Lung Disease in Cystic Fibrosis

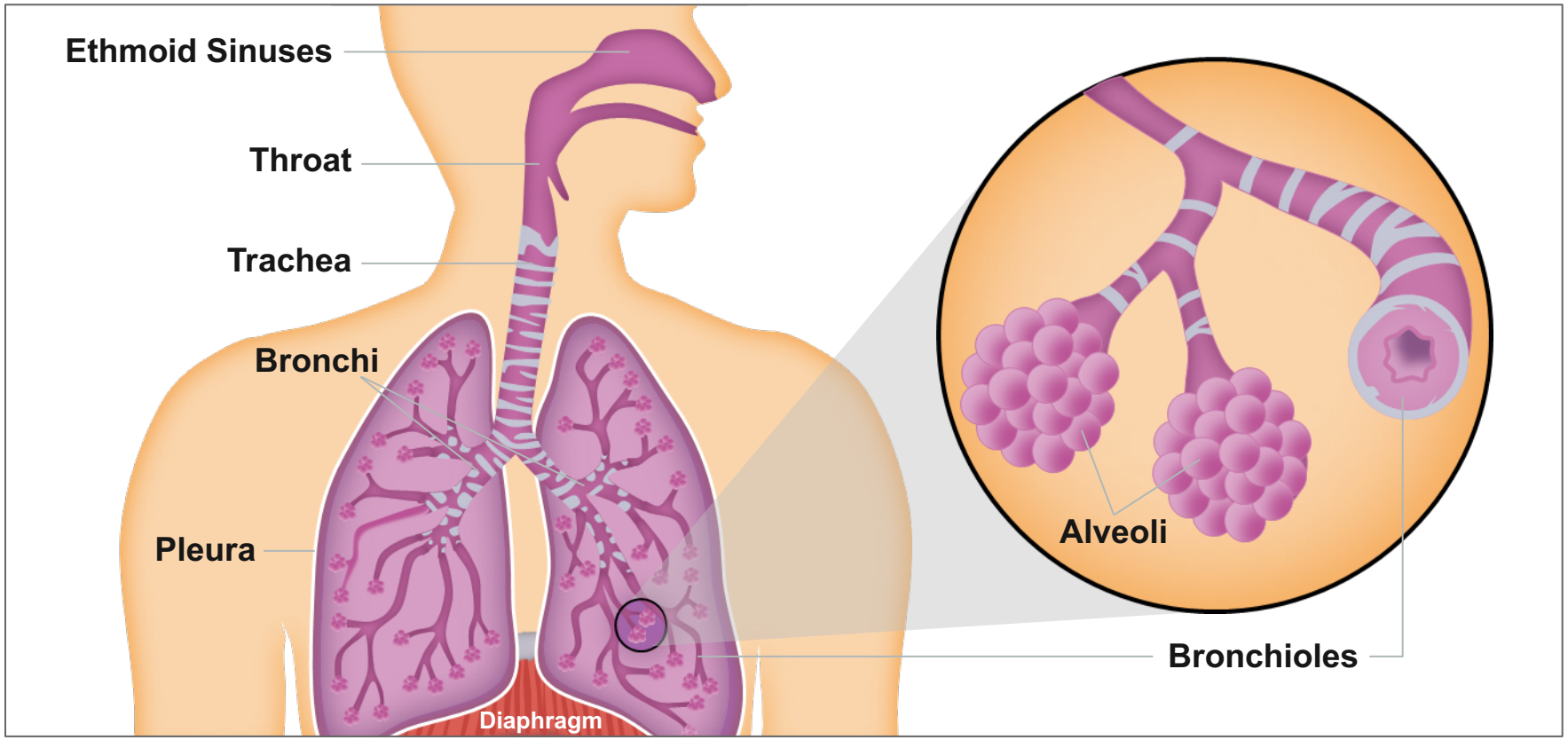
Objectives

- Examine the role of CFTR channels in development of CF lung disease
- Explore the natural history and progression of CF lung disease including the relationship with nutritional status
- Investigate the impact of pulmonary exacerbations and microbial ecology in CF lung disease

VERTEX

Respiratory Anatomy

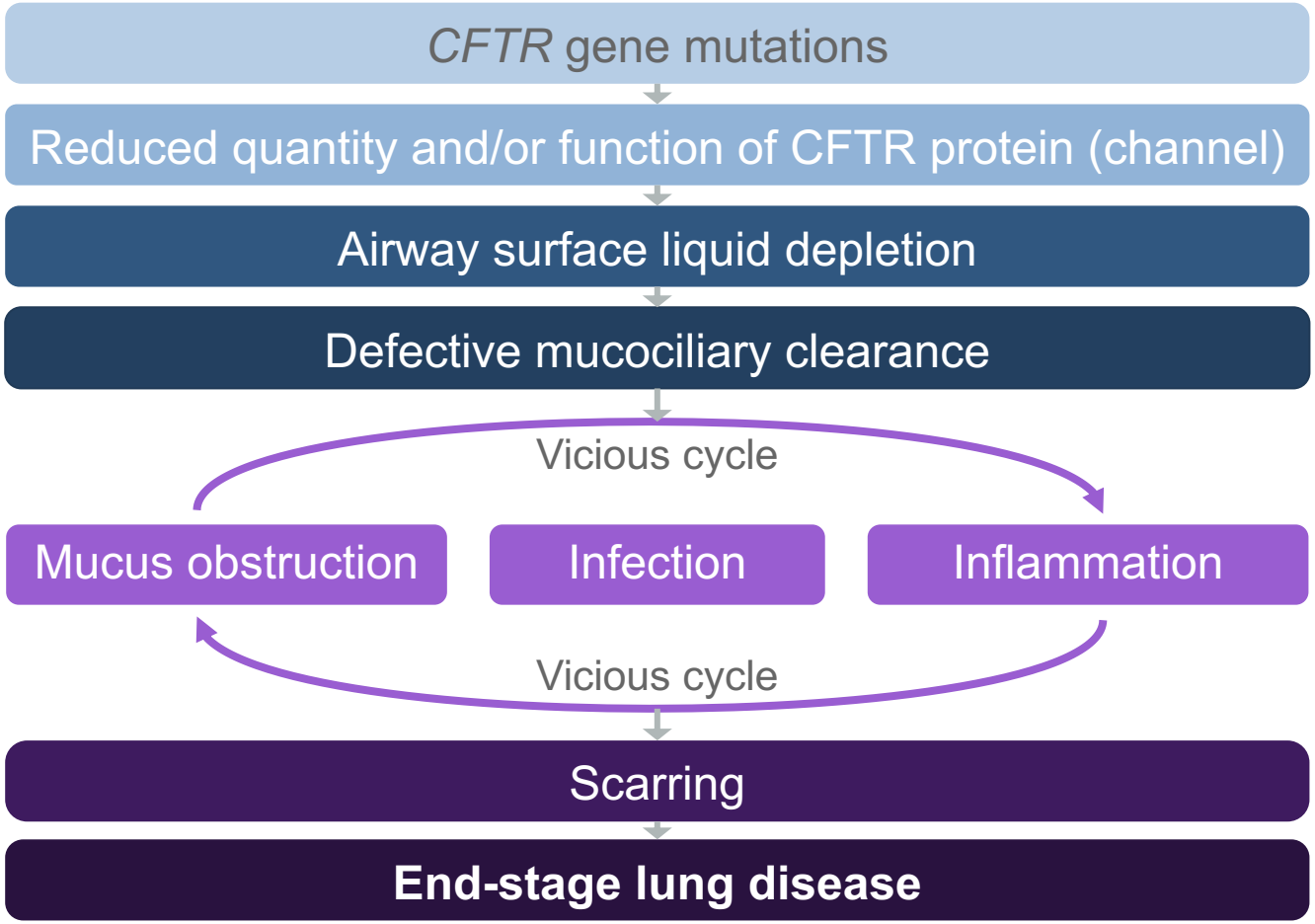
The respiratory system is comprised of airways that become progressively smaller and end in tiny sacs called alveoli



The Human Respiratory System. In: Tu J, et al. Computational Fluid and Particle Dynamics in the Human Respiratory System. *Springer*, 2013; Ch. 2.

The Role of CFTR Channels in Development of CF Lung Disease

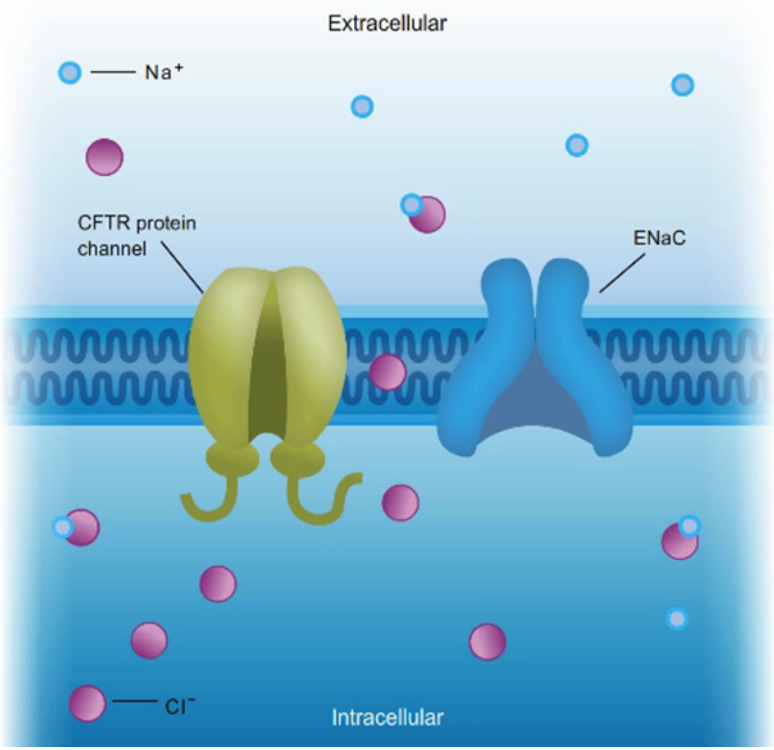
Pathophysiologic Cascade of CF Lung Disease Can Lead to End Stage Lung Disease



Adapted from Ratjen FA. *Respir Care* 2009;54:595–605

CFTR Channels Regulate Fluid and Electrolyte Balance in Epithelial Tissues

CFTR channels act in tandem with ENaC to regulate fluid and electrolyte balance[1,2]



CFTR gene mutations can result in CFTR protein channel abnormalities – the underlying defect of CF disease[3]

CFTR, Cystic Fibrosis Transmembrane conductance Regulator; ENaC, epithelial sodium channels.

1. MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10; 2. Goralsk JL et al. *Curr Opin Pharmacol* 2010;10:294–9; 3. Rowe SM et al. *N Engl J Med* 2005;352:1992–2001

CFTR Gene Mutations Give Rise to CFTR Protein Channel Defects That Reduce Cl^- and Other Ion Transport

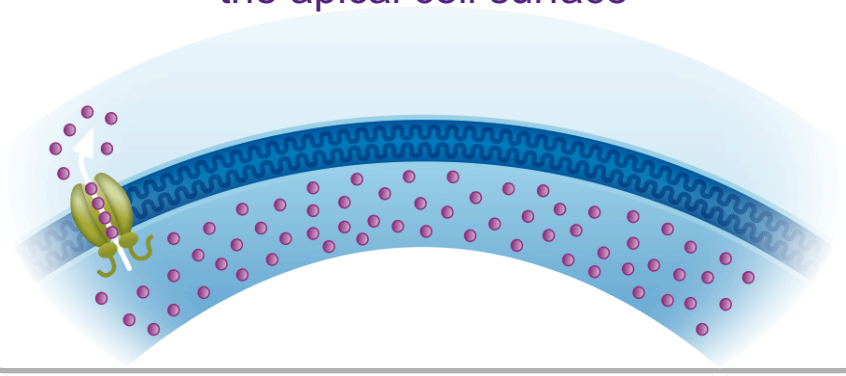
CFTR Quantity

Number of CFTR Channels in the Apical Surface

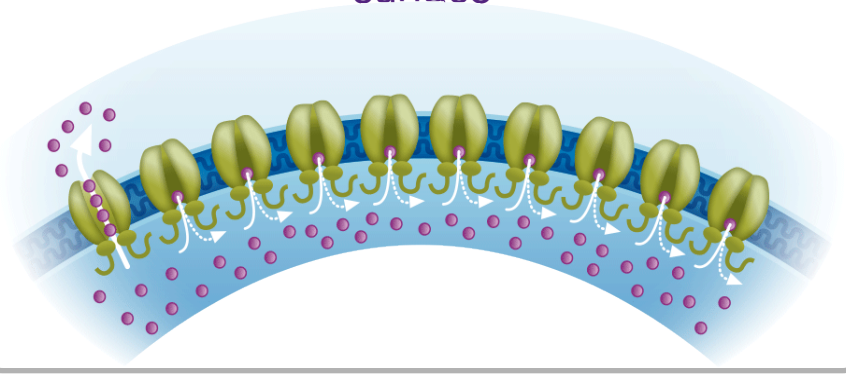
CFTR Function

Channel Open Probability ✖ Channel Conductance

Mutations that reduce the QUANTITY of functional CFTR proteins that reach the apical cell surface



