₁ 76%; placebo group: n = 87, median age 15.8 yr, mean (SD) FEV₁ 76%**

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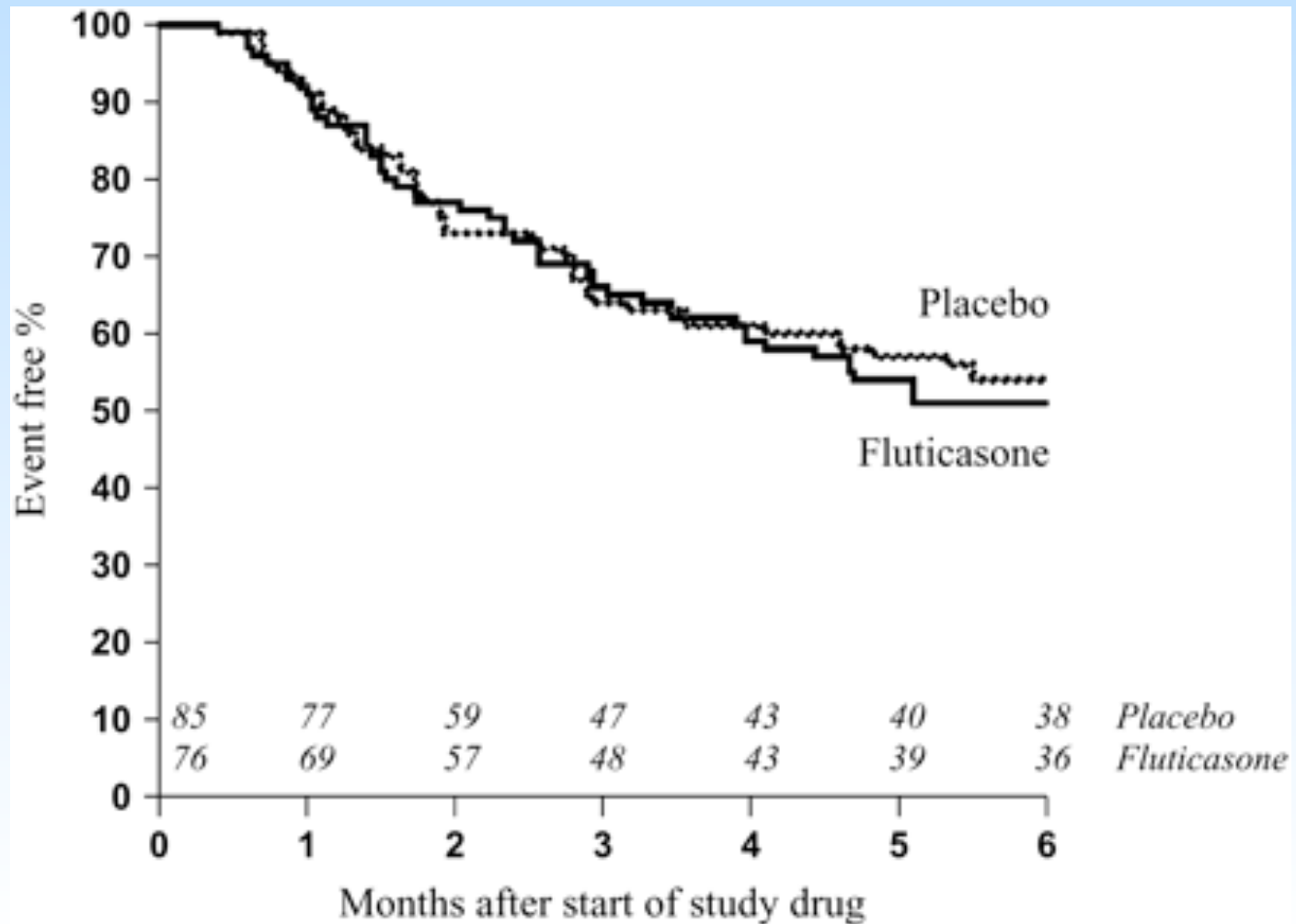
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- no difference in time to 1st exacerbation (primary outcome) with hazard ratio (95% confidence interval) of 1.07 (0.68 to 1.70) for FP vs placebo
- no effect of age, atopy, corticosteroid dose, FEV₁, or *Pseudomonas aeruginosa* status
- no change in lung function or differences in antibiotic or rescue bronchodilator use

