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# Pharmacological Management of Cystic Fibrosis - Exploring the Therapeutic Advancements in Cystic Fibrosis

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# Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.

# Objectives

- Describe the pathophysiology of cystic fibrosis (CF)
- Discuss updates in therapeutic management for patients with acute and chronic CF
- Formulate appropriate counseling points for a CF patient

# What is Cystic Fibrosis?

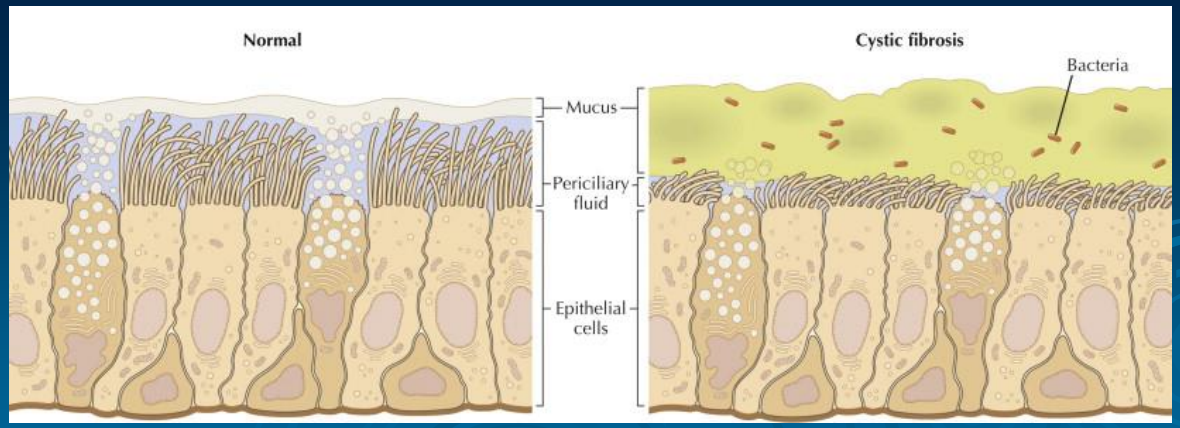
- Progressive, genetic disease that causes persistent lung infections & limits the ability to breathe over time
- Characterized by early colonization & infection of the airways
- Produces buildup of mucus in the lungs, pancreas & other organs

# Epidemiology

- More than 30,000 people in the United States living with CF
- ~1,000 new cases are diagnosed each year
- More than half the population is over the age of 18
- Frequently occurs in those of northern European ancestry
- Lung disease is the major cause of morbidity and mortality in patients with CF

# Pathophysiology

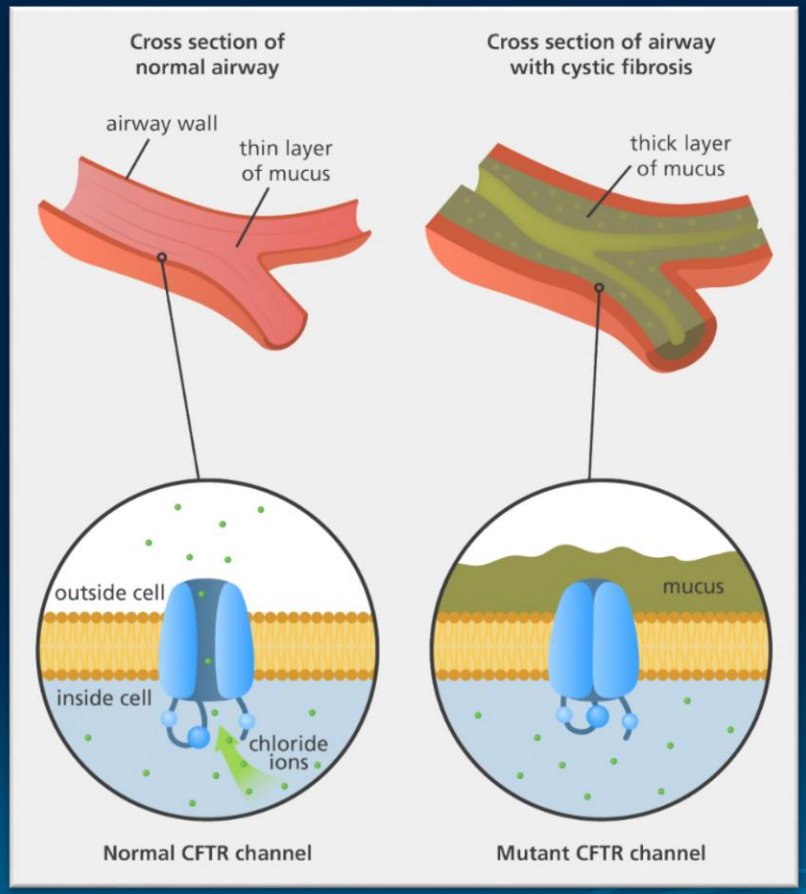
- Autosomal recessive genetic disorder
- Caused by mutations in the gene encoding for the CFTR protein on chromosome 7
- Absence or dysfunction of the CFTR results in dehydrated, thickened secretions that obstruct epithelium lined ducts resulting in tissue damage
- Affects all exocrine glands

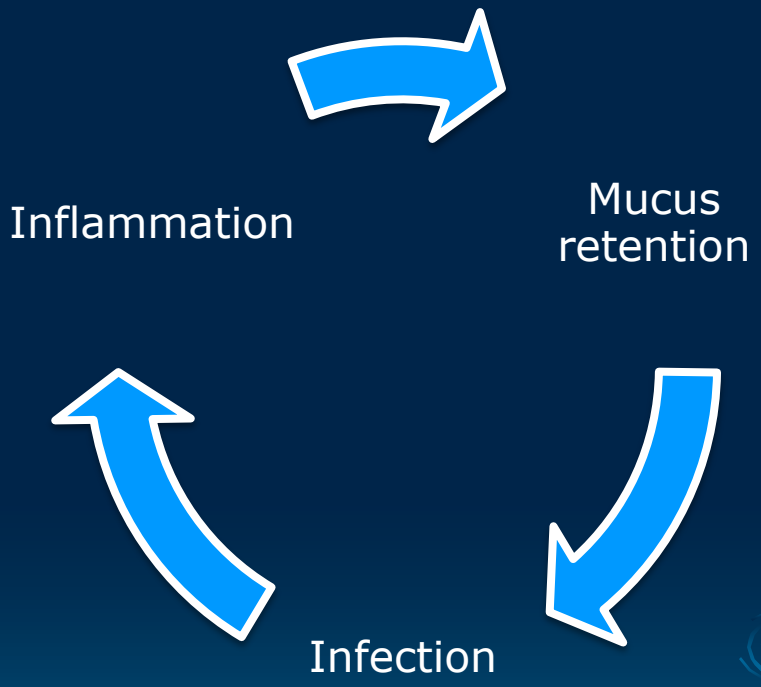



McNally P. Cystic Fibrosis. Netter's Pediatrics.2011;41:246-249.