Mutations that reduce the **FUNCTION** of CFTR proteins at the apical cell surface

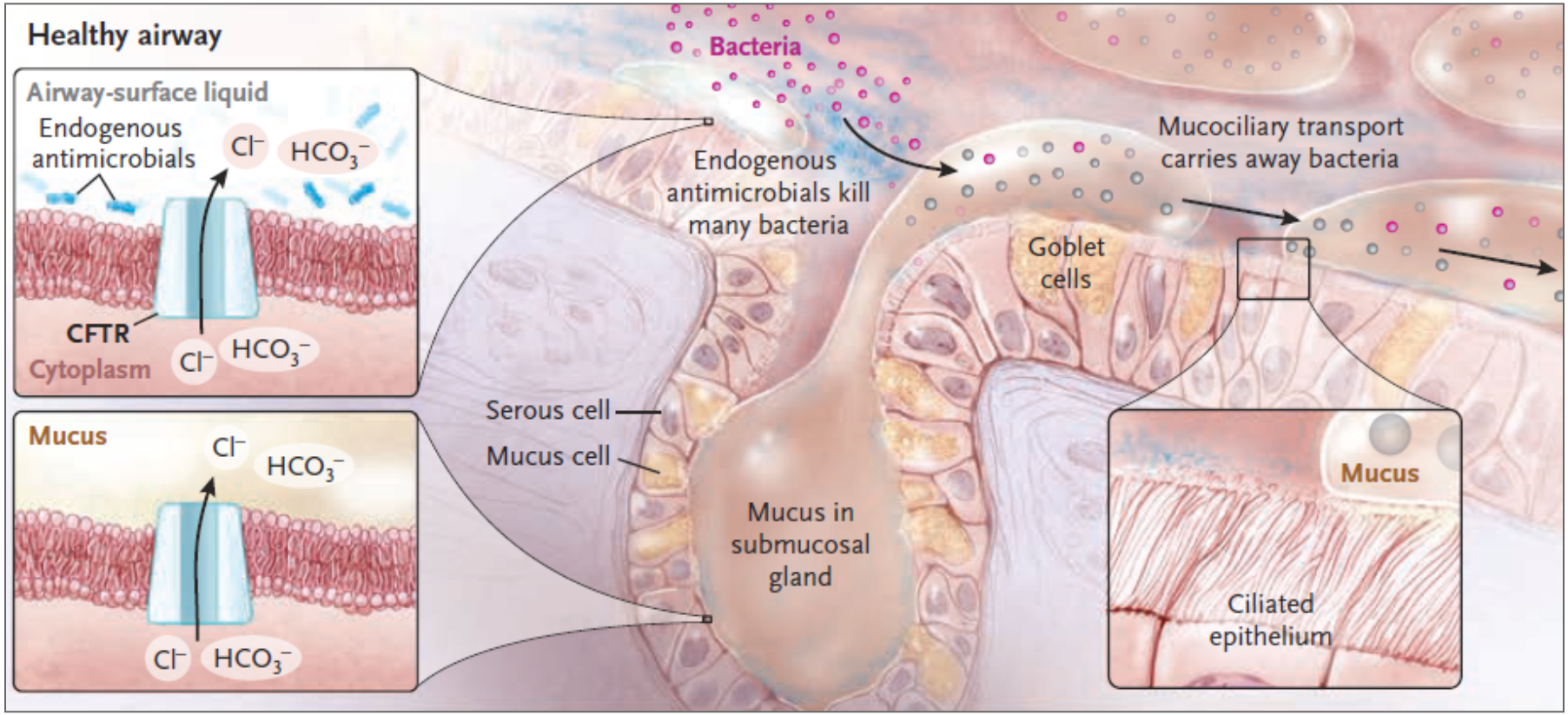


MacDonald KD et al. *Paediatr Drugs* 2007;9:1–10

VERTEX

Lung Clearance in the Healthy Airway Is an Active Process

Lung clearance mechanisms include a combination of airway surface liquid, mucus secretion and transport, and antimicrobial action, which together prevent infection and contamination

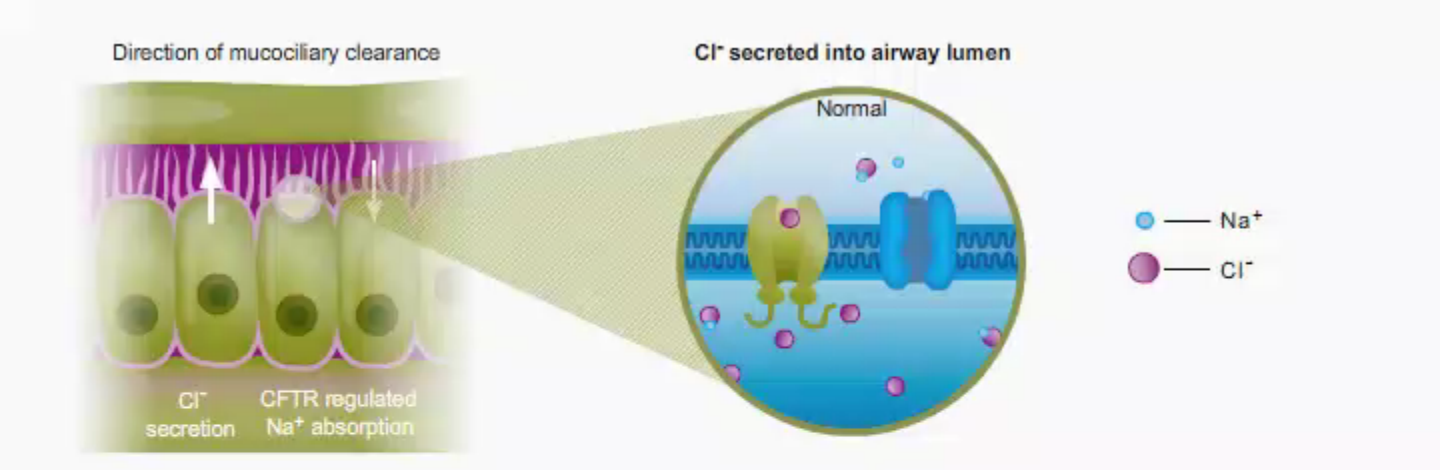


Stoltz DA, et al. *N Engl J Med* 2015; 372:351-362

Defective CFTR Reduces Chloride Transport in the CF Airway

Non-CF

Normal ASL height[1,2]



CF

Dehydrated ASL resulting in mucus and pathogen build-up[1,2]

ASL: Airway surface liquid

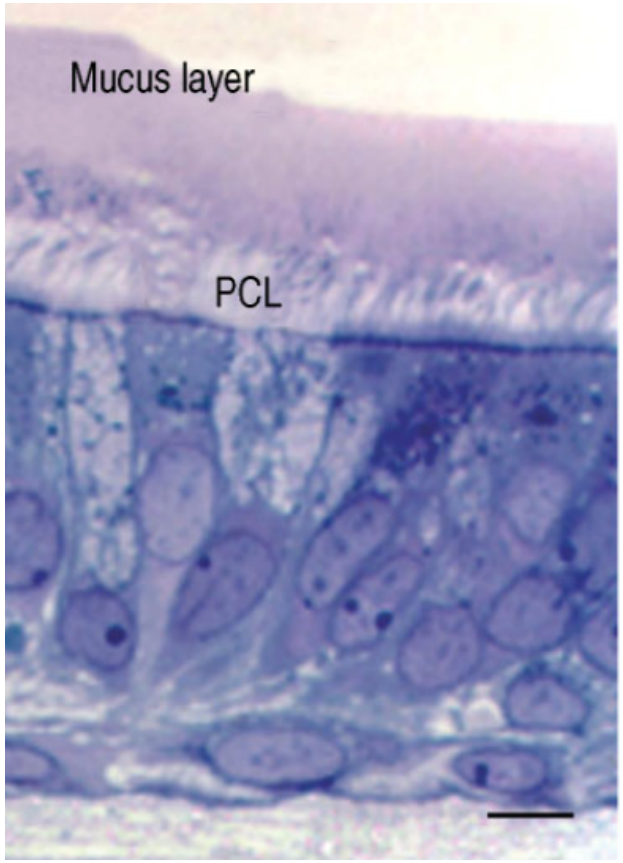
1. Rowe SM et al. *N Engl J Med* 2005;352:1992–2001; 2. Proesmans M et al. *Eur J Pediatr* 2008;167:839–49; 3. Boucher RC. *Eur Respir J* 2004;23:146–58

Normal Mucus Transport Is Essential for Lung Clearance

Mucus clearance is the primary defense against inhaled infectious agents and toxic particles.[1]

ASL = Mucus layer + PCL

Epithelium



Mucus layer traps inhaled particles[1,2]

Beating action by cilia facilitates transport of mucus-trapped particles out of lung[1,2]

PCL supports cilia and lubricates apical surface of the epithelium[1,2]

Goblet cells in epithelium secrete mucins that form mucus layer[2]

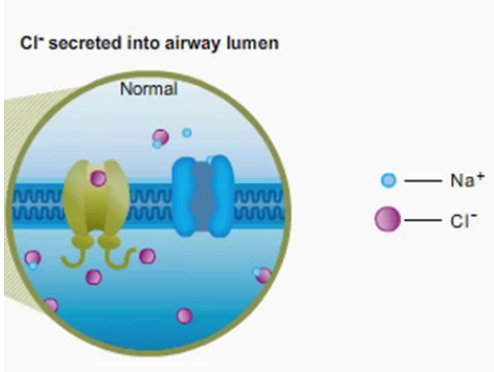
Action of CFTR and ENaC channels in epithelial cells maintains PCL[2]

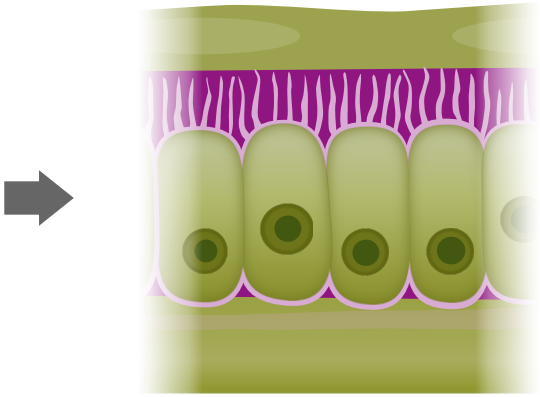
ASL = airway surface liquid; PCL = periciliary liquid.

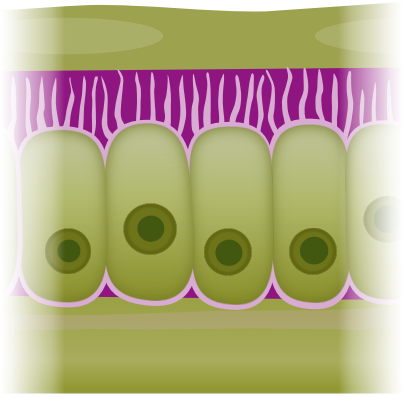
1. Button B, et al. *Science*. 2012;337(6097):937-941. 2. Stoltz DA, et al. *N Engl J Med*. 2015;372(4):351-362.

VERTEX

Normal Cl- Transport Leads to Normal ASL and Effective Mucus Clearance







Cl⁻ secretion

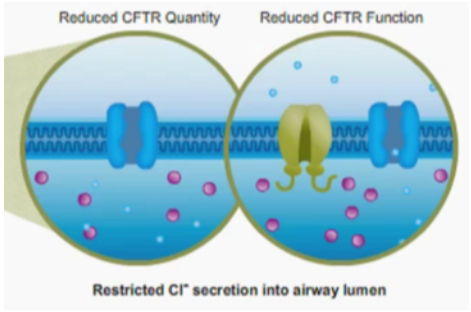
ASL hydration

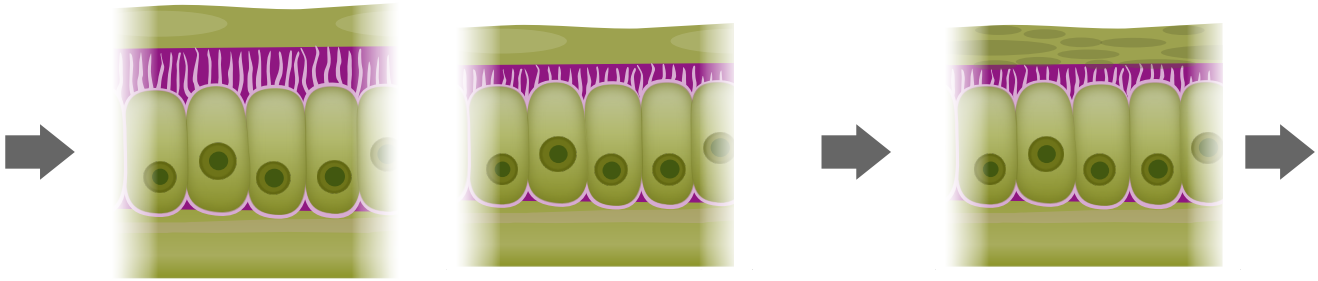
Mucociliary clearance

ASL = airway surface liquid; PCL = periciliary liquid.