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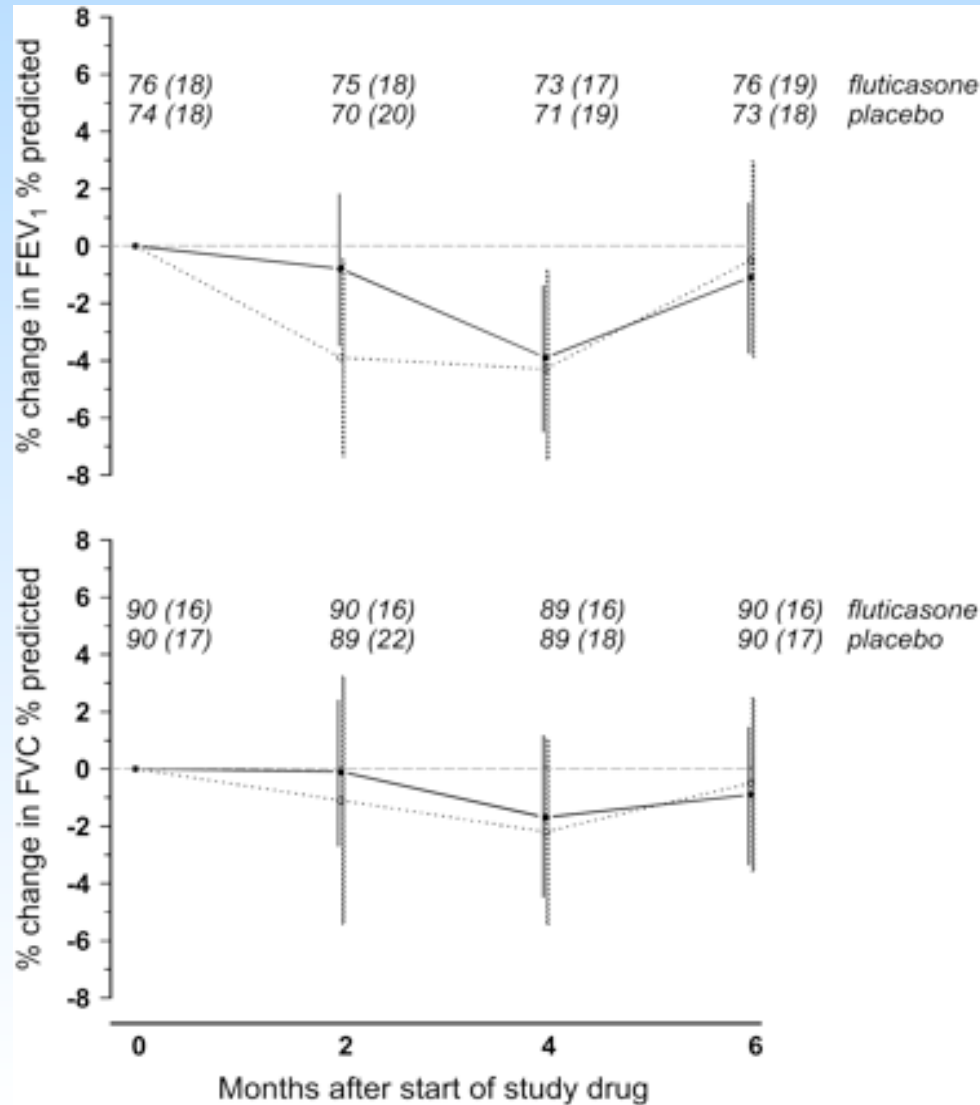
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Control of airway inflammation in CF

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Control of airway inflammation in CF

Relationship between ICS therapy & rate of PFT decline in children with CF
Ren et al., *J Peds* 2008; 153: 746-51

- **ESCF database 1994-2004**
- **~3000 patients 6-17 yrs old**
- **Grouped according to ICS use (unspecified)
>80% clinic visits**
- **Primary outcome was rate of decline of FEV₁
before vs after starting ICS**
- **Comparison group never received ICS over 4 yrs**

Control of airway inflammation in CF

Relationship between ICS therapy & rate of PFT decline in children with CF
Ren et al., *J Peds* 2008; 153: 746-51

Rate decline FEV ₁		
	Before ICS/index date	After ICS/index date
ICS group	-1.5±0.45%pred/yr	-.44±0.41%pred/yr
Ctl group	-1.1±0.25%pred/yr	-1.4±0.25%pred/yr

Control of airway inflammation in CF

Relationship between ICS therapy & rate of PFT decline in children with CF

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But...ICS associated with:

- ↓ Ht for age Z-scores
- ↑ insulin/oral hypoglycemic use
- ↑ proportion +cultures *S. maltophilia*, *B. cepacia*, *Aspergillus* spp

Control of airway inflammation in CF

Relationship between ICS therapy & rate of PFT decline in children with CF

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Limitations of retrospective analysis:

- Which ICS, what dose?
- Pts given ICS had more severe lung disease
- Were pts on ICS more likely to be screened for CFRDiabetes?

Control of airway inflammation in CF

Pick your poison carefully!