CFTR: cystic fibrosis transmembrane conductance regulator

# Pathophysiology




What is cystic fibrosis? Stories. https://www.yourgenome.org/facts/what-is-cystic-fibrosis. Published January 25, 2016. Accessed January 3, 2019.

# CFTR Regulator Function

- Largely expressed in the apical membranes of epithelial cells that line the cylindrical structures of tissues that secrete fluids rich in mucus & other proteins
- Belongs to family of transmembrane proteins called adenosine triphosphate (ATP) binding cassette transporters
- 1° role is to transport anions through the apical membrane of epithelial cells creating an osmotic gradient for fluid secretion
- Function is to regulate:
  - Chloride channel in apical membranes
  - Epithelial sodium channels
  - $HCO_3^-$

Cantin AM, Hartl D, Konstan MW, Chmiel JF. Inflammation in cystic fibrosis lung disease: pathogenesis and therapy. *J Cyst Fibros*. 2015;14:419-430.

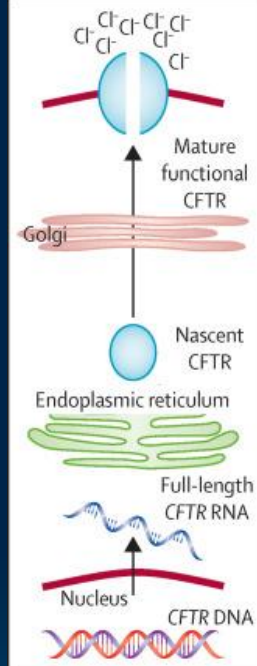
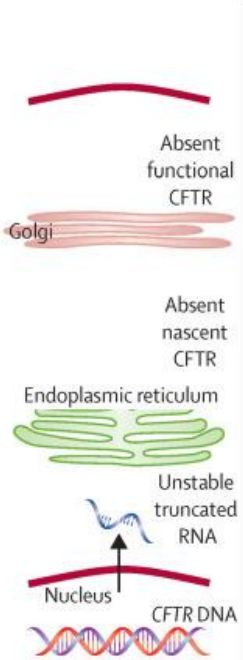
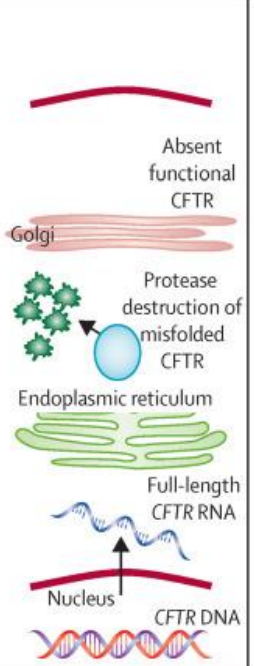
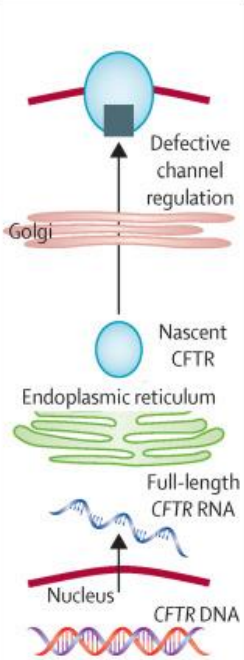
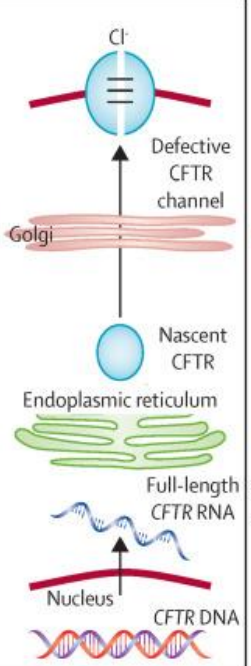
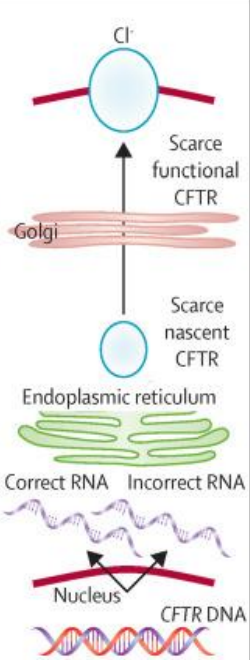
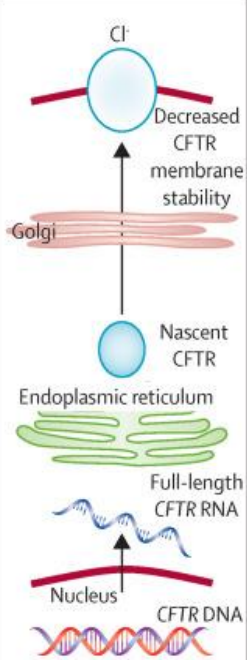
# CFTR Mutations

- ~2,000 mutations have been identified in the CFTR gene since its discovery in 1989
  - ~242 mutations have been confirmed to cause CF
  - Mutation F508del accounts for 70% of all mutations
    - ~50% of patients worldwide are homozygous & 40% are heterozygous

- Mutations can be broadly classified into 6 categories

Cystic Fibrosis Foundation patient registry 2015: annual data report. Bethesda: Cystic Fibrosis Foundation; 2016.

# CFTR Mutations

| Normal | I | II | III | IV | V | VI |
|---|---|---|---|---|---|---|
|  |  |  |  |  |  |  |
| CFTR defect | No functional CFTR protein | CFTR trafficking defect | Defective channel regulation | Decreased channel conductance | Reduced synthesis of CFTR | Decreased CFTR stability |
| Type of mutations | Nonsense; frameshift; canonical splice | Missense; aminoacid deletion | Missense; aminoacid change | Missense; aminoacid change | Splicing defect; missense | Missense; aminoacid change |
| Specific mutation examples | Gly542X<br>Trp1282X<br>Arg553X<br>621+1G→T | Phe508del<br>Asn1303Lys<br>Ile507del<br>Arg560Thr | Gly551Asp<br>Gly178Arg<br>Gly551Ser<br>Ser549Asn | Arg117His<br>Arg347Pro<br>Arg117Cys<br>Arg334Trp | 3849+10kbC→T<br>2789+5G→A<br>3120+1G→A<br>5T | 4326delTC<br>Gln1412X<br>4279insA |

Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519–2531.