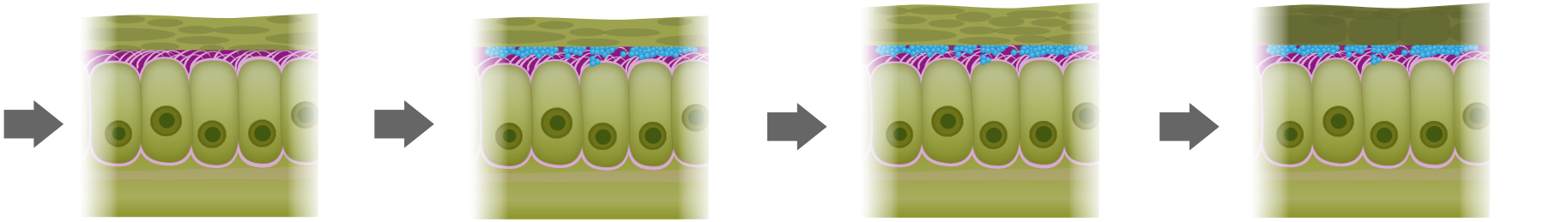
Button B, et al. *Cold Spring Harb Perspect Med*. 2013;3(8). pii: a009720. doi: 10.1101/cshperspect.a009720.

Impaired Cl^- Transport Leads to Depleted ASL and Failure of Mucus Clearance





Decreased Cl^- secretion → ASL depletion → Mucus concentration

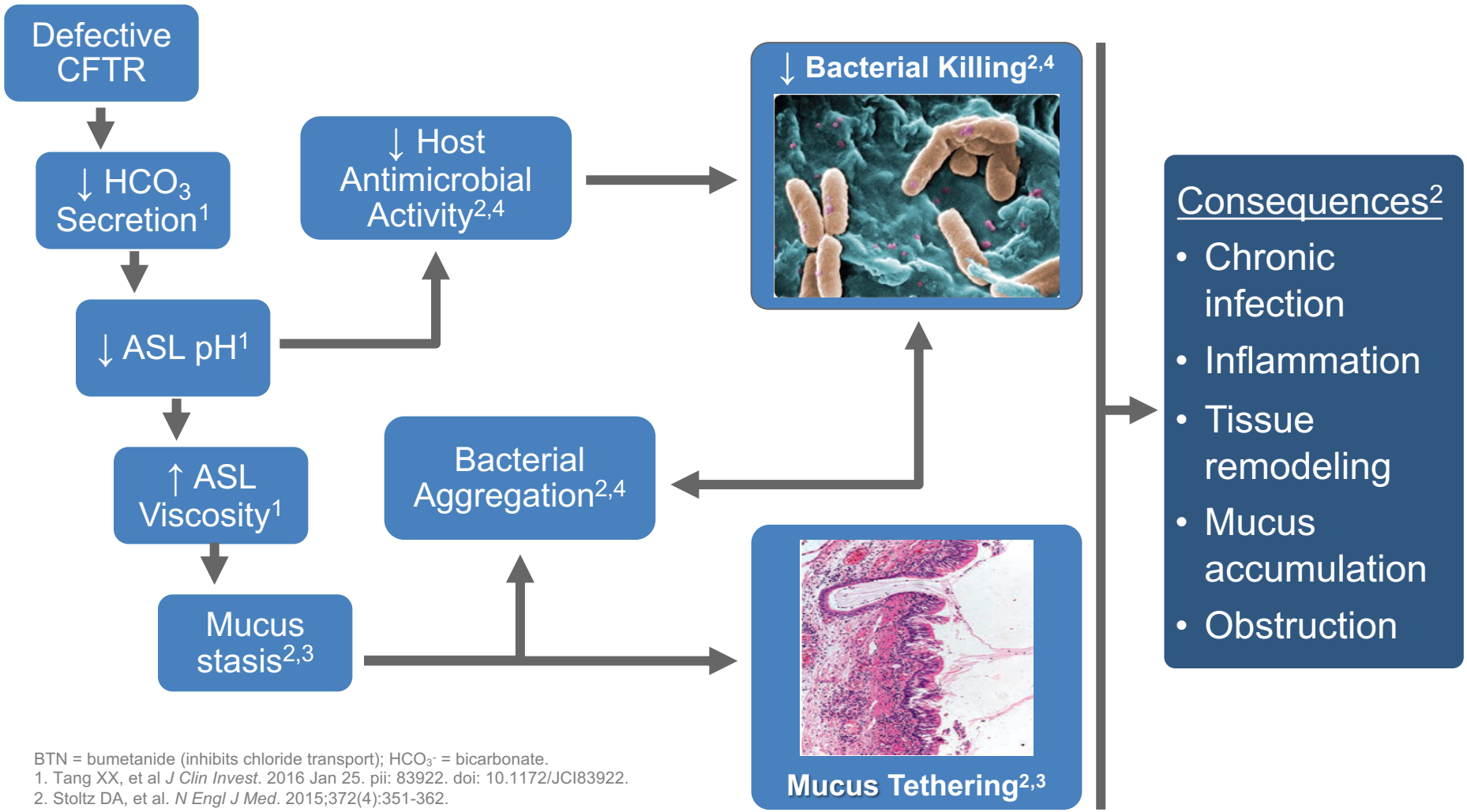


Collapse of PCL and cilia → Mucus clearance failure → Mucus thickening and adhesion → Mucus plugging

ASL = airway surface liquid; PCL = periciliary liquid.

Button B, et al. *Cold Spring Harb Perspect Med*. 2013;3(8). pii: a009720. doi: 10.1101/cshperspect.a009720.

Defective CFTR Contributes to Mucus Stasis and Plaque Formation, Mucus Tethering, and Bacterial Aggregation

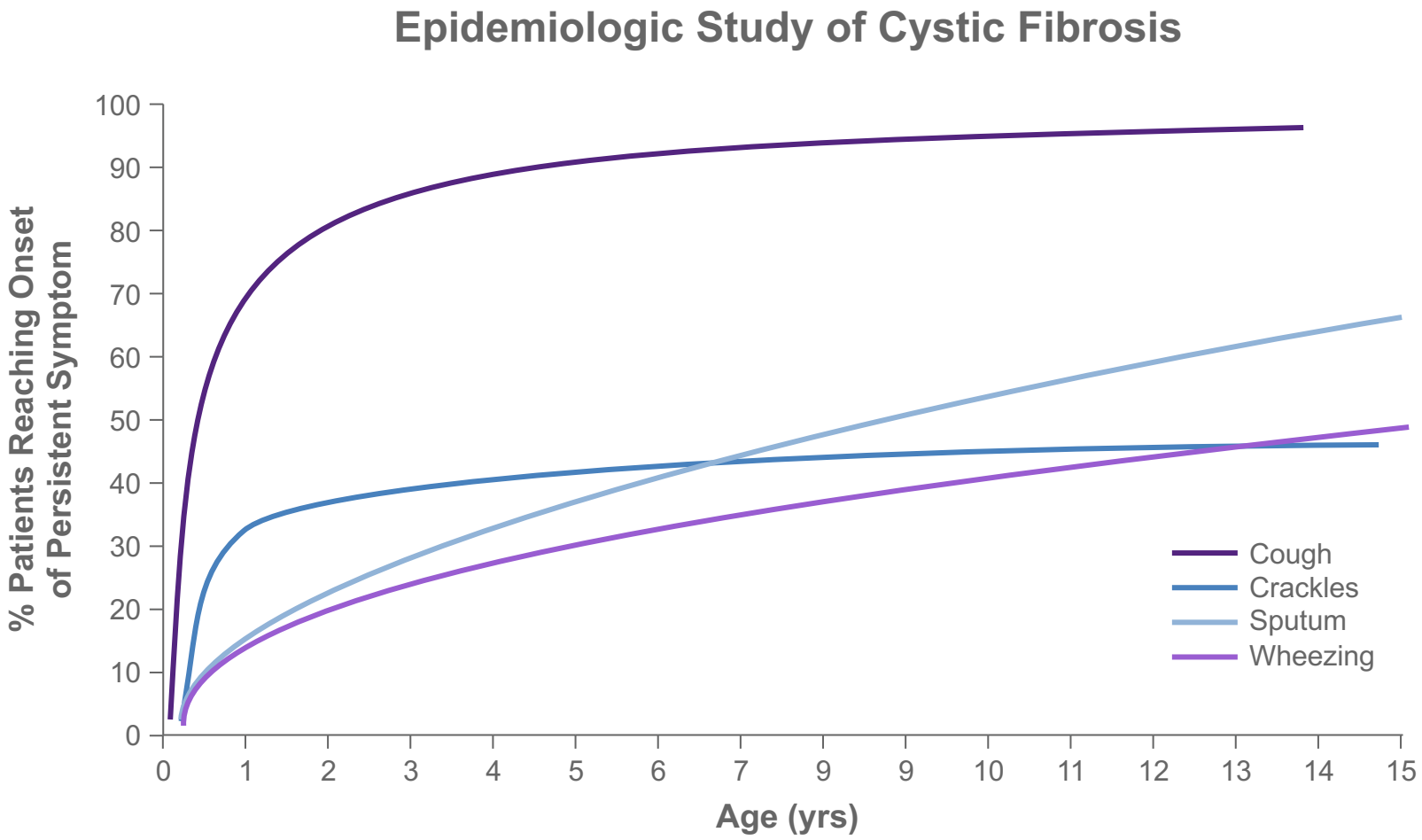


BTN = bumetanide (inhibits chloride transport); HCO_3^- = bicarbonate.

1. Tang XX, et al *J Clin Invest*. 2016 Jan 25. pii: 83922. doi: 10.1172/JCI83922.
2. Stoltz DA, et al. *N Engl J Med*. 2015;372(4):351-362.
3. Hoegger MJ, et al. *Science*. 2014;345(6198):818-822.
4. Staudinger BJ, et al. *Am J Respir Crit Care Med*. 2014;189(7):812-824..

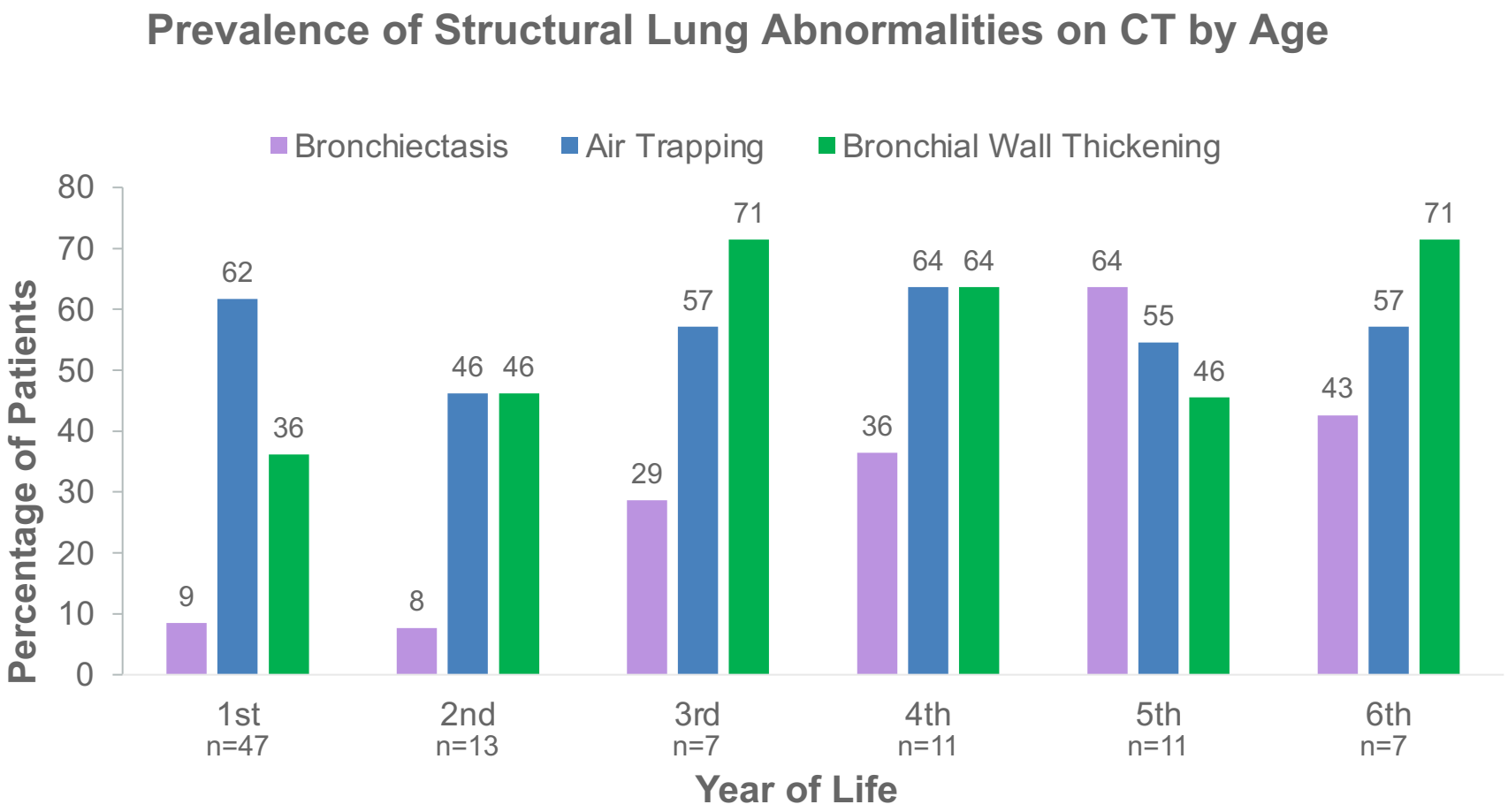
The Natural History and Progression of CF Lung Disease

