1-27-2019

I Can't Breathe - Cystic Fibrosis

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Alex

Dum Spiro Spero:

While I Breathe I Hope

Brenan P; His daughter's Legacy: "Alex: The Life of a Child". The Washington Post. 1986

I can't breathe

Cystic Fibrosis

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Objectives

- Define Cystic Fibrosis (CF), how it manifests and its incidence
- List the different classes of genetic mutations
- Discuss diagnosis and testing
- Describe the therapeutic management of CF
- Recognize the medications that are currently under investigation

Question 1

1. Cystic fibrosis is part of the Newborn screening in all 50 states
   A. True
   B. False

Question 2

1. Cystic Fibrosis a disease that affects: Sweat glands, GI tract, Lungs, and Reproductive System
   A. Yes
   B. No

Question 3

1. In CF patients Azithromycin is only used because of its antimicrobial properties
   A. Yes
   B. No

What is Cystic Fibrosis?

Cystic fibrosis is a progressive, genetic disease that causes persistent lung infections and limits the ability to breathe over time

Epidemiology

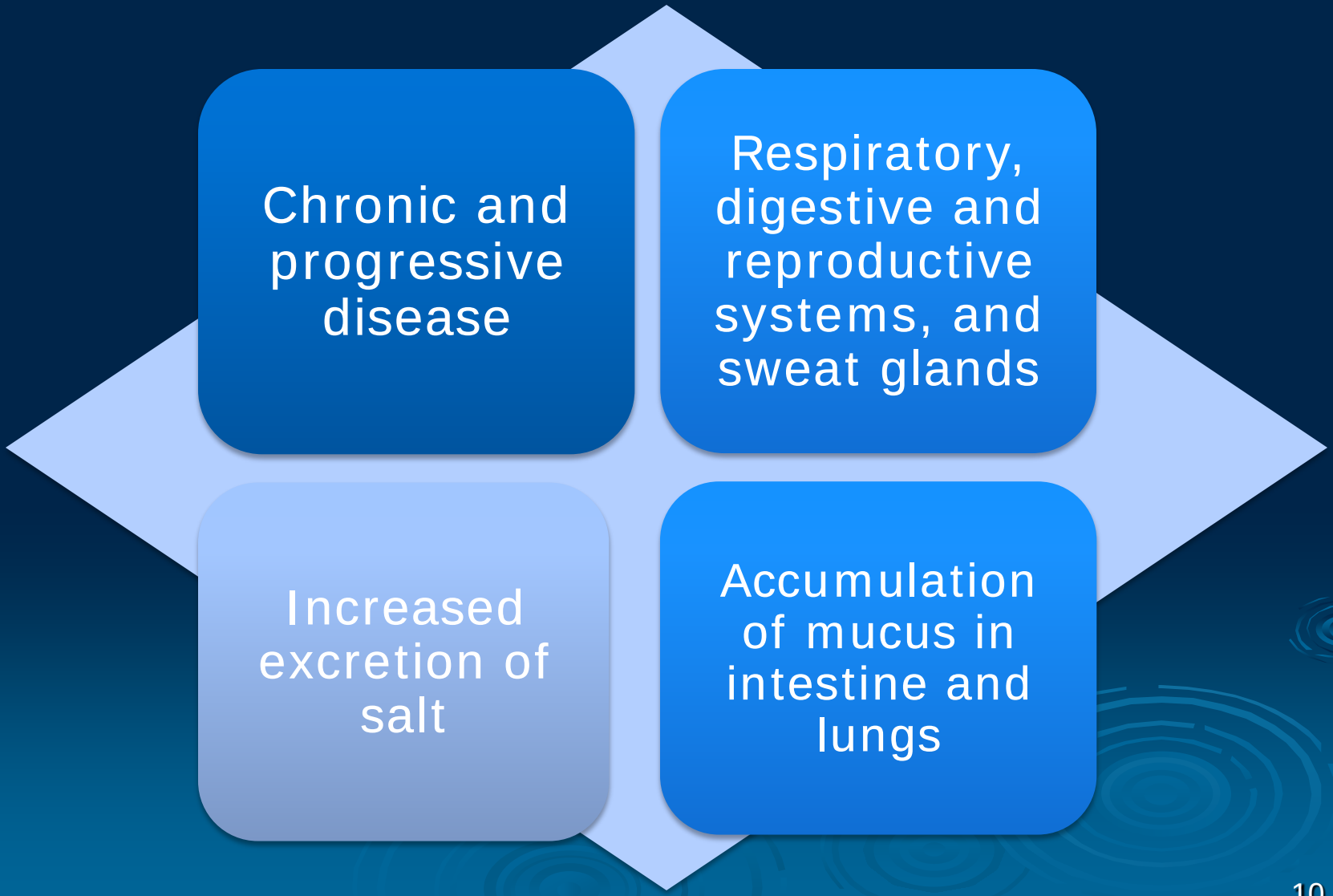
- CF patients: 29,887
- Newly diagnosed: 880
- Detected by newborn screening:58.4%
- Adults >18 years: 53.5%
- Caucasians: 93.6%
- Males: 51.6%

Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018

Question 1

1. Cystic fibrosis is part of the Newborn screening in all 50 states
   A. True
   B. False

Pathophysiology



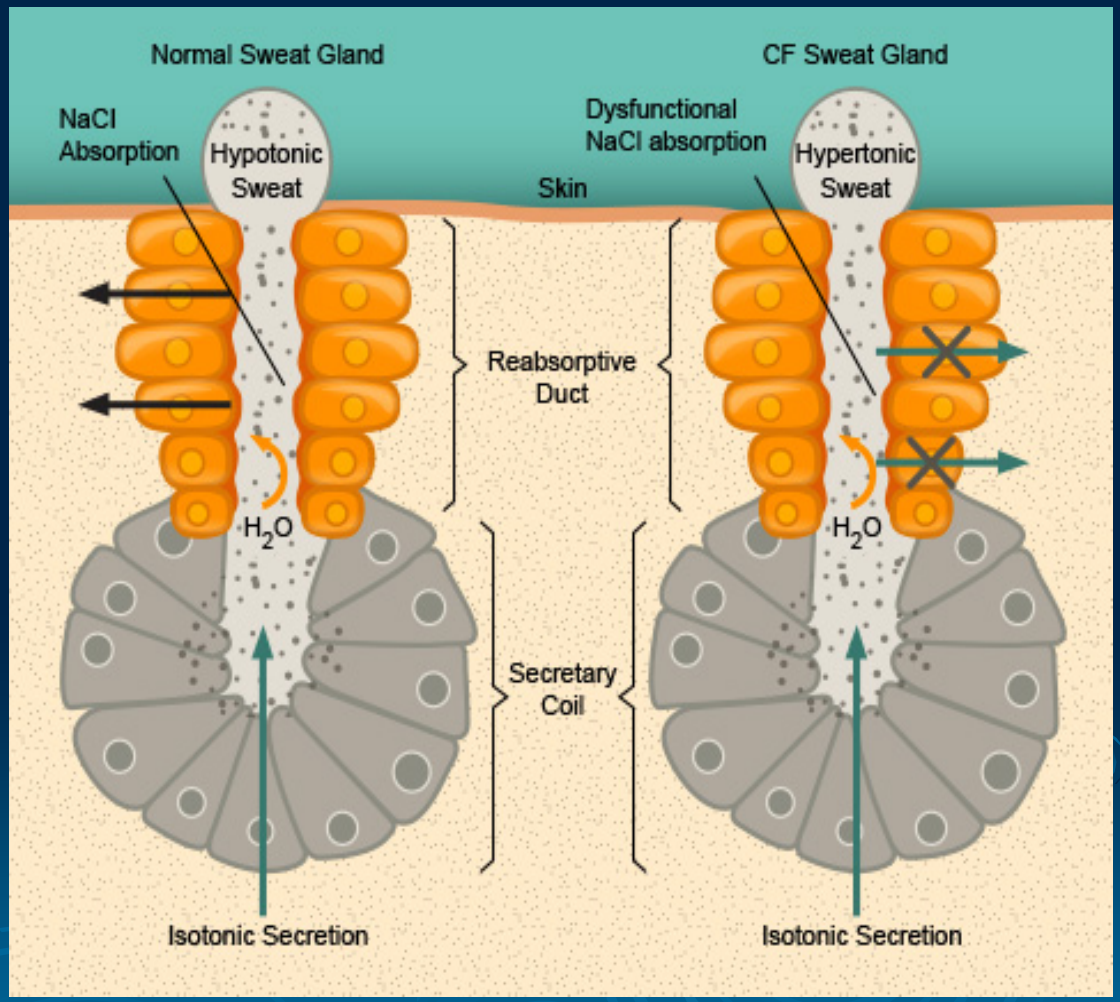
Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018

Question 2

1. Cystic Fibrosis a disease that affects: Sweat glands, GI tract, Lungs, and Reproductive System
   A. Yes
   B. No

Sweat Glands

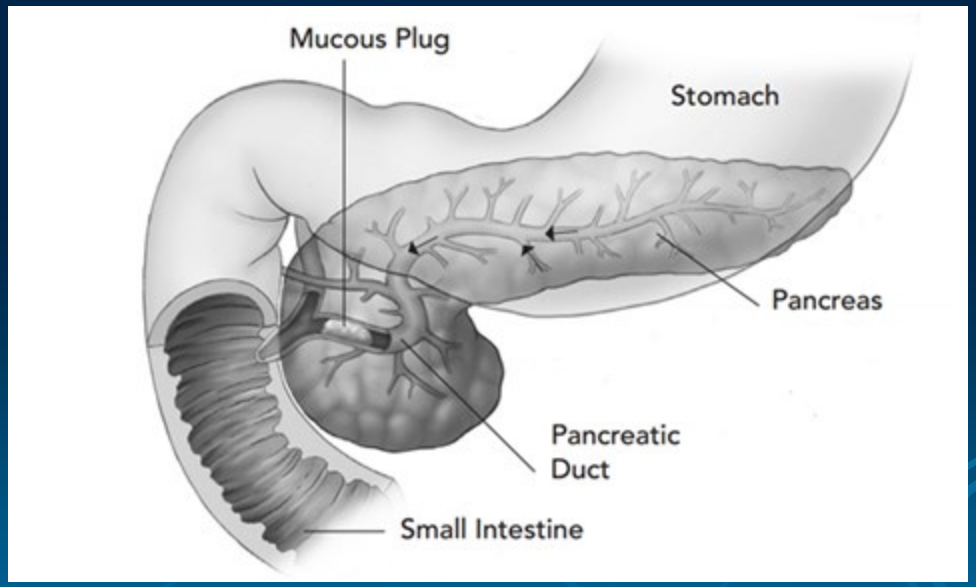
Mutation of Cystic Fibrosis Transmembrane Regulator (CFTR) protein prevents reabsorption of chloride ions



Science of CF: CFTR: Function. Johns Hopkins Cystic Fibrosis Center
http://www.cftr.info/about-cf/pathophysiology-of-cf/sweat-gland/how-cf-modifies-sweat-chloride-levels-at-the-cellular-level/