# Diagnosis of Cystic Fibrosis

- Prenatal Screening
- Newborn Screening
- Sweat Test

# Prenatal/Newborn Screening

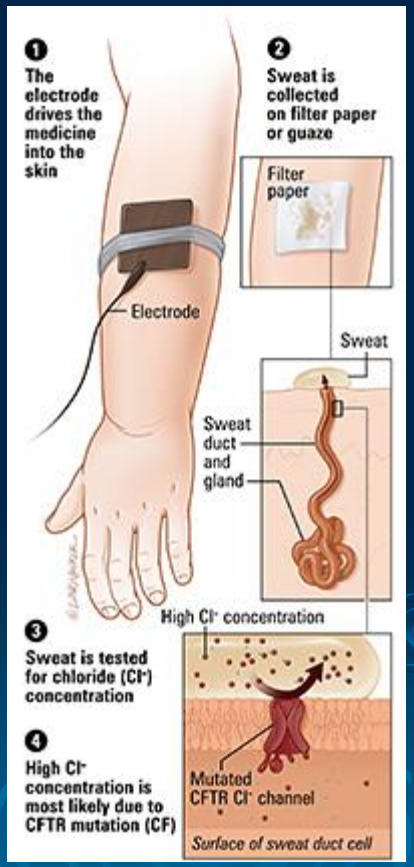
- Prenatal Screening
  - The American College of Obstetricians and Gynecologists recommends that pregnant women be offered screening for CFTR mutations
  - Prenatal diagnostic tests include chorionic villus sampling & amniocentesis
- Newborn Screening
  - Florida Statute 383.14(5)
  - All newborn screening programs rely on elevations of immunoreactive trypsinogen

Newborn Screening Program. Florida Department of Health. http://www.floridahealth.gov/programs-and-services/childrens-health/newborn-screening/nbs-disorder.html.

# Sweat Test

*"Woe is the child who tastes salty from a kiss on the brow, for he is cursed, and soon must die."*

- Gold standard
- Measurement of sweat $Cl^-$ by quantitative pilocarpine iontophoresis
- A sweat $Cl^-$ concentration $\geq$ 60 mmol/L indicates a diagnosis of CF
- A concentration of < 30 mmol/L indicates that CF is unlikely

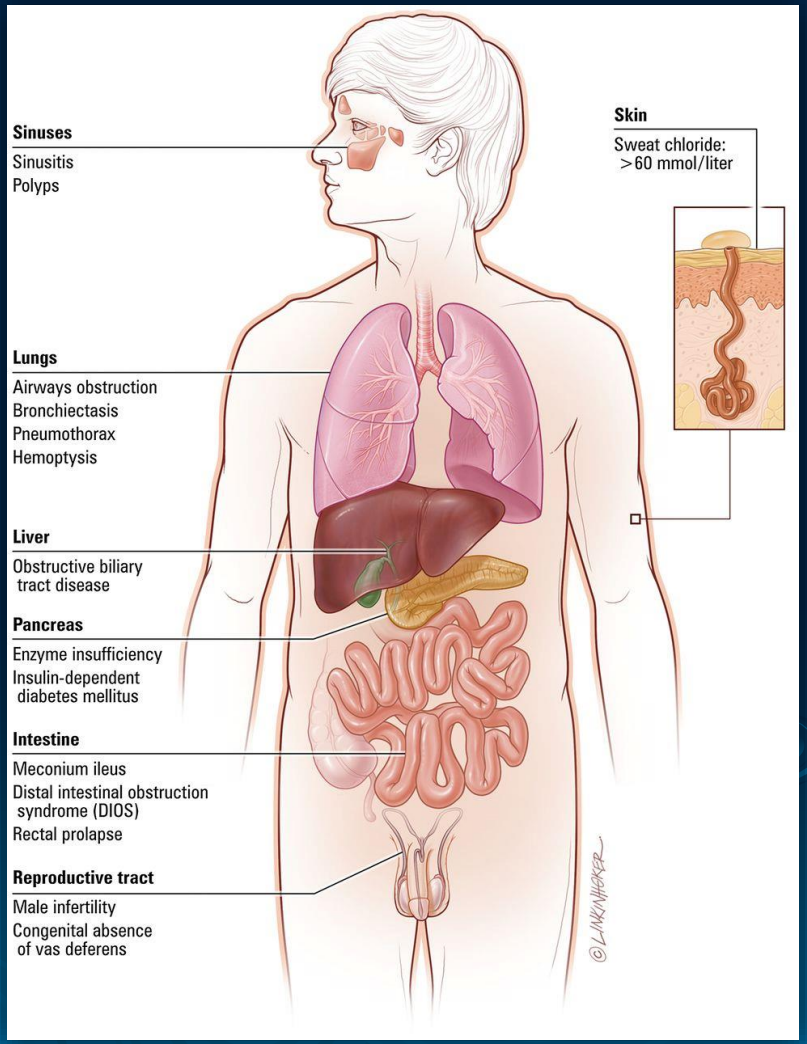



Diagnosis: Testing: Sweat Test. Johns Hopkins Cystic Fibrosis Center. https://www.hopkinscf.org/what-is-cf/diagnosis/testing/sweat-test/. Accessed January 3, 2019.

Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, Howenstine M, McColley SA, Rock M, Rosenfeld M, Sermet-Gaudelus I, Southern KW, Marshall BC, Sosnay PR. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *J Pediatr*. 2017 Feb;181S:S4-S15.e1.PMID: 28129811

# Clinical Presentation

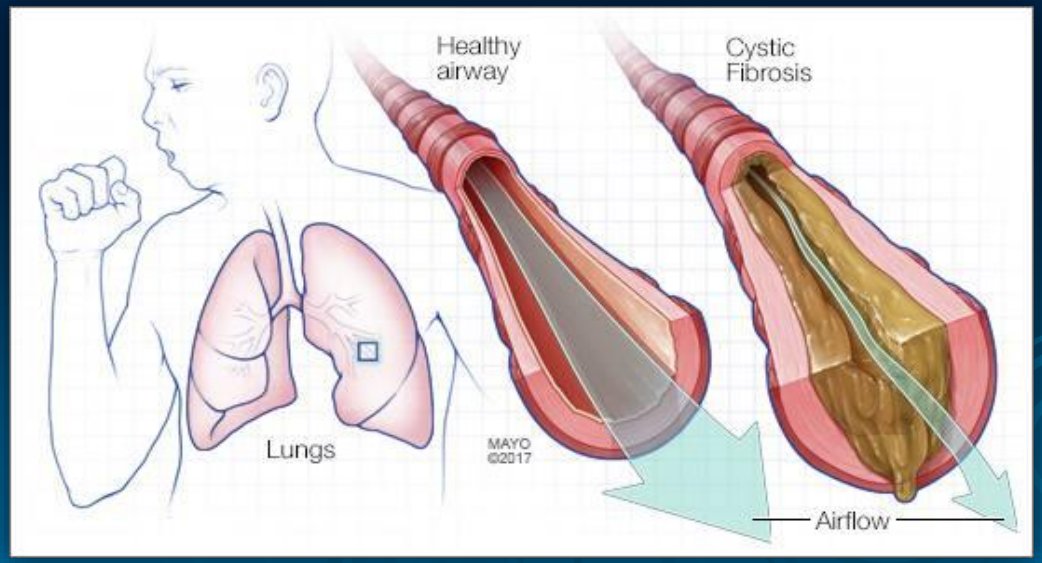
- **Manifestations of Cystic Fibrosis**
  - Gastrointestinal system:
    - Malnutrition
    - Meconium ileus
  - Endocrine system:
    - Cystic fibrosis-related diabetes
  - Reproductive system:
    - Azoospermia in males
    - Reduced fertility in females
  - **Respiratory system**