CF Pulmonary Symptoms Begin Early in Life



McColley SA et al. *Pediatr Pulmonol*. 2012;47:966-972

Lung Abnormalities Present in Infants Increase With Age in Patients With CF Diagnosed After NBS

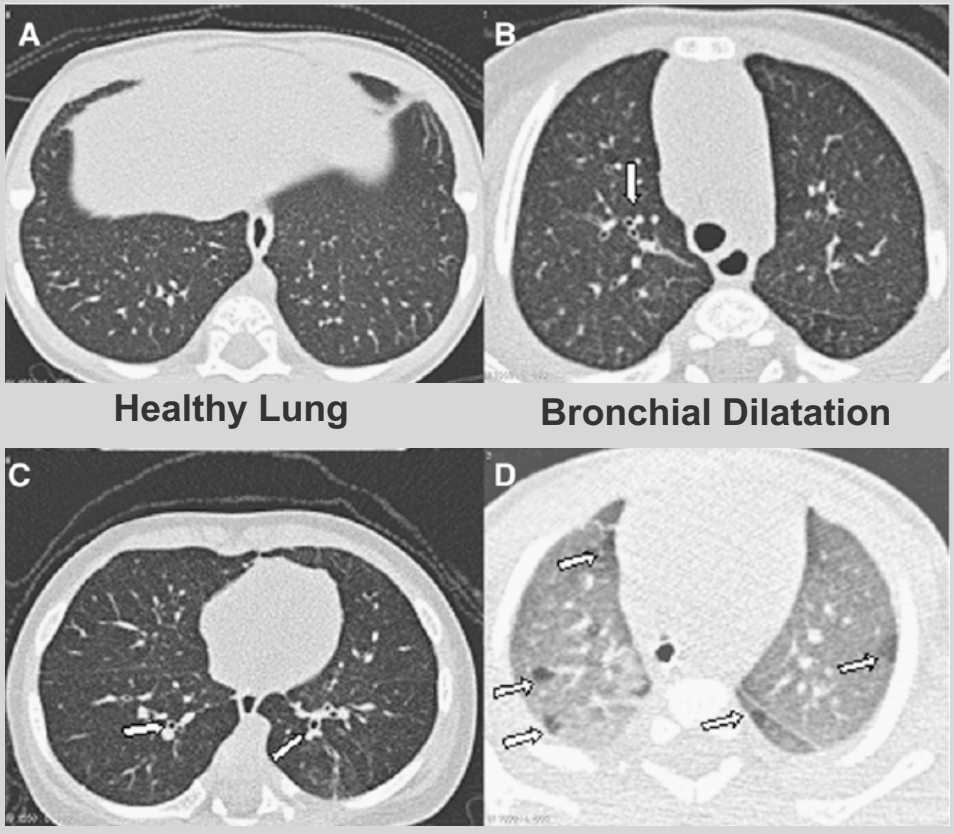


- The extent of lung abnormalities were associated with markers of airway inflammation

NBS = newborn screening; CT = computed tomography.
Stick SM, et al. *J Pediatr*. 2009;155:623-628.

Lung Abnormalities May Be Detected in Infants Diagnosed During Newborn Screening for CF

Computed Tomography Scans of Infants (mean age 28 days, N=57)[1]



Healthy Lung | Bronchial Dilatation

Bronchial Wall Thickening | Gas Trapping (arrows)

Based on CT scans (N=57)[1]
- Bronchial dilatation in 18.6%
- Bronchial wall thickening in 45%
- Gas trapping in 66.7%

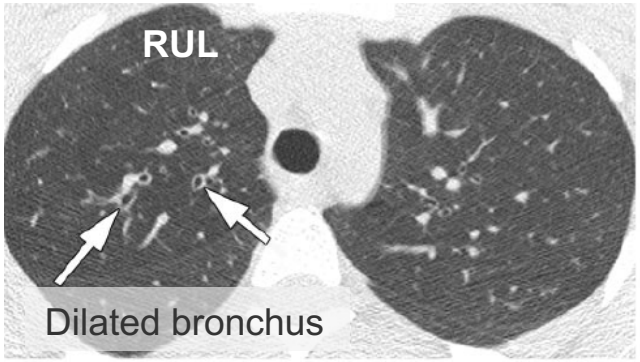
Study of infants with CF (n=71) and healthy controls (n=54)[2]
- Significantly worse LCI, FRC, FEV, FVC, and FEF z-scores
- Abnormal gas mixing
- Hyperinflation

CT = computed tomography; FEV = forced expiratory volume; FVC = forced vital capacity; FEF = forced expiratory flow; FRC = functional residual capacity; LCI = lung clearance index.

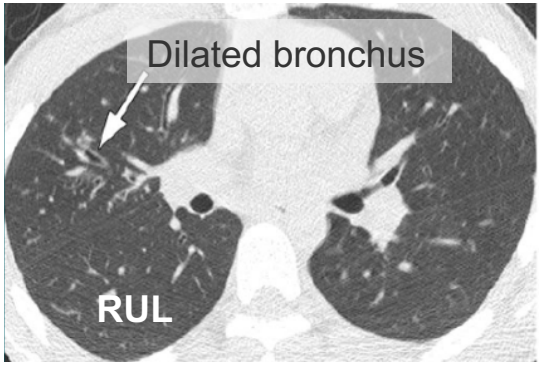
1. Sly PD, et al. *Am J Respir Crit Care Med*. 2009;180:146-152. 2. Hoo A-F, et al. *Thorax*. 2012;67:874-881.

Bronchiectasis Is the First Irreversible Change to Occur in CF Lungs

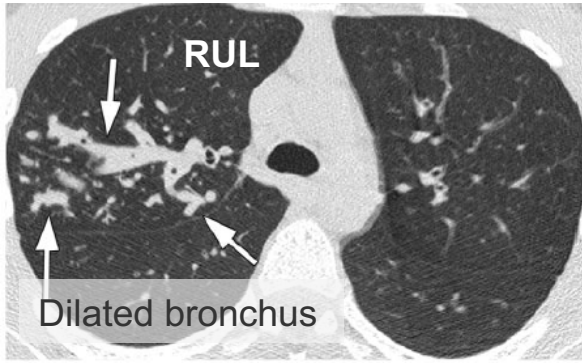
Bronchiectasis Severity[1]



PA culture-negative
RUL bronchiectasis: 0.67
Total lung bronchiectasis: 0.44
RUL overall: 1.67
Total lung overall: 1.28



Nonmucoid PA culture-positive
RUL bronchiectasis: 1.67
Total lung bronchiectasis: 0.51
RUL overall: 4.5
Total lung overall: 1.69



Mucoid PA culture-positive
RUL bronchiectasis: 2.25
Total lung bronchiectasis: 1.63
RUL overall: 11.25
Total lung overall: 5.67

- Develops first in right upper lobes; associated with mucoid *Pseudomonas aeruginosa*[1]
- In AREST CF, 29.3% had bronchiectasis at age 3 months and 83.7% at age 3 years[2]

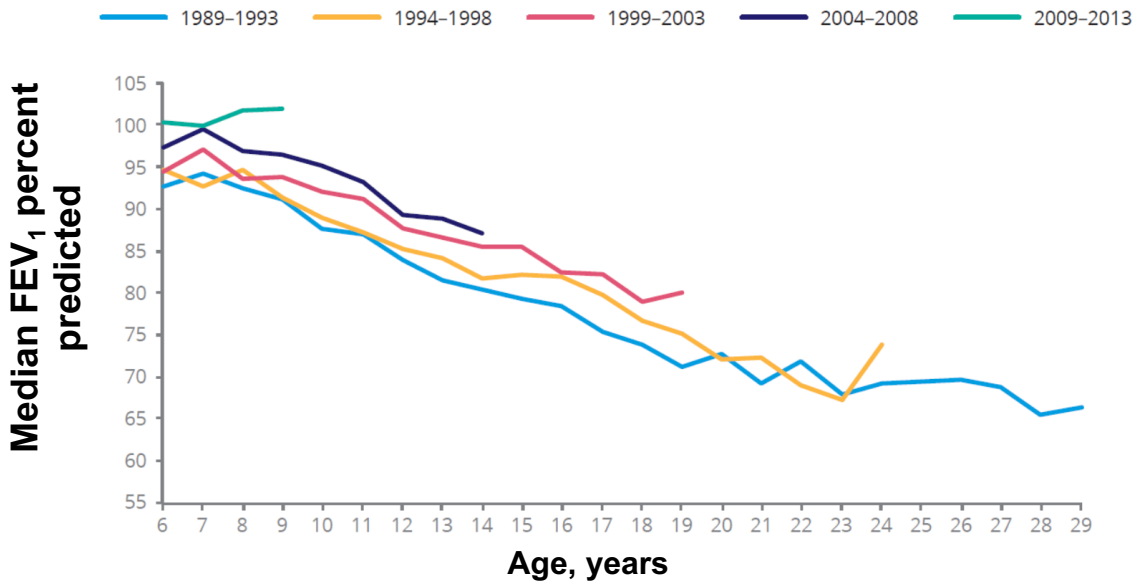
Total scores based on extent and severity of bronchiectasis, mucous plugging, peribronchial thickening, parenchymal opacity, ground-glass opacity, cysts or bullae, and air trapping. Maximum score for each lobe = 12.
Bronchiectasis defined as airway lumen diameter greater than the diameter of the accompanying artery or an artery equidistant from the hilum, nontapering bronchi, or a bronchus extending to the pleural surface.
LUL= left upper lobe; RUL = right upper lobe.
Reprinted, with permission, from *Radiology* 2009;252:534-543. © Radiological Society of North America.

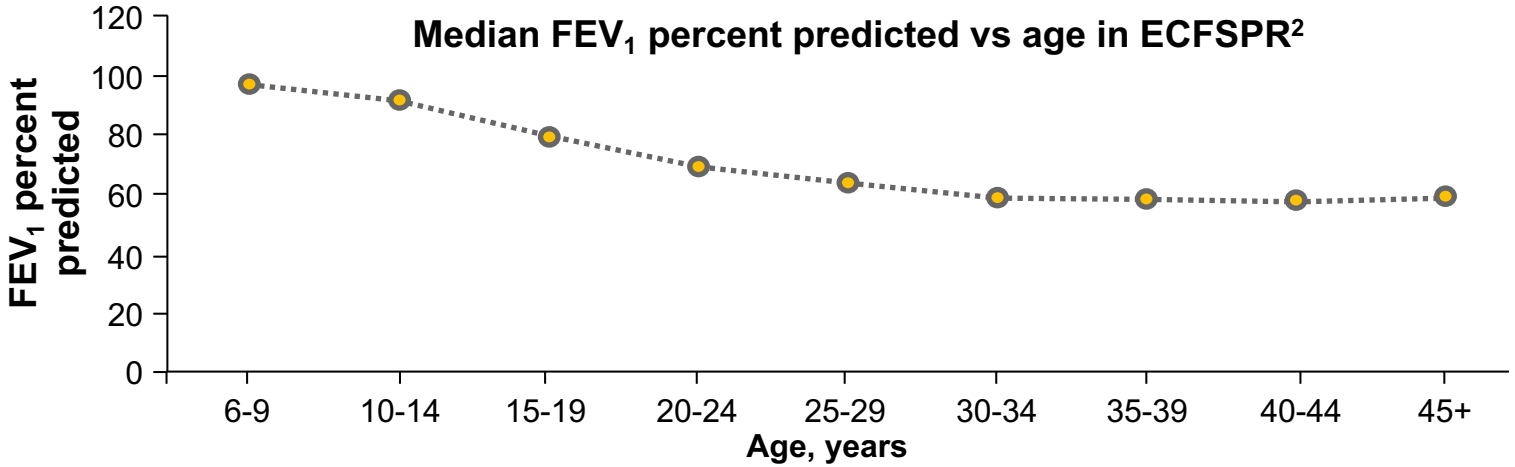
1. Farrell PM, et al. *Radiology*. 2009(2):534-543.
2. Sly PD, et al. *N Engl J Med*. 2013;368(21):1963-1970