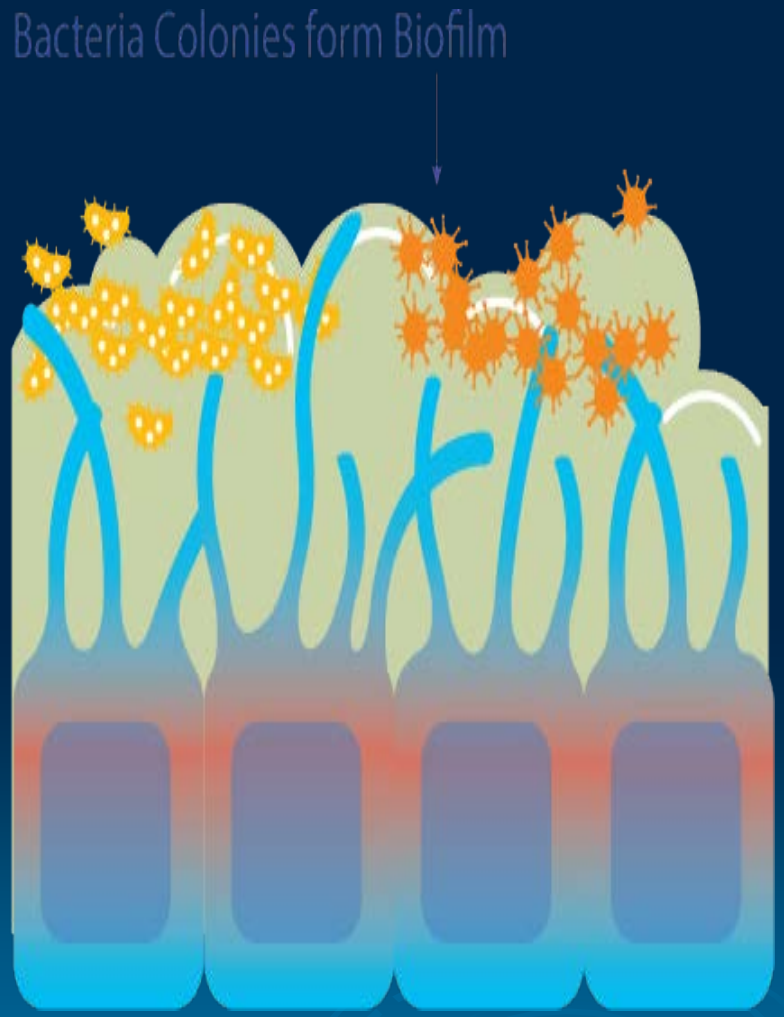
Pancreas and GI Tract

- Pancreatic ducts are blocked by thick mucus
- No release of pancreatic enzymes



Science of CF: CFTR: Function. Johns Hopkins Cystic Fibrosis Center

Airways



- Thickening of airway surface liquid (ASL)
- Impaired mucociliary clearance

Science of CF: CFTR: Function. Johns Hopkins Cystic Fibrosis Center
https://www.google.com/search?client=safari&channel