Shruti M. Paranjape, and Peter J. Mogayzel Jr Pediatrics in Review 2014;35:194-205

# Respiratory system

- Impaired mucociliary clearance resulting in thick sputum
- Respiratory compromise characterized by copious hyperviscous & adherent pulmonary secretions
- Development of polyps in the sinus cavity
- Chronic infections
- Digital clubbing




Mayo Clinic Q and A: Diagnosing cystic fibrosis. Mayo Clinic. https://newsnetwork.mayoclinic.org/discussion/mayo-clinic-q-and-a-diagnosing-cystic-fibrosis/. Accessed January 3, 2019.

# Respiratory system

- The dominant pathology in the lung is inflammation generated by failure to clear microorganisms & generation of a toxic pro-inflammatory local microenvironment

- Airway secretions contain a complex bacterial flora
  - *Staphylococcus aureus, Haemophilus influenzae, & Pseudomonas aeruginosa*

# Pharmacological Treatment

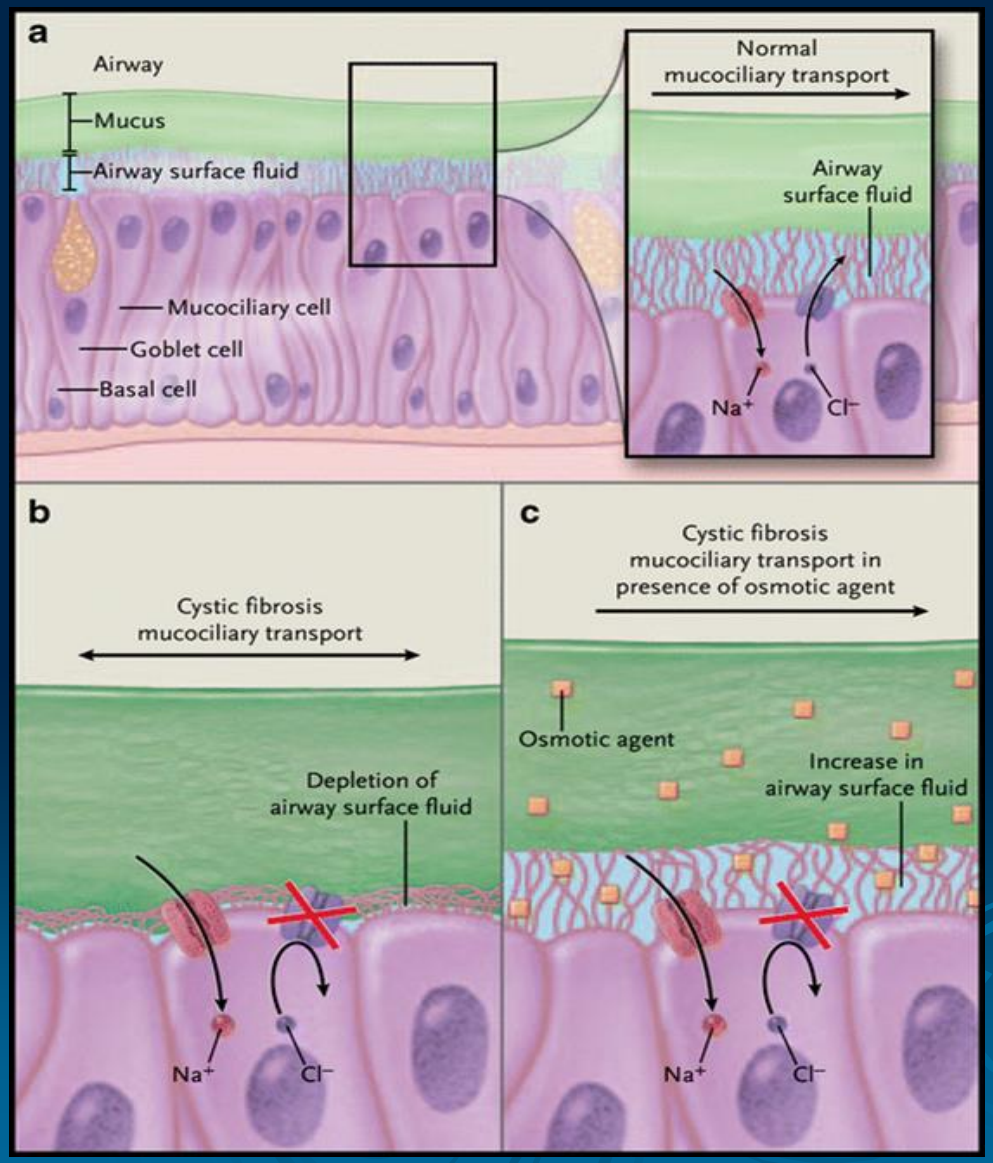
- Goals of therapy:
  - Improve symptoms
  - Minimize loss of lung function
  - Minimize adverse drug reactions due to acute treatment
- Effective airway clearance involves the use of a bronchodilator, a mucolytic medication & chest percussion
- Therapies directed towards the chronic infection in CF should reduce inflammation

# PHARMACOTHERAPY: MUCOCILIARY CLEARANCE

Dornase Alfa (Pulmozyme®)

Hypertonic Saline

# Mucociliary Transport




Ratjen F. Restoring airway surface liquid in cystic fibrosis. *N Engl J Med.* 2006;354:291-293.

# Dornase Alfa (Pulmozyme®)

- MOA: recombinant human deoxyribonuclease I (rhDNase)
  - Hydrolyzes the DNA in sputum of CF patients & reduces sputum viscoelasticity
- Dose:  2.5 mg single-use ampule inhaled once daily using a jet nebulizer/compressor system
- Ampules should be stored in their protective foil pouch under refrigeration & protected from light
- ADRs: Voice alteration, pharyngitis, rash, laryngitis, chest pain, conjunctivitis, rhinitis, dyspepsia & dyspnea

Pulmozyme [package insert]. South San Francisco, CA: Genentech, Inc; 2014.

Mechanism of Action: MOA
Adverse Drug Reaction: ADR

# Hypertonic Saline

- Sterile, preservative-free sodium chloride inhaled solution available in 3.5% & 7% strengths
- Indicated for ≥ 6 years old & those with an $FEV_1$ ≥ 40%
- MOA: Mucolytic agent
  - Restores moisture to pulmonary system
  - ↑ hydration of airway surface liquid via osmotic flow
- Dose: 4 mL/vial via inhalation BID
- ADRs: Increased cough, sore throat & chest tightness


Elkins MR, Robinson M, Rose BR, Harbour C, Moriarty CP, Marks GB, Belousova EG, Xuan W, Bye PT. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;354:229–240.