VERTEX

Lung Function Declines With Patient Age in CF

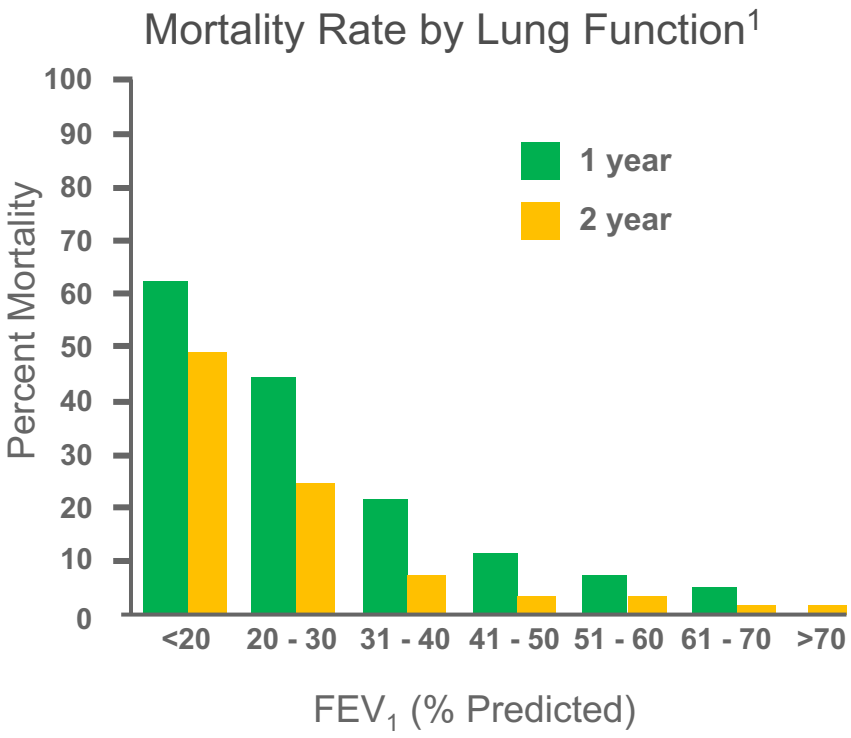
Median FEV1 percent predicted of individuals with CF, by birth cohort (Canada)[1]

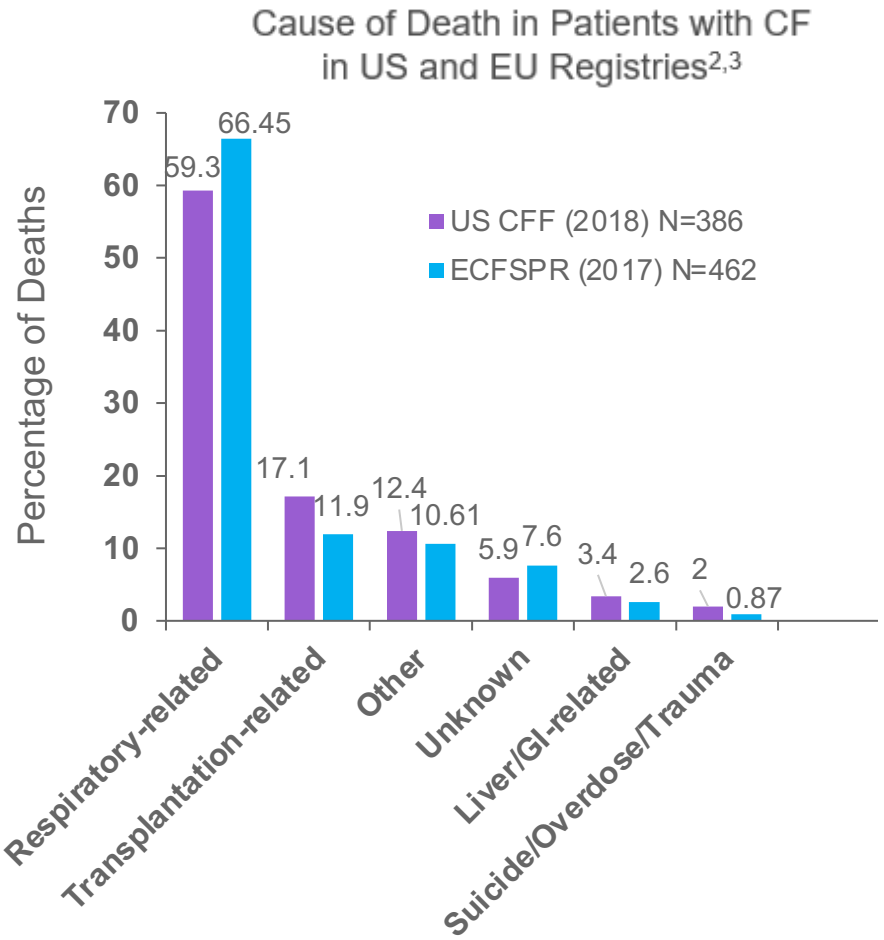




1. Cystic Fibrosis Canada. (2018). The Canadian Cystic Fibrosis Registry 2018 Annual Data Report. 2. Zolin A, et al. ECFSPR Annual Report 2013

Lung Disease Is the Strongest Predictor of Mortality in CF

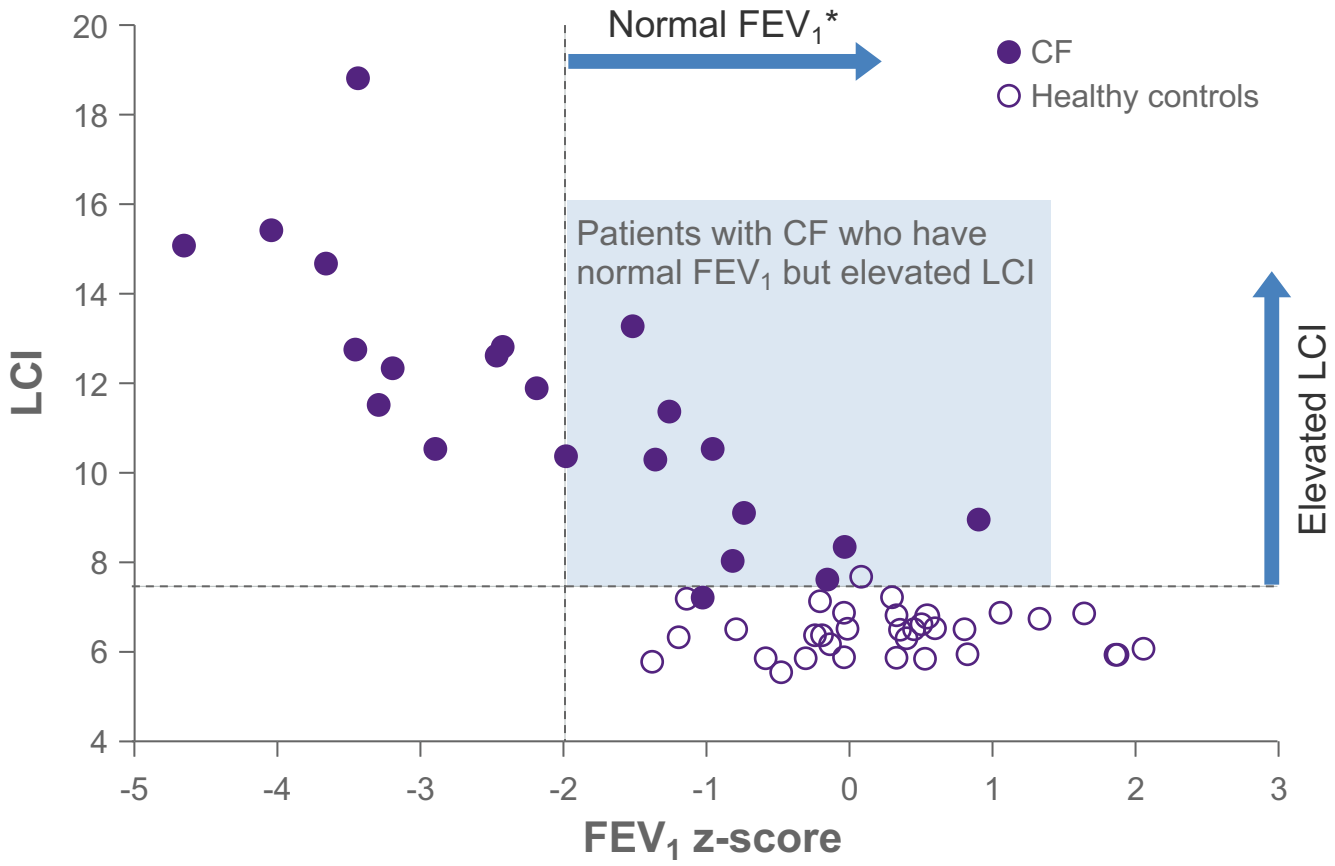




Left figure: From *The New England Journal of Medicine*, Kerem E et al, Prediction of mortality in patients with cystic fibrosis, 326, 1187-1191. Copyright © 1992 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

1. Kerem E et al. *N Engl J Med*. 1992;324(18):1187-1191. 2. Cystic Fibrosis Foundation (CFF) Patient Registry. 2018 Annual Data Report. Bethesda, MD: CFF; 2019. 3. Zolin A, et al. ECFSPR Annual Report 2017

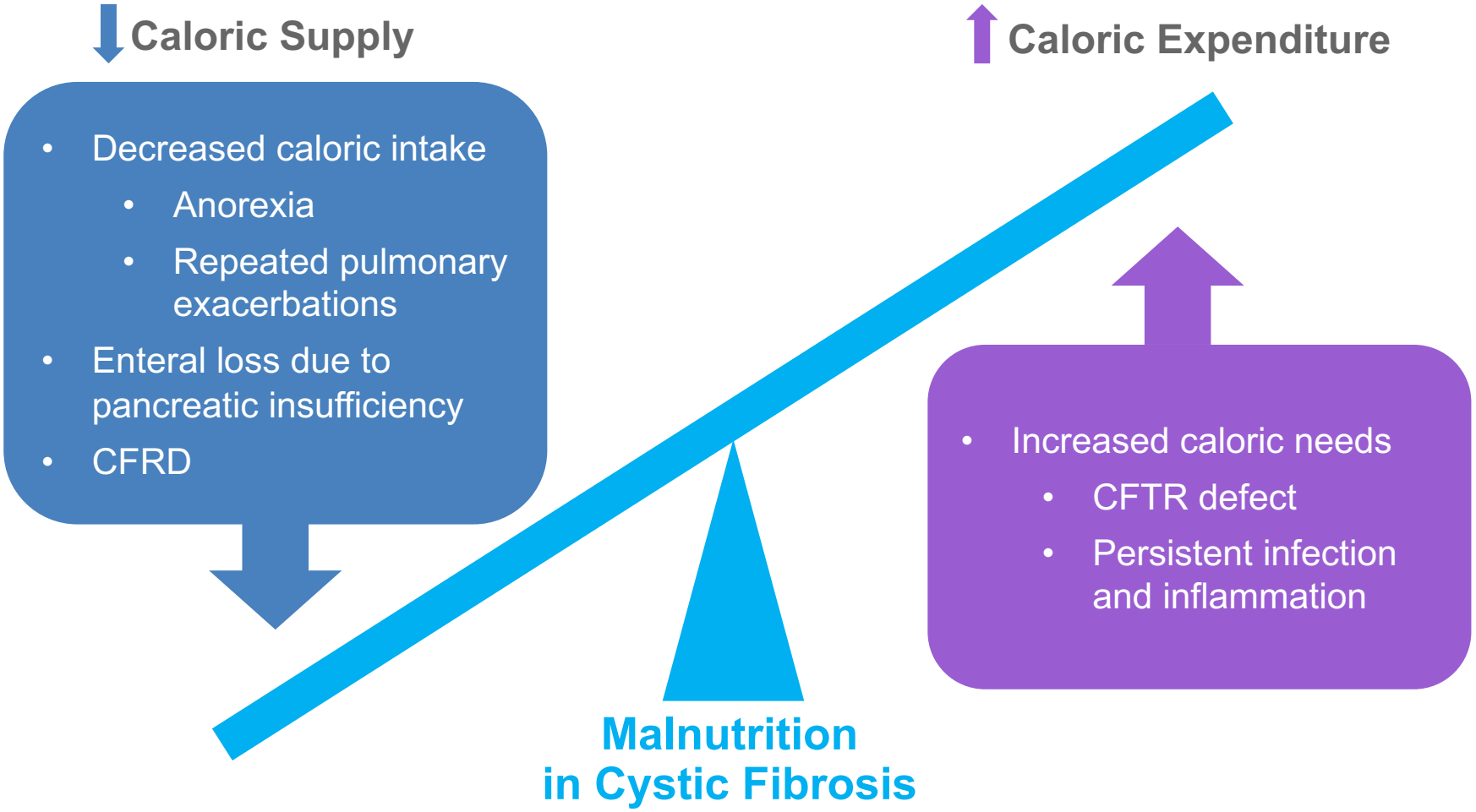
LCI Detects Early Airway Disease in Children Before Noticeable FEV_1 Decline



- 11/22 (50%) children (aged 6 to 16 years) with CF had a FEV_1 z-score within the normal range, but only 1/22 (5%) had a normal LCI

*FEV_1 results were converted into standard deviation scores (z-scores) using published reference data, with a z-score of less than -1.96 being categorized as abnormal.
Aurora P et al. *Thorax.* 2004;59(12):1068-1073.