Overall Consequences

01

Malnutrition

02

Poor growth

03

Respiratory infections

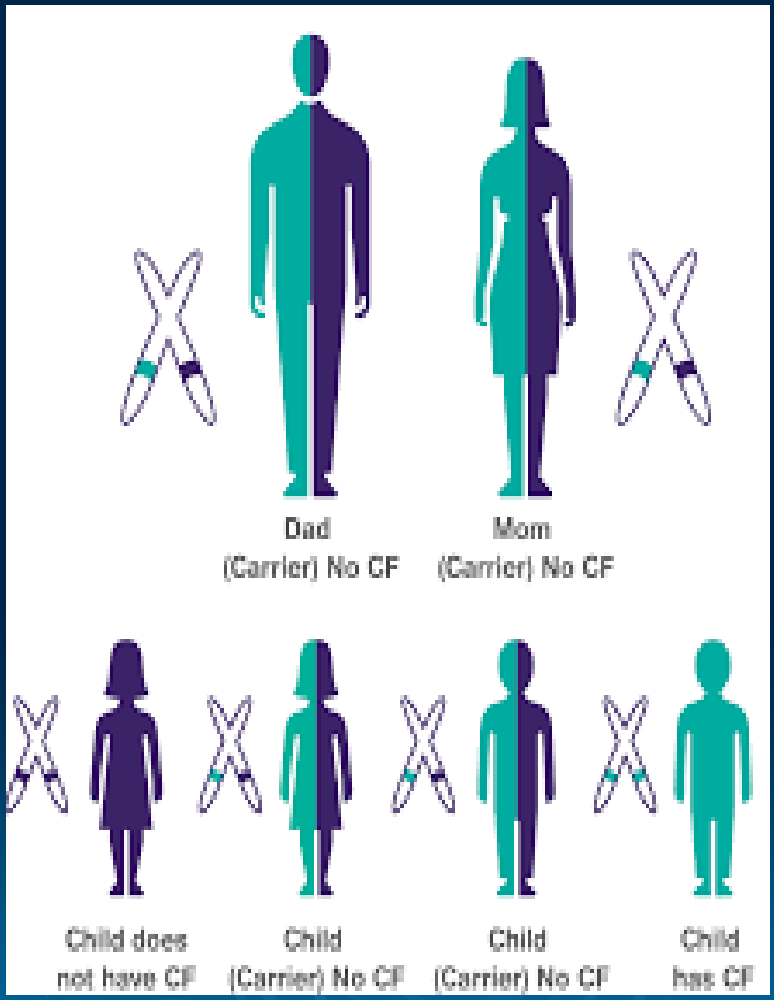
04

Permanent lung damage

Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018

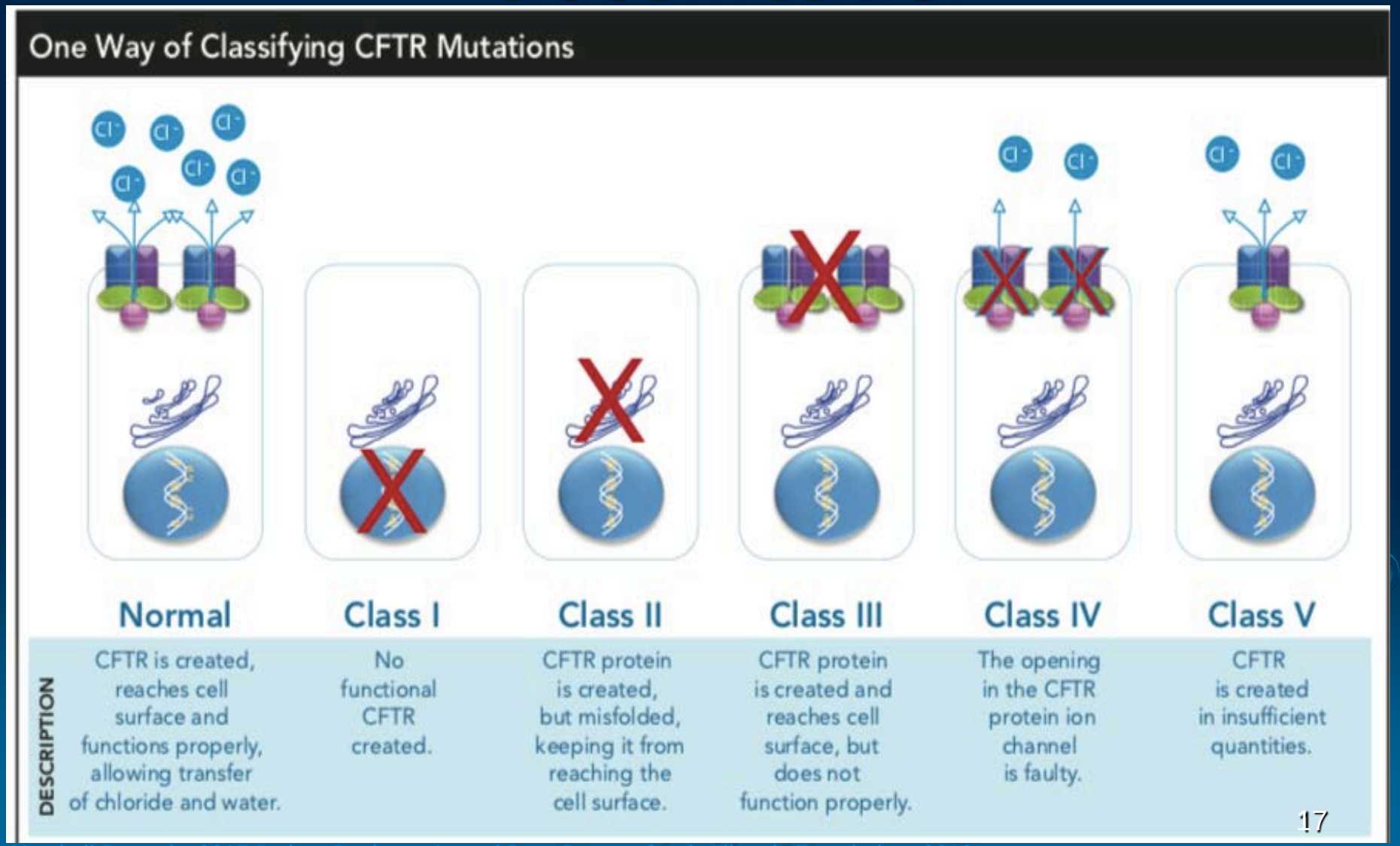
Genetics

- Autosomal recessive genetic disorder
- 25% probability for the offspring



Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018
https://www.kalydeco.com/condition-overview

Cystic fibrosis mutation classification



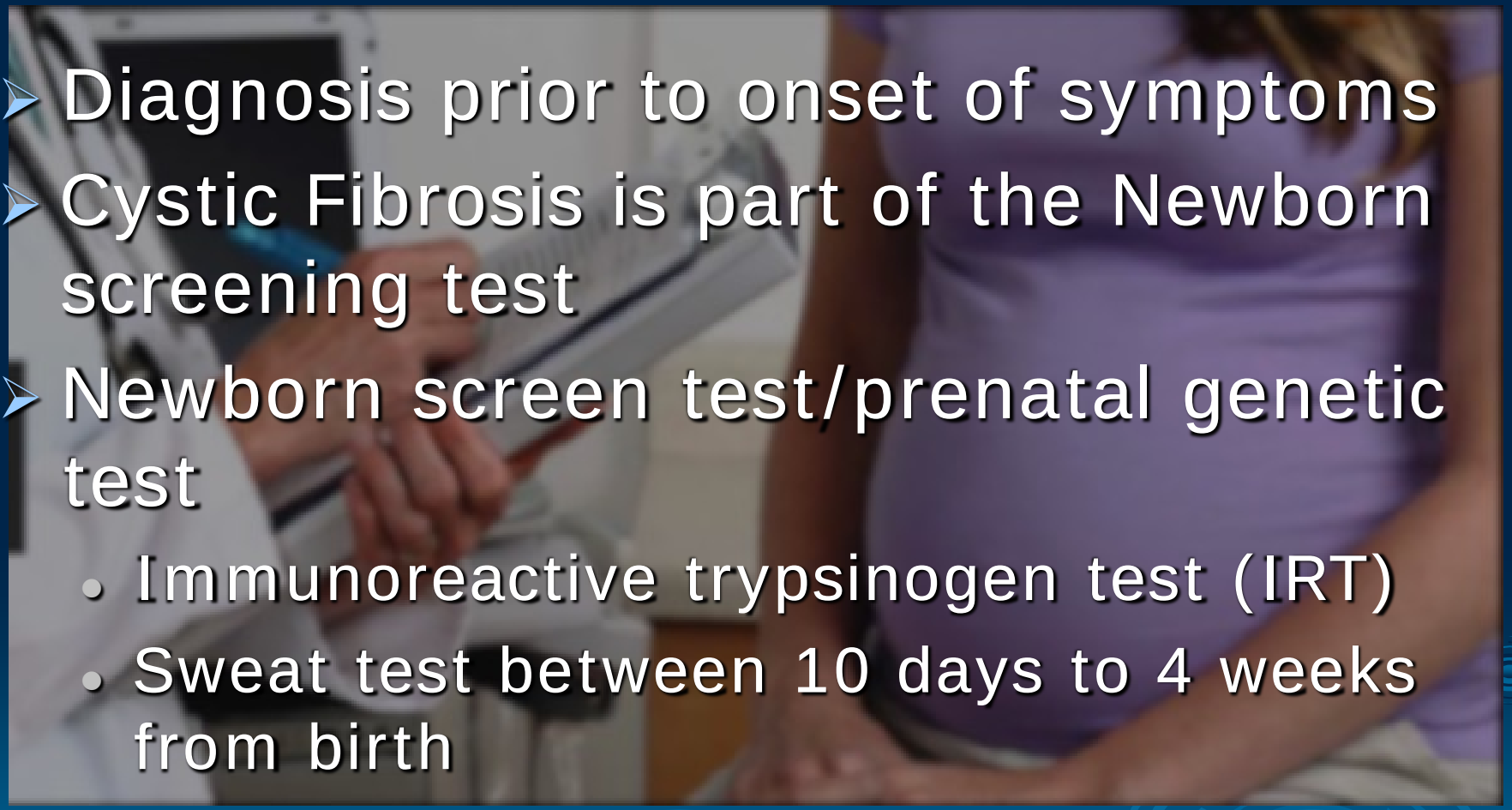
Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018