Mechanism of Action: MOA
Forced Expiratory Volume: FEV

# PHARMACOTHERAPY: RESTORATION OF CFTR FUNCTION

Ivacaftor (Kalydeco®)

Lumacaftor + Ivacaftor (Orkambi®)

Tezacaftor + Ivacaftor (Symdeko®)

# Ivacaftor (Kalydeco®)

- MOA: Potentiator of the CFTR protein
  - Facilitates increased chloride transport
- Baseline & follow-up ophthalmological exams are recommended in pediatrics initiating Ivacaftor
- Assess ALT & AST prior to initiation, every 3 months during the 1st year of treatment & annually thereafter
- ADRs: HA, oropharyngeal pain, URI, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea & dizziness

Kalydeco (ivacaftor) [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2018.

Headache: HA
Upper Respiratory Infection: URI

# Ivacaftor (Kalydeco®)

| Dosing Regimen | |
|---|---|
| Age ≥ 6 years | 150 mg tablet PO every 12 hours |
| Age 1-5 years and weighing 7 kg to < 14 kg | One 50 mg packet PO every 12 hours |
| Age 1-5 years and weighing ≥ 14 kg | One 75 mg packet PO every 12 hours |

- Available as oral tablets for patients ≥ 6 years old & oral granules for patients 1-5 years of age
- Once mixed, oral granules should be consumed within the hour
- Should be taken with fat containing foods
- Co-administration with:
  - Strong CYP3A inducers: not recommended
  - Strong CYP3A inhibitors: dose should be reduced to one tablet or one packet of oral granules twice a week

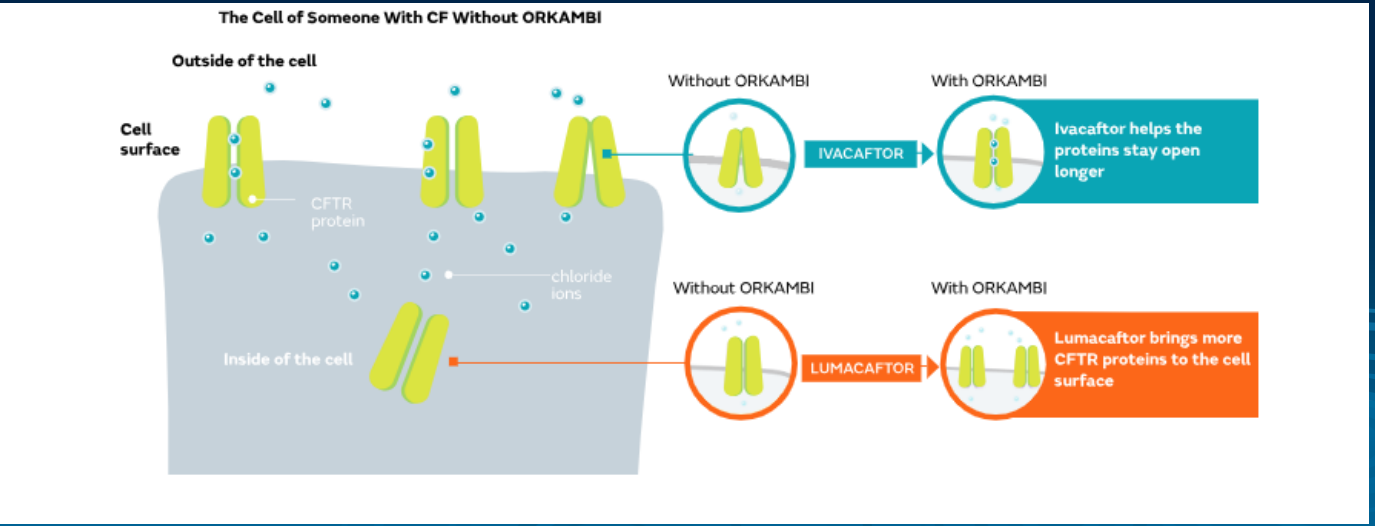
Kalydeco (ivacaftor) [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2018.

| Gene mutations responsive to Ivacaftor (Kalydeco®) | | | | | |
|---|---|---|---|---|---|
| E56K | G178R | S549R | S977F | F1074L | 2789+5G→A |
| P67L | E193K | G551D | F1052V | D1152H | 3272-26A→G |
| R74W | L206W | G551S | K10607 | G1244E | 3849+10kbC→T |
| D110E | R347H | D579G | A1067T | S125IN | |
| D110H | R352Q | 711+3A→G | G1069R | D1270N | |
| R117C | A455E | E831X | R1070Q | G1349D | |
| R117H | S549N | S945L | R1070W | S1255P | |

Kalydeco (ivacaftor) [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2018.

# Lumacaftor + Ivacaftor (Orkambi®)

- Indicated for pts ≥ 2 years who are homozygous for the F508del mutation in the CFTR gene
- MOA:
  - Lumacaftor improves the conformational stability of F508del-CFTR
  - Ivacaftor is a CFTR potentiator that facilitates increased $Cl^-$ transport




Orkambi [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; September 2016.

# Lumacaftor + Ivacaftor (Orkambi®)

| Dosing Regimen | |
|---|---|
| **Age** | |
| 2-5 years of age and weighing > 14 kg | One lumacaftor 100 mg/ ivacaftor 125 mg packet of granules every 12 hours |
| 2-5 years of age and weighing ≥ 14 kg | One lumacaftor 150 mg/ ivacaftor 188 mg packet of granules every 12 hours |
| 6-11 years of age | Two lumacaftor 100 mg/ivacaftor 125 mg tablets every 12 hours |
| 12 years and older | Two lumacaftor 200 mg/ivacaftor 125 mg tablets every 12 hours |

- Should be taken with fat containing foods
- ADRs: dyspnea, nasopharyngitis, nausea, diarrhea, URI, fatigue, ↑ blood CPK, rash, flatulence, rhinorrhea & influenza

Orkambi [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; September 2016.