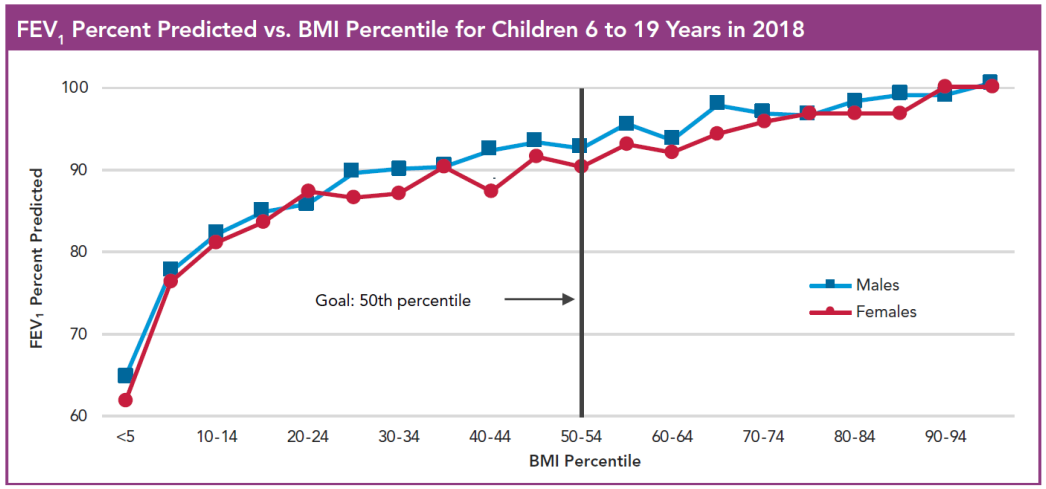
CF Pulmonary and Pancreatic Disease are Intimately Linked



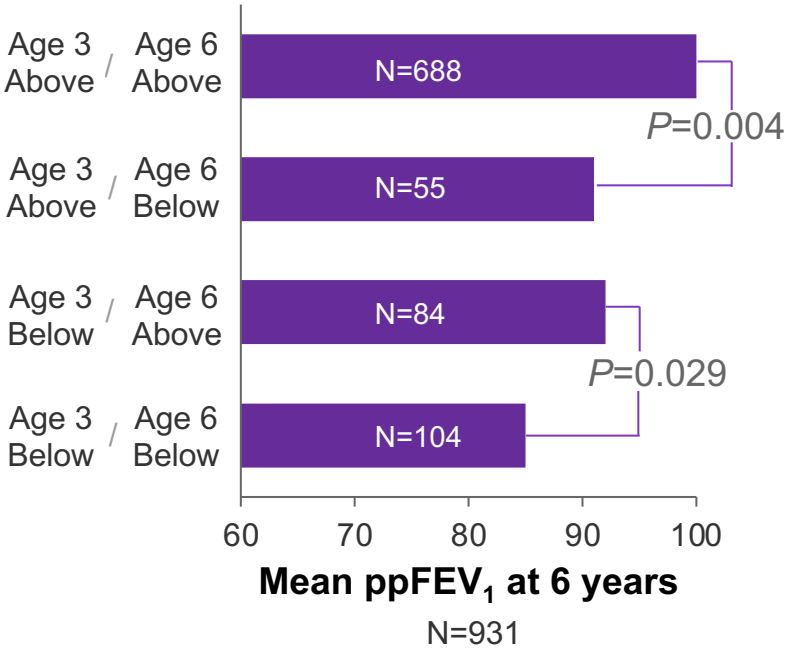
Reprinted from *Advances in Pediatrics*, 55, Amin R, Ratjen F, Cystic fibrosis: a review of pulmonary and nutritional therapies, 99-121, Copyright 2008, with permission from Elsevier.

Growth and Nutritional Status Associated With Pulmonary Function in Patients With CF

Higher BMI is associated with better FEV_1 in children with CF aged 6 to 19 years (US Data)[1]



WFA >10th percentile at age 3 years and 6 years associated with better FEV_1 at age 6 years in CF[2]



BMI, body mass index; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; WFA, weight for age.

1. Cystic Fibrosis Foundation (CFF) Patient Registry. 2018 Annual Data Report. Bethesda, MD: CFF; 2019. 2. Konstan M et al. *J Pediatr.* 2003;142(6):624-630.

The Impact of Pulmonary Exacerbations in CF Lung Disease

Pulmonary Exacerbations Affect Lung Function and Survival

While there is no consensus definition on what constitutes a pulmonary exacerbation, the criteria of Fuchs et al.1 have been widely used and adapted:

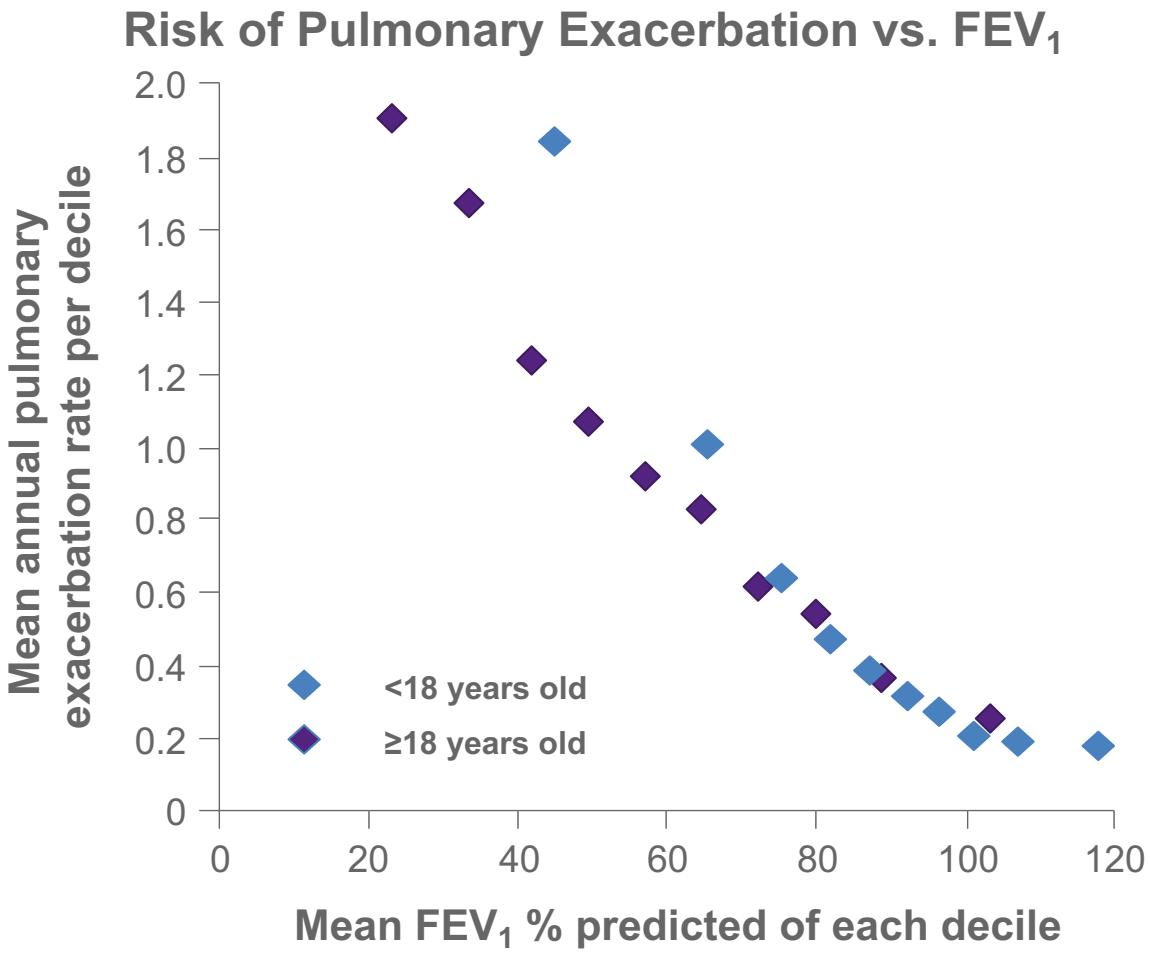
IV antibiotics for any 4

- Change in sputum
- New or Increased hemoptysis
- Increased cough
- Increased dyspnea
- Increased malaise, fatigue or lethargy
- Temperature over 38ºC
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in chest physical examination
- Pulmonary function decreased by 10%
- Radiographic changes indicative of lung infection

Each acute pulmonary exacerbation has an effect on 5-year survival equivalent to a 12% reduction in % predicted FEV_1[2]

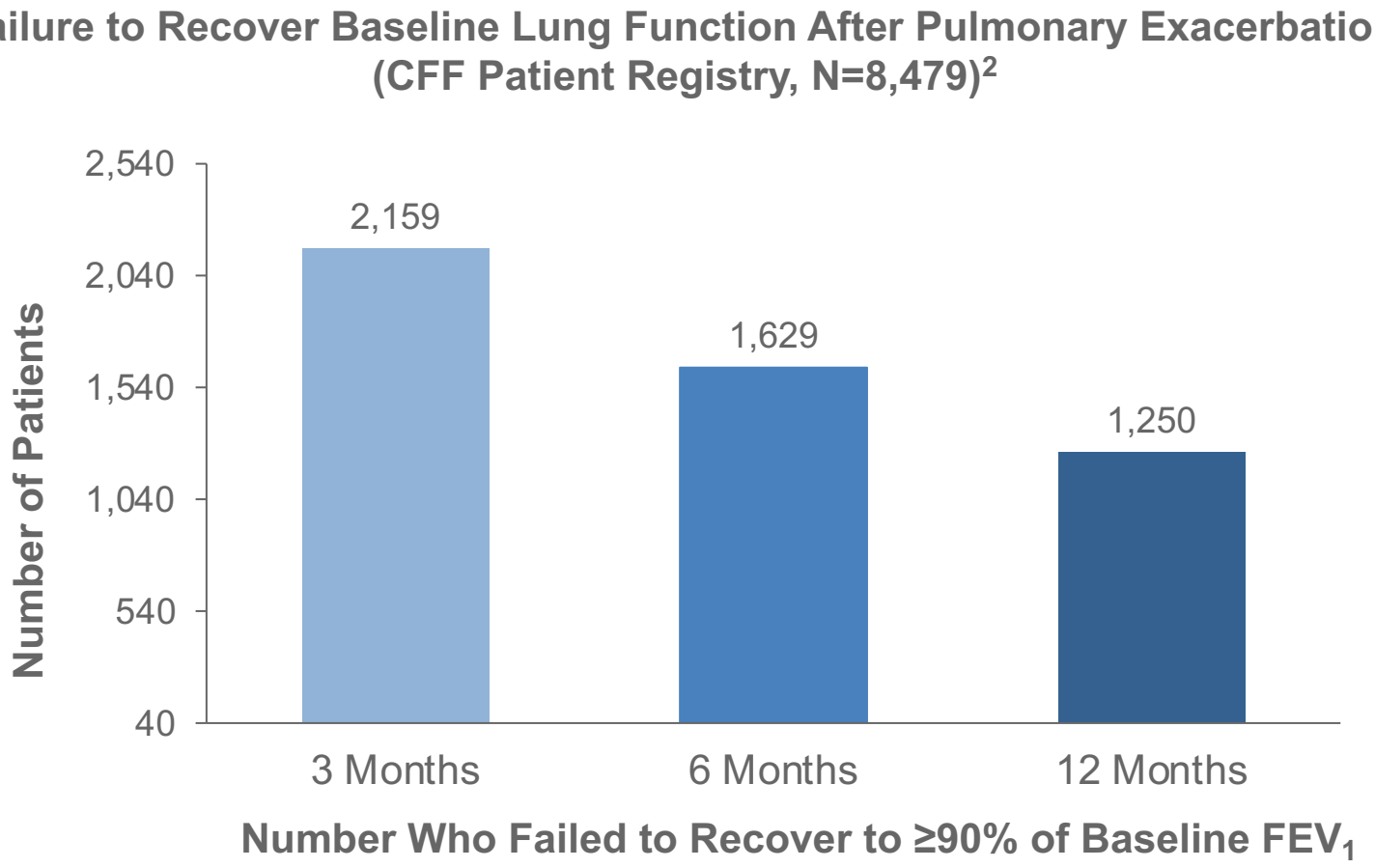
1. Fuchs HJ, et al. *N Engl J Med*. 1994;331:637-642. 2. Liou TG, et al. *Am J Epidemiol*. 2001;153(4):345-352.

Pulmonary Exacerbations Are More Likely With Lower FEV_1



Adapted by permission from BMJ Publishing Group Limited. *Thorax*, Goss CH, Burns JL, 62, 360-367, copyright 2007.