Statistics

- Mortality: 380 patients
- Pancreatic enzyme replacement therapy: 85.7%
- Supplemental feeding tube: 10.9%
- Supplemental feeding tube oral: 44.9%

Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018

Diagnosis

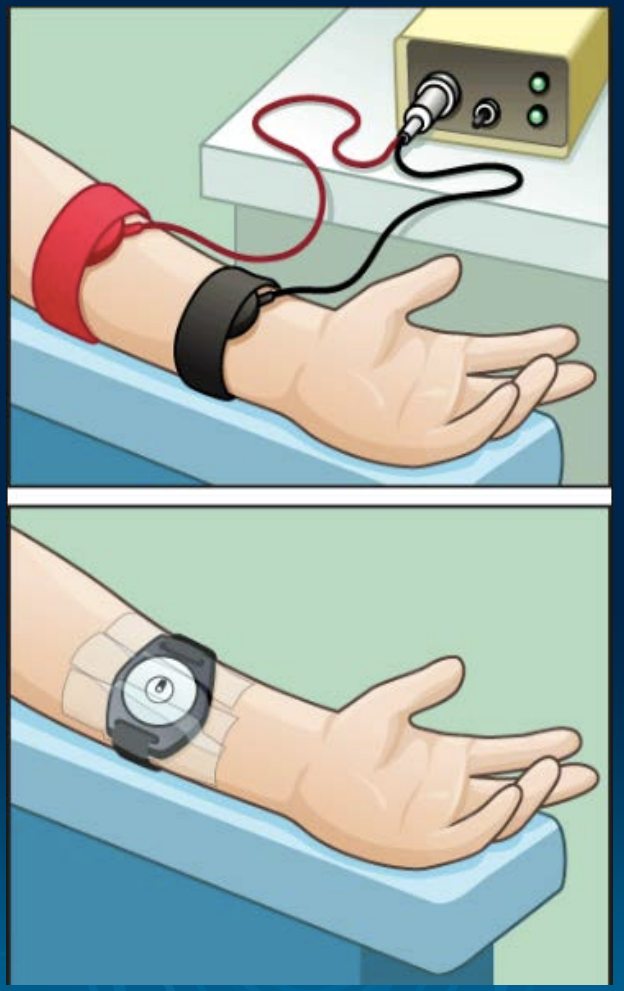


- Diagnosis prior to onset of symptoms
- Cystic Fibrosis is part of the Newborn screening test
- Newborn screen test/prenatal genetic test
  - Immunoreactive trypsinogen test (IRT)
  - Sweat test between 10 days to 4 weeks from birth

Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018
https://www.healthline.com/health/cystic-fibrosis-carrier
https://www.cff.org/What-is-CF/Testing/Sweat-Test/

The gold standard test

- Sweat Test
  - Measures the amount of chloride in the sweat
  - Electrodes attached
  - Electrode 1 contains pilocarpine gel
    - A weak electrical current pushes the medication through skin ~5minutes
  - Remove electrodes, clean and dry skin
  - Collect sweat for 30 minutes



Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018
Sweat Test. What is CF. Cystic Fibrosis Foundation
https://kidshealth.org/en/parents/sweat-test.html

Newborn Screening (IRT)

Negative Test

Sweat test

Positive Test

Cl<29mmol/L Negative

Cl 30-59mmol/L Inconclusive

Cl>60mmol/L Positive

Cystic Fibrosis related Metabolic Syndrome (CRMS)

Cystic Fibrosis Transmembrane Receptor (CFTR) gene mutation and related conditions

<2 CF causing genetic mutation

>2 CFTR gene mutation

CFTR related disorders

Marshall B. et al.; eport. Cystic Fibrosis Foundatio

https://kidshealth.org/en/parents/sweat-test.html

Therapy
Pancreas and GI tract

- Fecal pancreatic elastase-1 (FE-1)
  - Pancreatic insufficiency test
  - 2 weeks of age if no liquid stools
- Pancreatic enzyme replacement therapies (PERT)
  - Patients with 2 mutation in the group I-III
  - Fecal elastase value < 200 micrograms/stool
  - Signs of malabsorption

Schwarzenberg SJ. et al.; Pancreatic enzymes Clinical Care Guidelines. Cystic Fibrosis foundation.2018
Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis March 2018

Therapy
PERT

- Infants: 450-900 lipase U/g or 2000-4000 U/120ml of formula
- Older children and adults: 500-4000 lipase U/g of fat ingested or 500-2500 U/kg/meal, 250-1250 U/kg/snack
- Doses > 2500 lipase U/kg/meal or 4000 U/g of fat → Investigate
  - Doses >6000 lipase U/kg/meal → associated with fibrosing colonopathy

Schwarzenberg SJ. et al.; Pancreatic enzymes Clinical Care Guidelines. Cystic Fibrosis foundation.2018
Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis March 2018

PERT Pearls

- Only dispense prescribed product brand
- Enteric coated microencapsulated enzymes are most effective
- Excessive doses of PERT may result in abdominal pain/constipation
- Fat soluble vitamins measured once a year