Creatinine Phosphokinase: CPK

# Tezacaftor + Ivacaftor (Symdeko®)

- Indicated for pts ≥ 12 years of age who are homozygous for the F508del mutation or who have ≥ 1 mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor

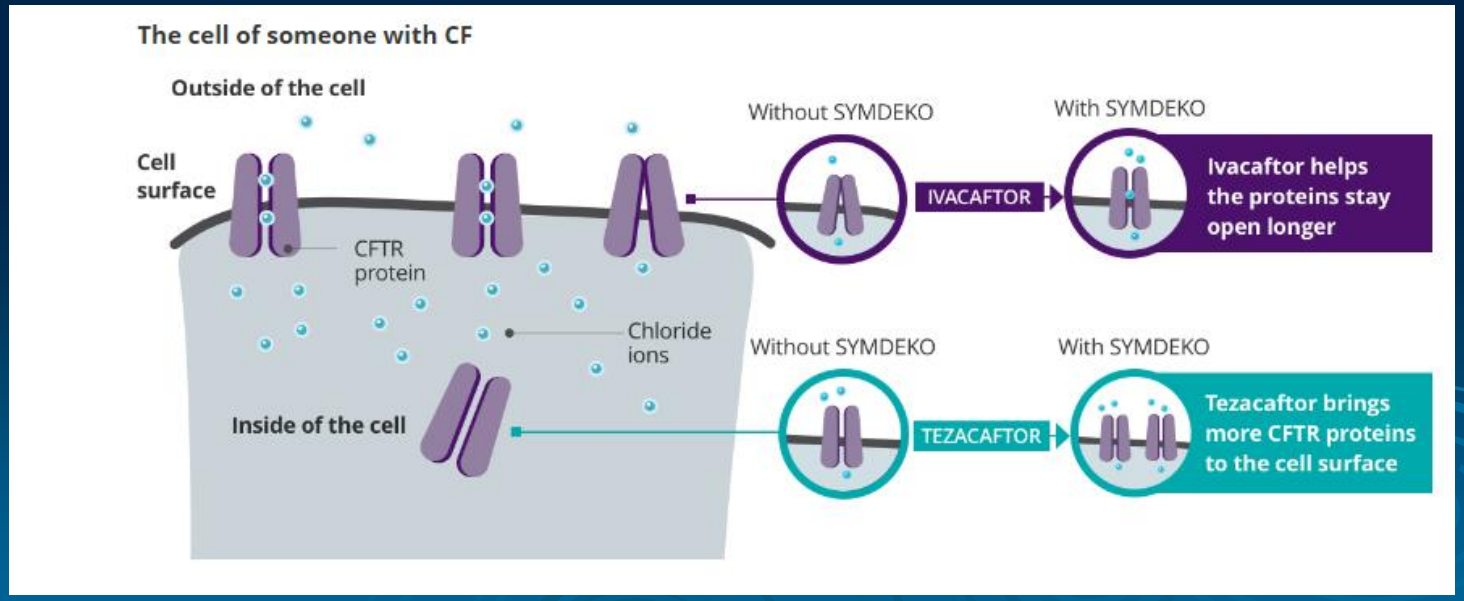
| Gene mutations responsive to Tezacaftor + Ivacaftor (Symdeko®) | | | | |
|---|---|---|---|---|
| F508del | R117C | D579G | K1060T | 2789+5G→A |
| E56K | E193K | 711+3A→G | A1067T | 3272-26A→G |
| P67L | L206W | E831X | R1070W | 3849+10kbC→T |
| R74W | R347H | S945L | F1074L | |
| D110E | R352Q | S977F | D1152H | |
| D110H | A455E | F1052V | D1270N | |

Symdeko [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; February 2018

# Tezacaftor + Ivacaftor (Symdeko®)

MOA:

- Tezacaftor: Facilitates cellular processing & trafficking of CFTR to ↑ amount of mature CFTR protein delivered to the cell surface
- Ivacaftor: CFTR potentiator that facilitates increased $Cl^-$ transport




Symdeko [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; February 2018

# Tezacaftor + Ivacaftor (Symdeko®)

- Packaged as tezacaftor 100 mg/ivacaftor 150 mg fixed dose combination tab & ivacaftor 150 mg tab
- Dose: One tab (tezacaftor 100 mg + ivacaftor 150 mg) in AM and one tab (ivacaftor 150 mg) in PM
- Should be taken with fat containing foods
- Requires dose reduction in pts with hepatic impairment & those taking concomitant CYP inducers or inhibitors
- ADRs: HA, nausea, sinus congestion & dizziness

Symdeko [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; February 2018

Mechanism of Action: MOA
Headache: HA

# PHARMACOTHERAPY: ANTI-INFECTIVES

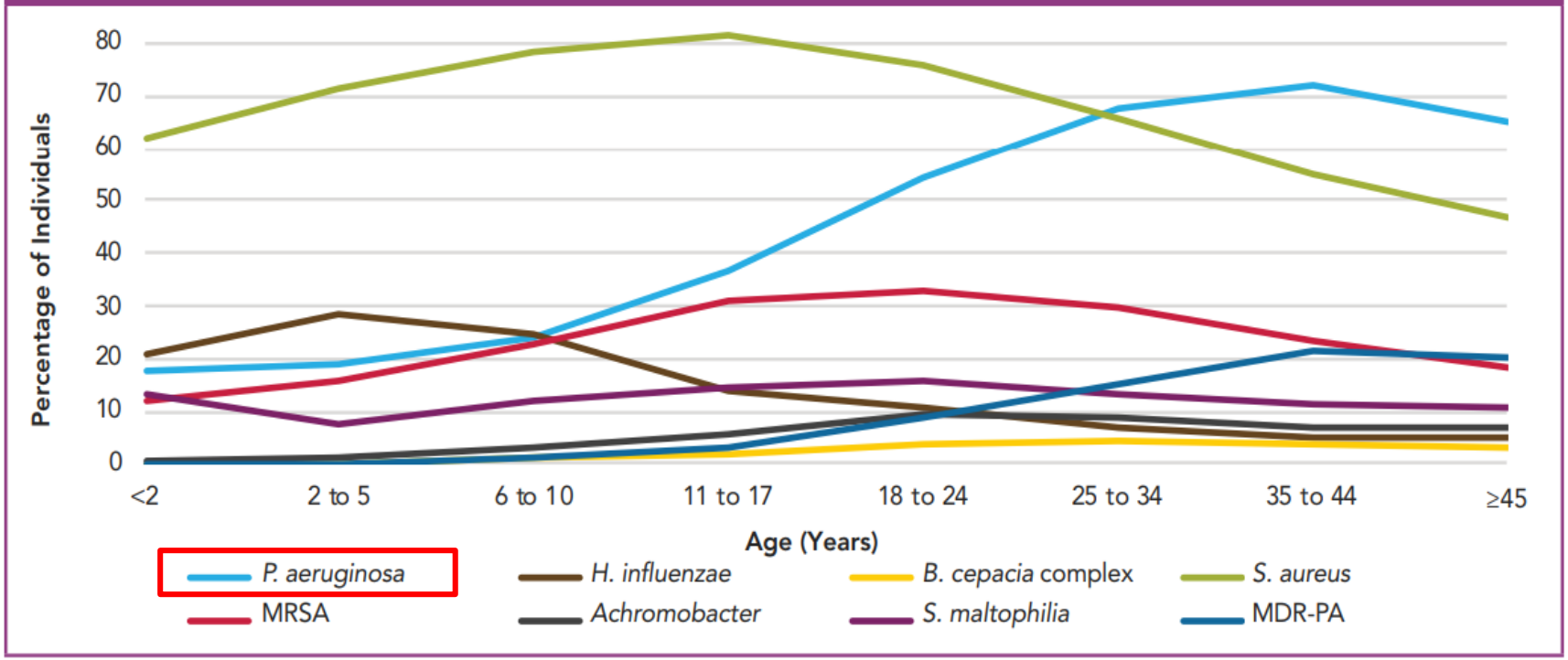
Amikacin Liposome Inhalation Suspension (Arikayce®)

Azithromycin (Zithromax®)

Aztreonam (Cayston®)

Tobramycin (TOBI Podhaler®, Bethkis®)

## Prevalence of Respiratory Microorganisms by Age Cohort, 2017




Cystic Fibrosis Foundation Patient Registry. 2017 Annual Data Report. Bethesda, Maryland. Cystic Fibrosis Foundation; 2018.