Lung Function Worsens With Each Pulmonary Exacerbation

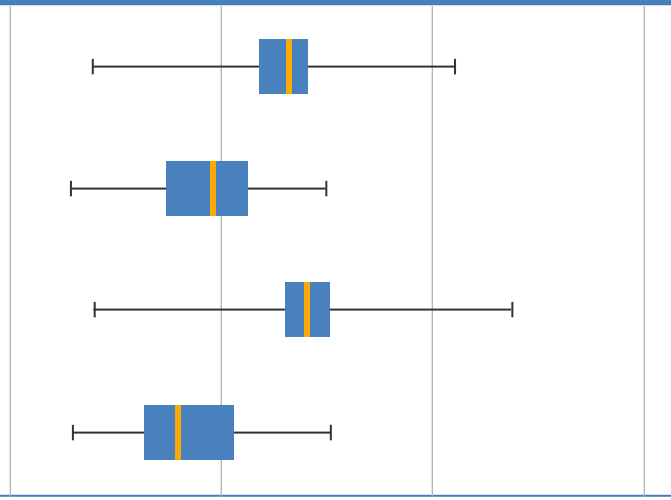


1. Adapted from Goss CH, Burns JL. *Thorax.* 2007;62(4):360-367. 2. Sanders DB, et al. *Am J Resp Crit Care Med*. 2010;182:627–632.

Treatment May Involve Hospitalization and/or IV Antibiotics for >1 to 2 Weeks

- In the US in 2013, 26.8% of children and 44.0% of adults with CF (35.3% of all patients) had a pulmonary exacerbation[1]
  - >10% of adults ages 18 to 30 years experienced ≥3 exacerbations

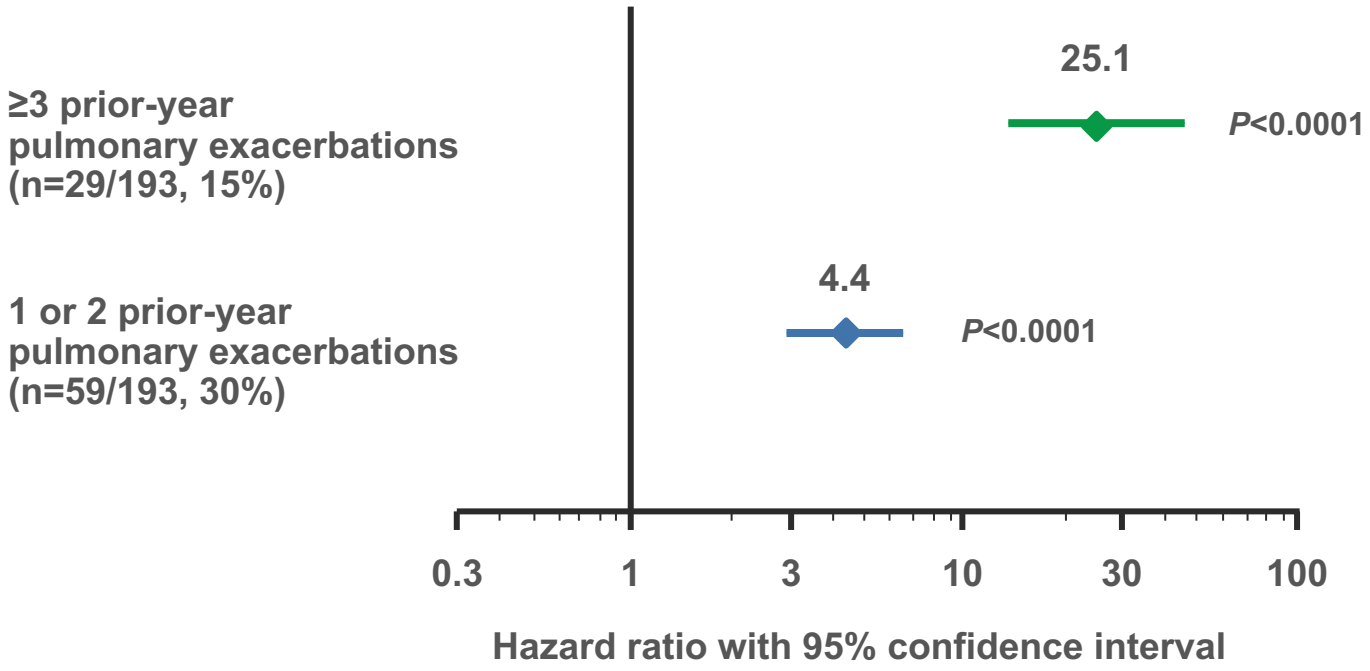
Median Exacerbation Treatment Duration in Days, by Center (US 2018 data)[2]



	Median	Min	Max
Total duration of IV antibiotic treatment for a pulmonary exacerbation in patients under 18 years	13.0	6.5	17.5
Duration of hospital stay for treatment of a pulmonary exacerbation in patients under 18 years	10.0	3.0	15.5
Total duration of IV antibiotic treatment for a pulmonary exacerbation in patients 18 years and older	14.0	9.5	18.0
Duration of hospital stay for treatment of a pulmonary exacerbation in patients 18 years and older	8.0	3.0	14.0

1. CFF 2013 Annual Data Report to the Center Directors, 2014. 2. Cystic Fibrosis Foundation (CFF) Patient Registry. 2018 Annual Data Report. Bethesda, MD: CFF; 2019.

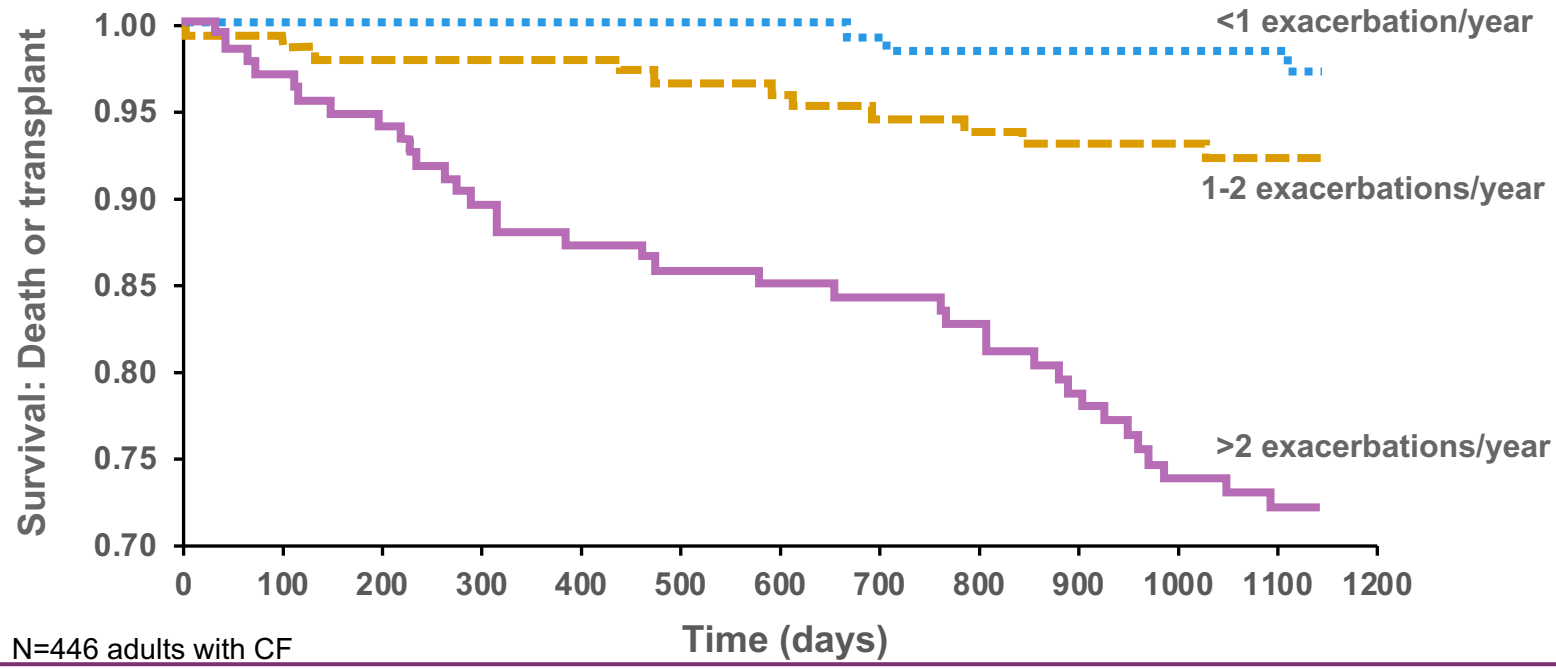
The Strongest Predictor of Pulmonary Exacerbation Is Prior Pulmonary Exacerbation



VanDevanter DR et al. *J Cyst Fibros*. 2015;14(6):763-769

Frequency of Pulmonary Exacerbations Is Associated With Risk of Death or Transplant

Survival: Death or Transplant by Number of Pulmonary Exacerbations



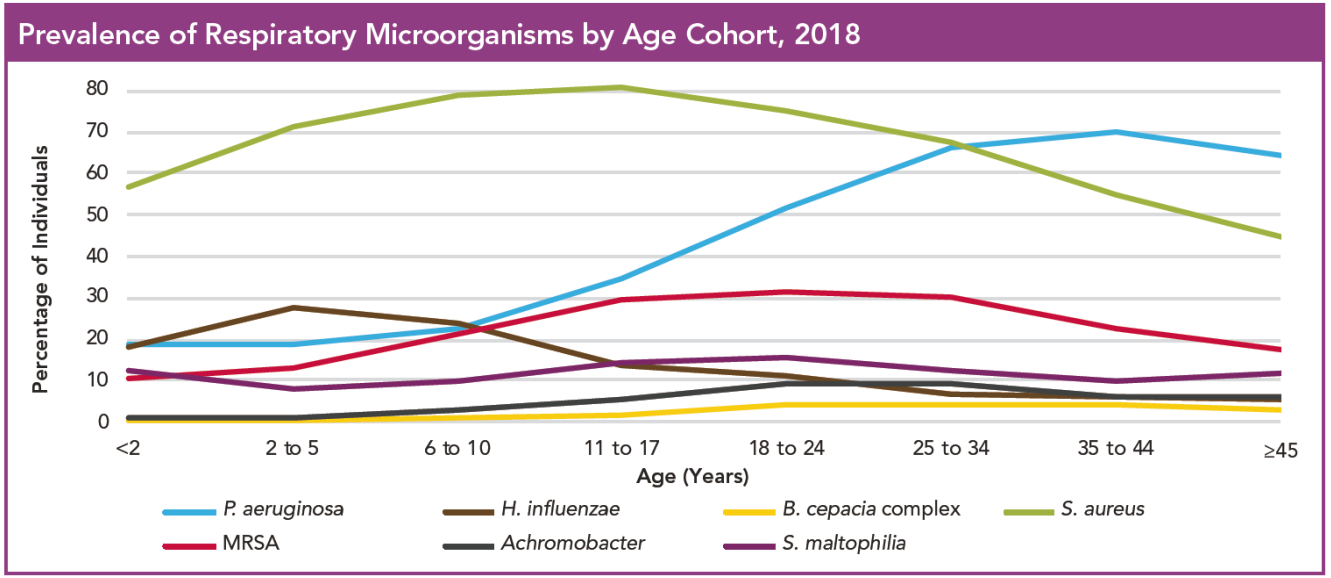
N=446 adults with CF

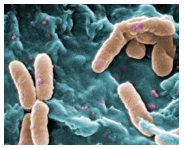
- Having more than 2 exacerbations per year leads to a greater than 4-fold increased risk of death or transplant compared with having no exacerbations

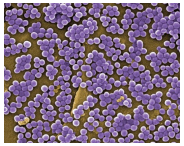
The Impact of Microbial Ecology in CF Lung Disease

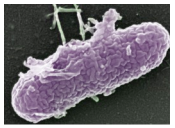
Opportunistic Pathogens Impact CF Lung Disease

Prevalence of Respiratory Microorganisms by Age Group in 2018 (US Data)[1]