Schwarzenberg SJ. et al.; Pancreatic enzymes Clinical Care Guidelines. Cystic Fibrosis foundation.2018
Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis March 2018

Therapy
Pancreas and GI tract

- Acid blockers to treat acid reflux (GERD), decrease acidity of environment or increase effectiveness of PERT
  - Proton Pump Inhibitors 48.5% of CF patients
  - H2 blockers 17.5%

Schwarzenberg SJ. et al.; Pancreatic enzymes Clinical Care Guidelines. Cystic Fibrosis foundation.2018
Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis March 2018

Therapy
Lungs

Bronchodilators	• 2-4 times a day to open airways
Hypertonic saline (HyperSal, PulmoSal)	• 2-4 times a day as osmotic agent
Dornase alfa (Pulmozyme)	• 2.5mg daily as mucolytic
Chest Physiotherapy	• To mobilize mucus
Antibiotics	• To prevent/treat lung infections

Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis March 2018

Therapy
Respiratory

- Short acting beta adrenergic receptor agonists
  - Immediately prior to nebulized hypertonic saline
  - As a rescue for airway hyperreactivity
- No clear benefit
  - Ipratropium
  - Tiotropium
  - Theophylline

Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018
Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis. 2018

Reusable Nebulizer Pearls

- Use bronchodilators 15-30 min before airway clearance treatments
- Common side effects are tremor, nausea, rapid heart rate, nervousness
- Clean and disinfect after each use

Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018
Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis. 2018

Inhaled Hypertonic Saline 7%

- 6 years and older
- Moderate to severe lung disease
- Pretreat with bronchodilator
- Bronchospasms

1- Restore hydration
2- Increase expectoration
3- Increase mucociliary function

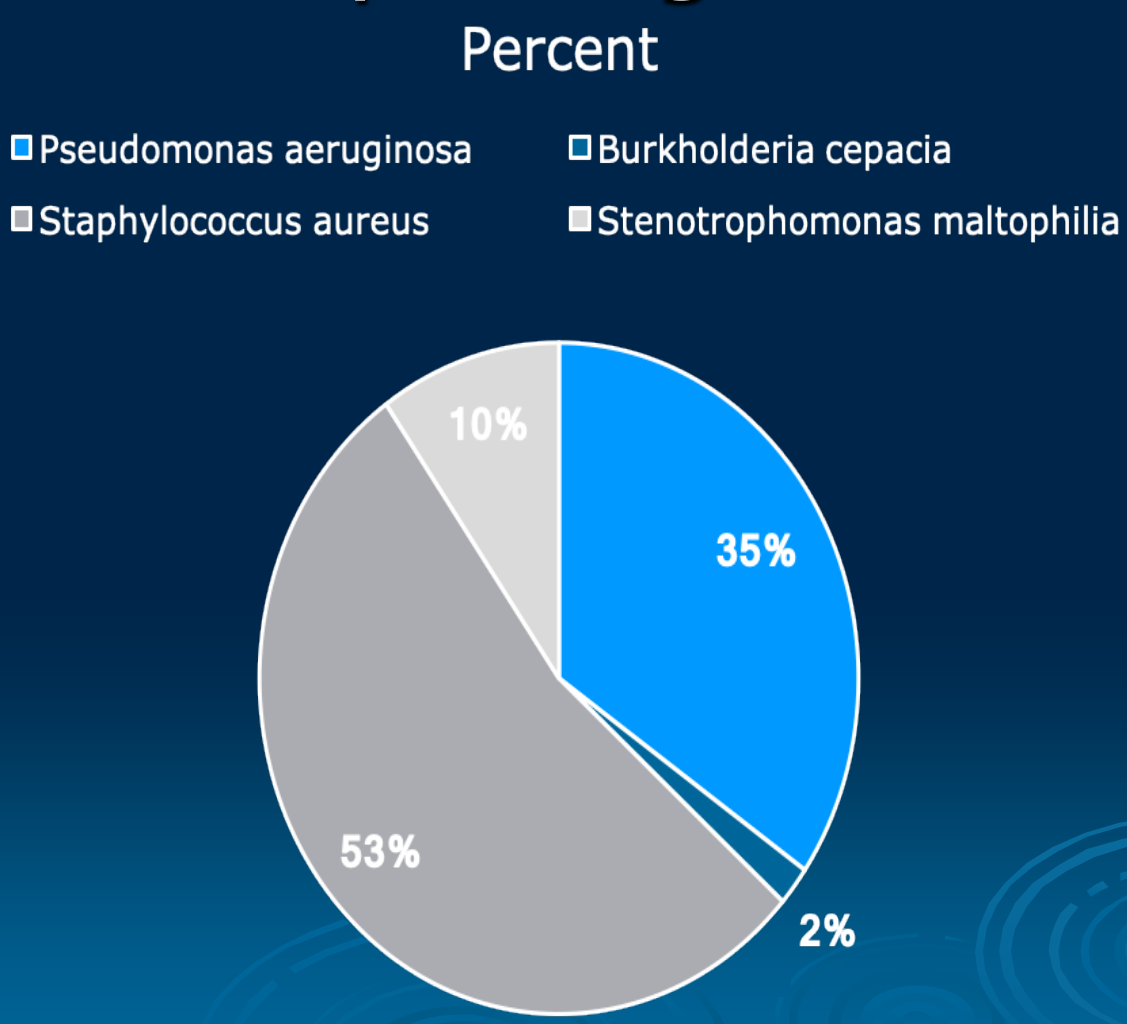
Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis March 2018
Simon RH, et al.; Cystic Fibrosis: Overview of the treatment of lung disease. Up-to-date

Dornase alfa (Pulmozyme)

- 6 years and older
- Mucolytic which decreases viscosity
- Reduces the decline in lung functioning and pulmonary exacerbations
- Side effects: Hoarseness, sore throat, and change in voice

Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis March 2018
Simon RH, et al.; Cystic Fibrosis: Overview of the treatment of lung disease. Up-to-date
Yang C et al.; Dornase alfa for cystic fibrosis. Cochrane Database Sys Rev. 2016