# *Pseudomonas aeruginosa*

- Gram negative rod widely distributed in nature & commonly present in moist environments
- Most frequently encountered lung pathogen in CF
- ~80% of patients are chronically colonized by *Pseudomonas aeruginosa* by the age of 20
- Colonization & infection with *Pseudomonas aeruginosa* remains the most important contributor to CF morbidity & mortality

# Amikacin Liposome Inhalation Suspension (Arikayce®)

- Approved in Sep. 2018 under the Accelerated Approval Pathway
- Criteria for indication:
  - Adults with *Mycobacterium avium* complex (MAC)
  - Limited/no alternative treatment options
  - Failed to achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy
- MOA: Disruption & inhibition of protein synthesis in the target bacteria by binding to the 30S ribosomal subunit

Arikayce [package insert]. Bridgewater, NJ: Insmed Incorporated; 2018.

# Amikacin Liposome Inhalation Suspension (Arikayce®)

- Dose: Once daily oral inhalation of the contents of one 590 mg/8.4 mL Arikayce® vial
  - To be used only with the Lamira™ Nebulizer System

- ADRs: Dysphonia, cough, bronchospasm, hemoptysis, musculoskeletal pain, fatigue/asthenia & exacerbation of underlying pulmonary disease

ARIKAYCE®
(amikacin liposome inhalation suspension)

Arikayce [package insert]. Bridgewater, NJ: Insmed Incorporated; 2018.

# Azithromycin (Zithromax®)

- MOA: Inhibits RNA-dependent protein synthesis at the chain elongation step by binding to the 50S ribosomal subunit
  - Contains anti-inflammatory properties that may benefit CF patients
  - Exact mechanism in CF is still unknown
- Dose:
  - < 40 kg: 250 mg three times weekly
  - ≥ 40 kg: 500 mg three times weekly
- ADRs: Nausea, diarrhea, & wheezing

# Azithromycin (Zithromax®)

- Treatment of pts with CF chronically infected with *P. aeruginosa* with azithromycin led to ↓ morbidity & mortality
  - Pulmonary function & nutritional status improved
  - Pulmonary exacerbation rates decreased

- Emergence of macrolide-resistant nontuberculous mycobacteria is of concern when considering chronic azithromycin therapy
  - MDs considering azithromycin therapy should assess patients with CF for nontuberculous mycobacteria before & every 6 months after initiating azithromycin

Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with pseudomonas aeruginosa: a randomized controlled trial. JAMA. 2003;290(13):1749-1756.

# Aztreonam (Cayston®)

- An aerosolized formulation of the monobactam antibiotic aztreonam & lysine
- Indicated to improve respiratory symptoms in CF pts ≥ 7 years old with *Pseudomonas aeruginosa*
- MOA: Binds to penicillin-binding proteins of susceptible bacteria, which leads to inhibition of bacterial cell wall synthesis & death of the cell


McCoy K.S., Quittner A.L., Oermann C.M., Gibson R.L., Retsch-Bogart G.Z., and Montgomery A.B.: Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in Cystic Fibrosis. *Am J Respir Crit Care Med* 2008; 178: pp. 921-928
Cayston[package insert]. Foster City, CA: Gilead Sciences Incorporated; 2014.

# Aztreonam (Cayston®)

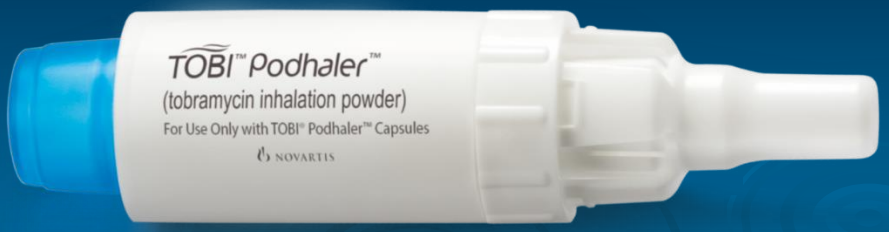
- Dose: Inhale one single use vial (75 mg aztreonam) reconstituted with 1 mL of sterile diluent TID for a 28 day course, followed by 28 days off drug
  - To be used only with the Altera® Nebulizer System

- ADRs: cough, nasal congestion, wheezing, pharyngolaryngeal pain, pyrexia, chest discomfort, abdominal pain & vomiting

Cayston[package insert]. Foster City, CA: Gilead Sciences Incorporated; 2014.

# Tobramycin (TOBI Podhaler®)

- MOA: Aminoglycoside antimicrobial that acts primarily by disrupting protein synthesis in the bacterial cell which eventually leads to cell death
- Dose: Inhalation of the contents of four TOBI Podhaler® capsules twice daily for 28 days, followed by 28 days off drug
  - One capsule contains 28 mg tobramycin
  - Capsules should be used with the Podhaler device only
- ADRs: cough, dyspnea, pyrexia, oropharyngeal pain, dysphonia, hemoptysis, & HA




TOBI [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015

# Tobramycin (Bethkis®)

- MOA: Aminoglycoside antimicrobial that acts primarily by disrupting protein synthesis in the bacterial cell which eventually leads to cell death
- Dose: One ampule BID by oral inhalation in repeated cycles of 28 days on drug, followed by 28 days off drug
  - One 4 mL ampule contains 300 mg tobramycin
  - Administered using a hand-held PARI LC PLUS Reusable Nebulizer with a PARI Vios Air compressor
- ADRs: ↓ FEV, rales, ↑ red blood cell sedimentation rate, & dysphonia
- Light sensitive
- Store in refrigerator

Bethkis [package insert]. Cary, NC: Chiesi, Inc.; 2017.