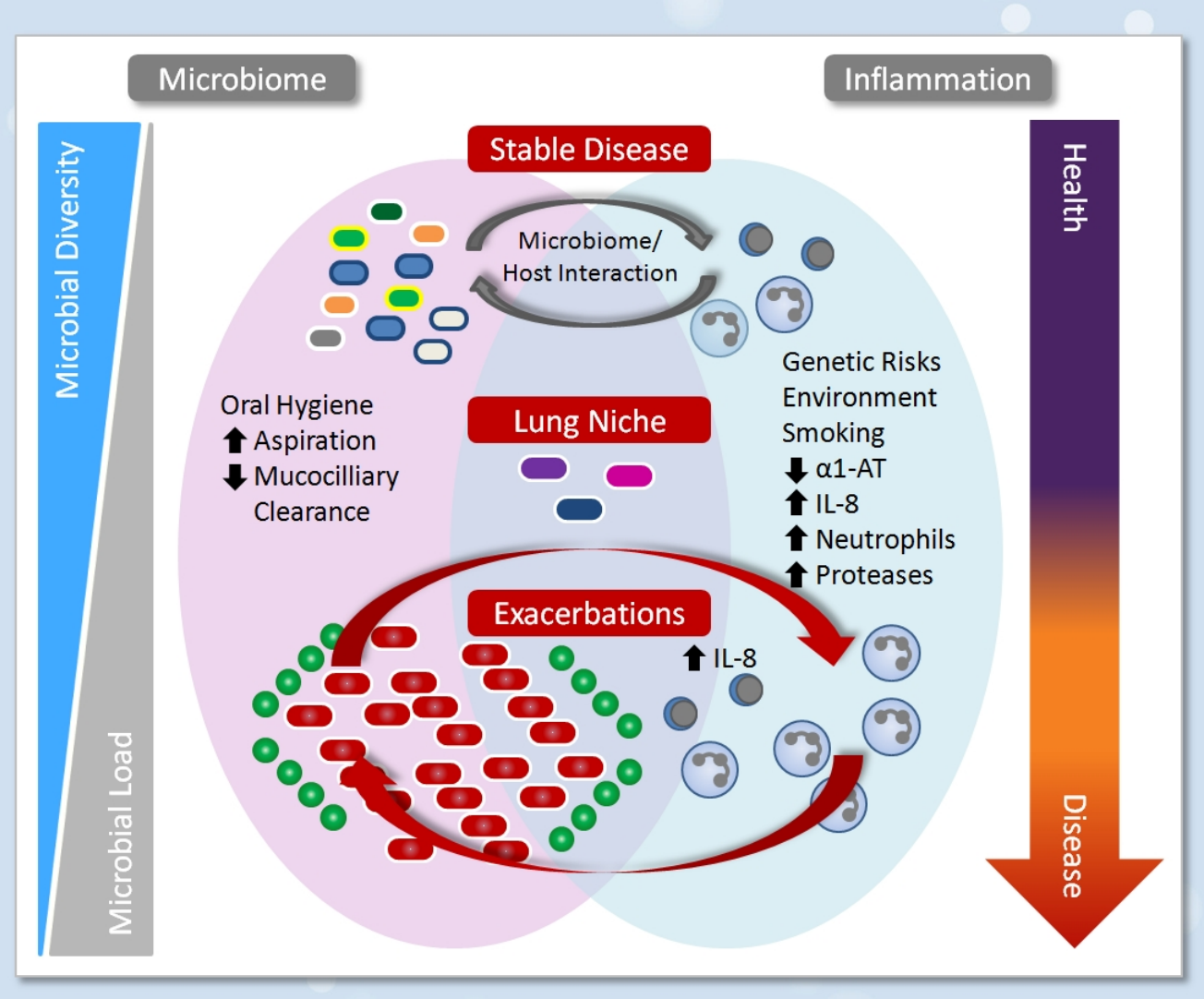
- Mucoid *P aruginosa* associated with more severe lung disease[2]
- MRSA increasingly common, in parallel with community-acquired MRSA[1,2]
- Greater morbidity and mortality associated with *Burkholderia* than with *P. aeruginosa*.[3]

MRSA = methicillin-resistant *Staphylococcus aureas*.

1. Cystic Fibrosis Foundation (CFF) Patient Registry. 2018 Annual Data Report. Bethesda, MD: CFF; 2019 2. LiPuma JJ. *Clin Microbiol Rev*. 2010;23(2):299-323. 3. Folescu TW, et al. *BMC Pulm Med*. 2015;15:158. doi: 10.1186/s12890-015-0148-2.

Immune Response and Lung Microbiome Interactions

- In CF, a reduction in bacterial diversity is associated with disease progression and pathogen colonisation
- The low bacterial diversity observed in CF has been associated with increased inflammation, a more advanced disease stage and a worse prognosis
- Low microbiota diversity also precedes the development of an exacerbation



Segal LN et al. *Ann Am Thorac Soc*. 2014;11(1):108-116

Cystic Fibrosis Lung Disease Summary

- Mutations in CFTR impair lung function, inducing changes that increase mucosal viscosity, impair mucociliary transport, and promote growth of antibiotic-resistant bacterial species
- CF lung disease begins within the first 1-2 years of life and leads to irreversible structural damage with declining lung function over time, and increased mortality
- Poorer lung function is associated with worse nutritional status
- Pulmonary exacerbation rates increase with decreasing lung function and lead to increased risk of mortality and lung transplant
- Changes in lung microbiome contribute to lung disease and inflammation in patients with CF

VERTEX

Interactive Question 1

What is the earliest age CT scans can detect CF-related lung damage such as bronchial dilation, bronchial wall thickening, and gas trapping?

A. Infants
B. 1 year old
C. 2 years old
D. 6 years old

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Interactive Question 2

What is the strongest predictor of future pulmonary exacerbations?

A. CFTR genotype
B. Previous pulmonary exacerbations
C. Number of days receiving IV antibiotics
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Interactive Question 3

The lung microbiome of patients with CF is characterized by which of the following?

A. Decreased microbial diversity
B. Increased microbial load
C. Increased levels of microbial pathogens
D. All of the above

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More Information

Lung Disease in Cystic Fibrosis

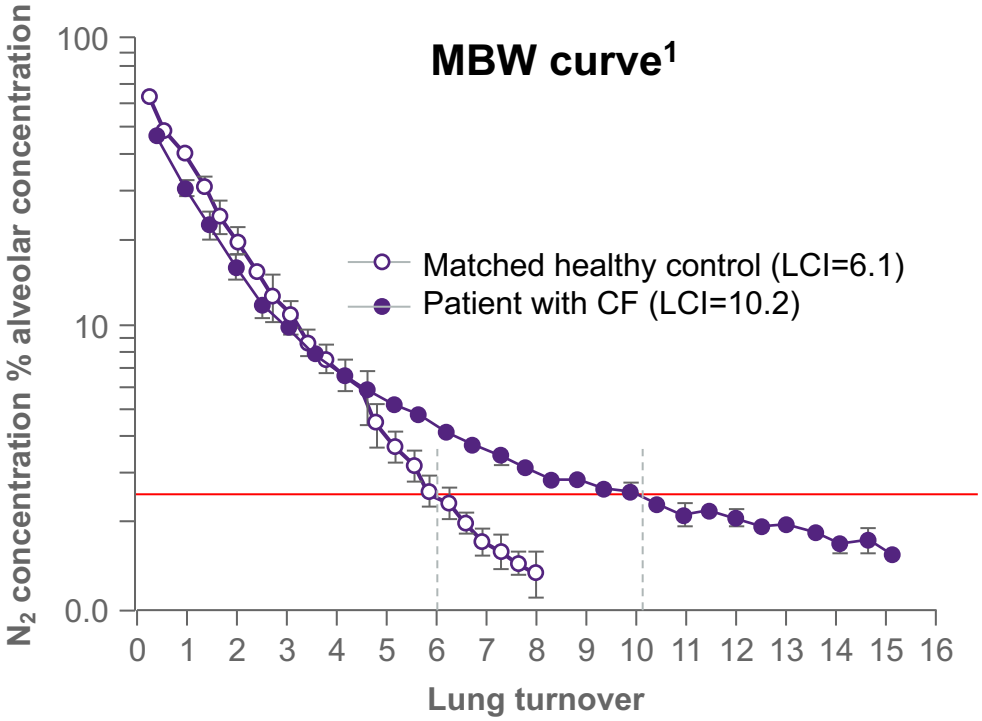
Mucociliary Clearance (MCC) is Assessed Using a Non-absorbable Tracer

- Subject inhales radiolabeled, non-absorbable marker
  - Nebulized technetium sulfur colloid (Tc-SC) aerosols containing submicronic particles 0.3 μm in size
  - Minimal tracer penetration into bloodstream
  - Bulk of Tc-SC mass remains suspended in mucus layer
- Subject sits or lies recumbent in front of γ-radiation camera
  - Thin plates known as collimators positioned between subject and camera to filter out scatter and ensure a focused image
  - Sensitivity and spatial resolution dependent on inhaled Tc-SC dose, camera resolution, and thickness of collimator
- Rates of MCC vary by lung region
  - Small airways: ~1 mm/min
  - Large airways: ~2 cm/min

Donaldson SH, et al. *Proc Am Thorac Soc*. 2007;4(4):399-405.

LCI Is a Numerical Value Derived From MBW Test Data

- LCI: number of breaths to reduce the tracer gas to 1/40th the starting concentration
- LCI values increase with lung disease severity[2]

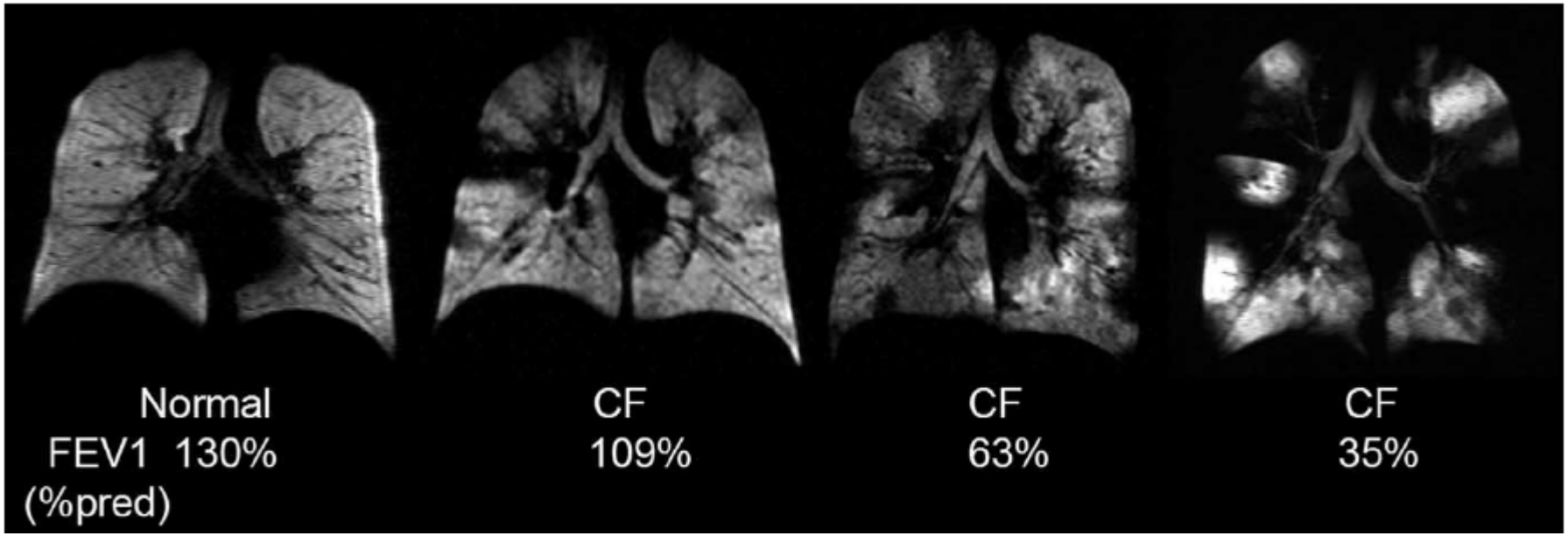


- LCI = CEV ÷ FRC
  - Cumulative expired volume (CEV): Volume of air required to wash out the tracer
  - Functional residual capacity (FRC): Volume of air in the lungs at the end of expiration
- LCI value increases with lung disease severity[2]

1. Verbank S et al. *Eur Respir J.* 2013;42(2):380-388. 2. Horsley A. *Respir Med.* 2009;103(6):793-799.

Hyperpolarized Gas Magnetic Resonance Imaging (HP-MRI) Detects Ventilation Defects

HP-MRI Images of Lungs of a Healthy Individual and 3 Patients with CF



- Inhaled hyperpolarized noble gases (^{3}He or ^{129}Xe) serve as contrast medium
- After inhalation of the gas, ventilated regions of the lung appear bright while poorly ventilated regions appear dark
- Technique permits high temporal and spatial resolution that may reflect important functional changes in CF

Reprinted from *Academic Radiology*, 12(11), Mentore K et al, Hyperpolarized HHe 3 MRI of the lung in cystic fibrosis: assessment at baseline and after bronchodilator and airway clearance treatment, 1423-1429, Copyright 2005, with permission from Elsevier.

Chronic Rhinosinusitis Is Common in Cystic Fibrosis

CRS Diagnostic Criteria

- Inflammation of the nose and paranasal sinuses with ≥2 of following symptoms for >12 weeks
  - Nasal blockage
  - Obstruction
  - Congestion
  - Nasal discharge
  - Facial pain/pressure
  - Reduced olfaction
- Plus ≥1 of following
  - Nasal polyps
  - Mucopurulent discharge
  - Edema/mucosal obstruction
  - Mucosal changes

Clinical Considerations

- Nearly 100% of CF patients have chronic rhinosinusitis and 86% have nasal polyps
- Mucus transport mechanisms affect nasal passages as well as lung airways
- CF-associated inflammation and remodeling promote nasal polyp formation
- Sinuses serve as a bacterial reservoir that transmits disease to lower airways

Illing EA, Woodworth BA. *Curr Opin Pulm Med*. 2014;20:623-31

VERTEX