Incidence of respiratory pathogens



Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018

MRSA Treatment

- Pulmonary exacerbations
  - Vancomycin IV
    - 45-60mg/kg/day divided Q6-8
    - 15-20mg/kg Q8-12hr adults
  - Linezolid
    - 10mg/kg IV/PO Q8hr for <12 years old
    - 600mg IV/PO Q12hr for >11 years old
    - Serotonin syndrome-drug interactions
    - Peripheral/optic neuropathies
    - Myelosuppression

Aksamit TR.; et al.; Antibiotic management of Lung Infection in Cystic Fibrosis. I. The Microbiome, Methicillin-Resistant *Staphylococcus aureus*, Gram Negative Bacteria, and Multiple Infections

MRSA treatment

- Outpatient setting
  - Two oral agents are recommended
    - Rifampin plus another oral agent
      - High mucosal concentration
      - Activity against biofilms
      - Do not give monotherapy
      - Worsening of GERD
      - Decrease oral contraceptive effectiveness
    - Add nebulized vancomycin to regime
      - Effective and well tolerated.
      - Ongoing studies investigating the use of inhaled vancomycin

Aksamit TR.; et al.; Antibiotic management of Lung Infection in Cystic Fibrosis. I. The Microbiome, Methicillin-Resistant *Staphylococcus aureus*, Gram Negative Bacteria, and Multiple Infections

Antipseudomonal Treatment
IV antibiotics

Column A Choose 1 from this column		
Tobramycin	2.5-3.3mg/kg IV/IM Q6-8 pediatric 5-7mg/kg IV Q24h adult	Ototoxicity, nephrotoxicity
Amikacin	10mg/kg/dose Q8hrs pediatric (traditional) 30mg/kg/dose Q24 pediatric (extended interval) 15-20 mg/kg/dose every 24hrs IV adult	Ototoxicity, nephrotoxicity
Colistin	3-5 ,g CBA/kg/day Q8hrs >5years old 3mg CBA/kg/day Q8hrs adults	Nephrotoxicity, neurotoxicity

Simon RH, et al.; Cystic Fibrosis: Overview of the treatment of lung disease. Up-to-date

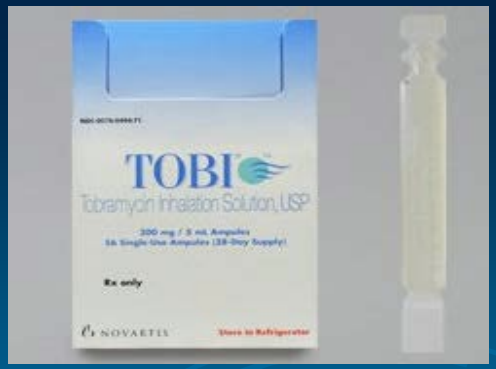
Antipseudomonal Treatment
IV antibiotics

Column B Add one to column A		
Ceftazidime	150-200mg/kg/day IV Q6h pediatric 90-150mg/kg/day IV Q8h adults	GI, rash
Meropenem	40mg/kg IV Q8h pediatric 2g IV Q8 adults	GI, rash, hepatitis, neutropenia
Ciprofloxacin	10mg/kg IVQ8hrs-or-20mg/kg PO Q12h pediatric 400mg Q8hr IV-or-750mg PO Q12h	GI, rare seizure, tendinopathy

Simon RH, et al.; Cystic Fibrosis: Overview of the treatment of lung disease. Up-to-date

Antipseudomonal Treatment
Inhaled Antibiotics

- Aztreonam (Cayston®) Inhalation solution
- Tobramycin (TOBI® Bethkis®, Kitabis Pak®) Inhalation solution
- Tobramycin (TOBI®, Podhaler™) Inhalation powder



Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis March 2018
https://www.mountainside-medical.com/products/tobi-podhaler-cystic-fibrosis-treatment-inhaler-28x8-224-count
https://www.webmd.com/drugs/2/drug-5456/tobi-inhalation/details
https://www.cayston.com/dosing-and-cleaning/preparing-cayston

Antipseudomonal treatment

- Combination of 2 antipseudomonal agents
- Eradication of pseudomonas infection treatment recommendation
  - 28 days of inhaled tobramycin
  - Followed by nebulized colistimethate plus oral ciprofloxacin for 3 months
- If failed eradication treatment, patient is diagnosed with chronic infection

Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis March 2018
Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018

Antipseudomonal treatment
Chronic infection

- Inhaled Tobramycin 300mg BID on alternative months
  - 6 years and older
  - Extended indefinitely
  - Tobramycin IV or IM: 10mg/kg/day divided 4 times a day
- Aztreonam 75mg on alternative months
  - Showed superiority to Tobramycin for lung functioning

Castellani C. et al.; European cystic fibrosis society clinical practice guidelines on screening, diagnosis and management of cystic fibrosis. Journal of Cystic Fibrosis March 2018
Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018

Inhaled Antibiotic Pearls

- Solutions are administered via nebulizer
- Refer patients to CF care teams for instructions about specific nebulizer usage/cleaning
- Powders: four capsules twice/day
  - Place one cap at a time in the inhalation device
  - Breath slowly and deeply
  - Hold breath for 5 seconds

Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis. 2018
Marshall B. et al., 2017 Patient Registry: Annual Data Report. Cystic Fibrosis Foundation. 2018

Azithromycin

- 6 years and older
- Antimicrobial and anti-inflammatory properties
- Chronic Pseudomonas aeruginosa infection-biofilms
  - Not antipseudomonal agent
- Improve lung function
- Linked to resistance when chronic use

Castellani C. et al.; ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis March 2018
Marshall B. et al.; 2017 Patient Registry. Annual Data Report. Cystic Fibrosis Foundation. 2018

Question 3

1. In CF patients Azithromycin is only used because of its antimicrobial properties
   A. Yes
   B. No

CFTR Modulator Therapies
Ivacaftor (Kalydeco)