Forced Expiratory Volume: FEV

# THE ROLE OF A PHARMACIST

# The Role of a Pharmacist

- Identify potential drug interactions
  - Kalydeco , Symdeko, and Orkambi
    - Substrates of CYP3A4
- Patient Counseling
  - Encourage adherence to medication regimen
  - Verify appropriate inhaler/nebulizer technique
  - Kalydeco, Symdeko, and Orkambi should be taken with high fat meals
- Ensure correct antibiotic selection in the setting of an acute exacerbation
  - Broad spectrum coverage
  - Two antipseudomonal agents

# Acute Exacerbations

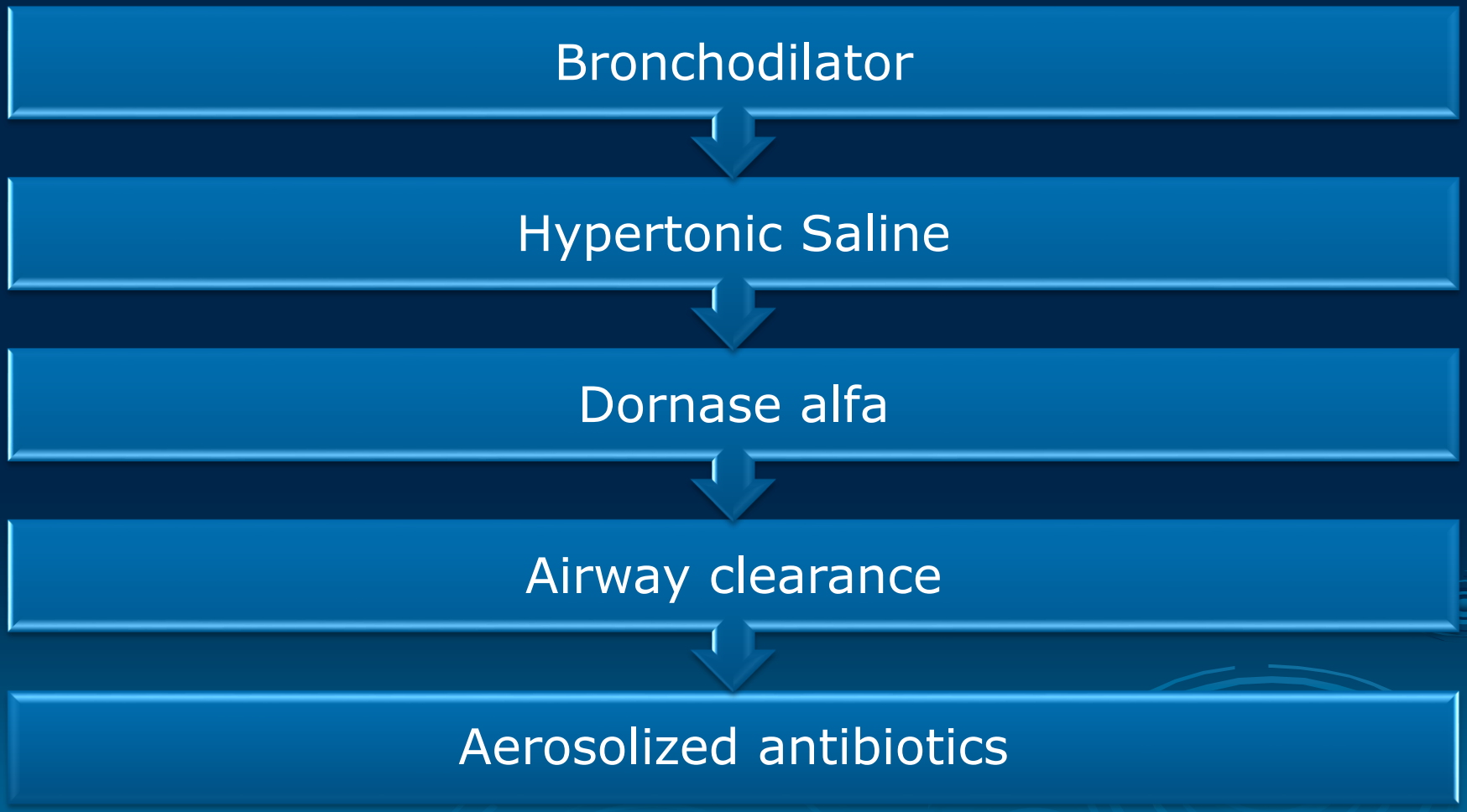
- Diagnosis of an acute exacerbation is based on changes from an individual pt's recent baseline health status
- Most exacerbations are not associated with the appearance of bacterial species or strains that are *new* to the pt
- Treatment:
  - Continuation of chronic treatment regimen
  - Glucocorticoids
  - Respiratory support
  - Systemic antibiotics

# Pharmacokinetics in CF Population

- Large volumes of distribution
- Enhanced metabolic clearance
- Increased risk for antimicrobial resistance
- Difficulty with lung tissue penetration

**Great difficulty in attaining & maintaining therapeutic drug concentrations!**

# Chronic CF Therapies: Recommended Order

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# WHAT'S NEXT?

The Future of CF

# New Therapies

- CF care has largely focused on the downstream effects of CFTR dysfunction
- New therapies aim to treat the underlying abnormality
- CF has among the highest number of gene-therapy trials
- CFTR pharmacotherapy:
  - CFTR gene mutations have different functional consequences
  - Must target the distinct classes of mutation
- Treating the early & root causes of CF will improve outcomes & reduce the burdens of treatment

# New Therapies

- Introduction of CFTR modulators has revolutionized CF care
- Drug screening campaigns have identified agents capable of suppressing CFTR nonsense alleles, augmenting potentiator activity & further promoting F508del correction
- Advancement of new drugs that address specific CFTR defects has been bolstered by clinical studies of F508del rescue in combination with ivacaftor

# Drug Development Pipeline

## Phase 1

- Eluforsen (QR-010)
- MRT5005
- AZD5634
- ALX-009
- SNSP113
- SPI-1005
- POL6014

## Phase 2

- QBW251
- FDL169
- GLPG2222
- PTI-428
- PTI-801
- VX-561
- OligoG
- SPX-101
- Inhaled Nitric Oxide
- Intravenous Gallium
- Acebilustat (CTX-4430)
- Lenabasum (JBT-101)
- LAU-7b

## Phase 3

- VX-445 + tezacaftor + ivacaftor
- VX-659 + tezacaftor + ivacaftor
- Inhaled Mannitol (Bronchitol®)
- Inhaled Levofloxacin (Quinsair®)
- Vancomycin Inhalation Powder (AeroVanc®)

# Summary

- CF is a disease state resulting from a dysfunction in the CFTR
- Multiple organ systems are affected in CF individuals
- Mortality is most commonly due to chronic organ damage or resistant pulmonary infections
- Breakthrough in CF treatment focuses on treating the basic defect of the disease: CFTR dysfunction

# Test Your Knowledge
# True or False?

- The most common cause of pneumonia in patients with cystic fibrosis is burkholderia cepacia. **FALSE**
- Inhaled antibiotics, such as Aztreonam (Cayston®) and Tobramycin (TOBI®), should be administered last in a patient's inhaled medication regimen after bronchodilators and other inhaled therapies. **TRUE**
- The most common CFTR gene mutation is delta F508. **TRUE**

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# Pharmacological Management of Cystic Fibrosis: Exploring the Therapeutic Advancements in Cystic Fibrosis

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