- Ivacaftor (Kalydeco):
  - 12 months to <6 years, and 7-14kg: 50mg granules PO Q12h
  - 12 months to <6 years and >14kg: 75mg granules PO Q12h
  - 6 years and older: 150mg PO Q12h

Kalydeco (Ivacaftor) Medscape. 2018
Kalydeco (Ivacaftor) Tablet Label. FDA package insert. 2012
Kalydeco (Ivacaftor) to Treat Cystic Fibrosis. Cystic Fibrosis News Today. 2018

CFTR Modulator Therapies
Ivacaftor (Kalydeco)

- 1 year and older
  - ARRIVAL Trial
- For most CFTR mutations
  - Not approved for two copies of the F508del mutation
- Side effects: headaches, upper respiratory tract infections, stomach pain, and diarrhea

Kalydeco (Ivacaftor) Medscape. 2018
Kalydeco (Ivacaftor) Tablet Label. FDA package insert. 2012
Kalydeco (Ivacaftor) to Treat Cystic Fibrosis. Cystic Fibrosis News Today. 2018

CFTR Modulator Therapies
Ivacaftor/Lumacaftor (Orkambi)

- Ivacaftor/Lumacaftor (Orkambi):
  - 2-5 years old
    - Weight <14kg: 100mg/125mg Oral granules PO Q12h
    - Weight >14kg: 150mg/188mg Oral granuel PO Q12h
  - 6-11 years old
    - 2 tablets PO Q12h (100mg/125mg per tab)
  - >12 years old
    - 2 tablets PO Q12h (200mg/125mg)

Approved for 508del homozygous

Orkambi (Ivacaftor/Lumacaftor) Medscape. 2018
Orkambi (Ivacaftor/Lumacaftor Tablet Label. FDA package insert. 2012

CFTR Modulator Therapies
Tezacaftor/Ivacaftor (Symdeko)

- Tezacaftor/Ivacaftor (Symdeko)
  - >12 years old
    - 100/150mg (tezacaftor/ivacaftor) QAM followed by 150mg Ivacaftor 12 hours later
  - For 26 specific types of mutations

Approved for 508del homozygous

Symdeko (tezacaftor/ivacaftor) Tablet Label. FDA package insert. 2018

CFTR Modulator Therapies
Pearls

- Taken with fatty meals i.e. eggs, peanut butter, cheese, etc.
- Mix granules with 5mL of yogurt, milk
- CYP3A metabolized

Immunizations

- Influenza:
  - >6 months: Inactivated vaccine
- PCV13:
  - Up to 24 months old
  - >65 years old
- PPSV23:
  - After 2 years of age
  - >65 years old
- Palivizumab:
  - Inconclusive conclusions

Do you need vaccines? Cystic Fibrosis Foundation.2018

Cystic Fibrosis Clinical Trials

RESTORE CFTR FUNCTION | ENROLLING

Phase 1/2 study of PTI-801 drug in healthy adults and then in adults with cystic fibrosis | Proteostasis PTI-801-01 ›

This study is taking place at multiple care centers across the U.S. It will look at the safety and tolerability of the drug PTI-801.

AGE	MUTATION(S)	FEV1% PREDICTED	NUMBER OF VISITS	LENGTH OF PARTICIPATION
18 Years and Older	Two Copies F508del	40 to 90%	8	30 days

MUCOCILIARY CLEARANCE | ENROLLING

SHIP CT: Study of hypertonic saline in preschoolers | SHIP002 ›

This study is taking place in Europe, Australia and the U.S. It will look at the safety and effectiveness of hypertonic saline compared to isotonic saline (normal saline) in children with CF.

AGE	MUTATION(S)	FEV1% PREDICTED	NUMBER OF VISITS	LENGTH OF PARTICIPATION
3 Years to 5 Years	No Mutation Requirement	No FEV1 Limit	6	54 weeks

ANTI-INFLAMMATORY | ENROLLING

Phase 2 study of lenabasum in people with CF ages 12 and older | Corbus JBT101-CF-002 ›

This study is taking place at multiple care centers across the U.S. It will look at the safety and effectiveness of the potential anti-inflammatory drug lenabasum and will use a placebo control.

AGE	MUTATION(S)	FEV1% PREDICTED	NUMBER OF VISITS	LENGTH OF PARTICIPATION
12 Years and Older	No Mutation Requirement	40 to 100%	10	32 weeks

ANTI-INFECTIVE | ENROLLING

TEACH: Testing the effect of adding oral azithromycin to inhaled tobramycin in people with CF | TEACH-IP-15 ›

This phase 2 study is taking place at multiple care centers across the U.S. It will look at the effect of adding oral azithromycin to inhaled tobramycin and will use a placebo control.

AGE	MUTATION(S)	FEV1% PREDICTED	NUMBER OF VISITS	LENGTH OF PARTICIPATION
12 Years and Older	No Mutation Requirement	25 to 100%	5	14 weeks

NUTRITIONAL-GI | ENROLLING

OPTION: Study of AzurRx MS1819 in people with cystic fibrosis and exocrine pancreatic insufficiency who are 18 years and older | AzurRX AZ-CF2001 ›

This study will look at the safety and effectiveness of the drug MS1819 as a pancreatic enzyme replacement therapy.

AGE	MUTATION(S)	FEV1% PREDICTED	NUMBER OF VISITS	LENGTH OF PARTICIPATION
18 Years and Older	No Mutation Requirement	30% or greater	10	11 weeks

OBSERVATIONAL | ENROLLING

PREDICT: NTM observational study | NTM-OB-17 (PREDICT) ›

This study is taking place at multiple care centers across the U.S. It will evaluate the current standard of diagnosing nontuberculous mycobacteria (NTM) in people with CF.

AGE	MUTATION(S)	FEV1% PREDICTED	NUMBER OF VISITS	LENGTH OF PARTICIPATION
6 Years and Older	No Mutation Requirement	No FEV1 Limit	20	5 years

Questions?

References

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