Cystic Fibrosis: An Improving Outlook?

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Conflict of Interest

I have no real or perceived conflict of interest that relates to this presentation. Any use of brand names or references to companies or foundations is not in any way meant to be an endorsement, but to merely illustrate a point of emphasis.

Objectives

- Review the history of Cystic Fibrosis, treatment options, therapies, and the CF Foundation
- Discuss lung transplantation and it's growing success
- Look at current and future treatment options in regards to medications and secretion clearance devices
- Observe the life expectancy trend as an indicator of an improving outlook
- Convince you that the outlook of CF is improving

Cystic Fibrosis

- Defined:

  A hereditary disorder affecting the exocrine glands. It causes the production of abnormally thick mucus, leading to the blockage of the pancreatic ducts, intestines, reproductive tracts and bronchi often resulting in respiratory infection.

- Approximately 30,000 affected by CF in the U.S.
- Leading fatal genetic disease in Caucasians worldwide

Cystic Fibrosis Foundation

- Almost solely responsible for all research relating to Cystic Fibrosis.
- CF is an orphan disease, meaning it receives NO federal funding
- 90% of money raised by CFF goes to research

History of CF & CF Foundation

- Can be found referenced as far back as 1857
  - Passage from the "Almanac of Children's Songs and Games from Switzerland" warned that 'the child will soon die whose forehead tastes salty when kissed.'
- Modern History starts with Dorothy Andersen M.D.
  - A pathologist at NY Babies Hospital wrote the first comprehensive medical report on CF, giving a clear description in 1938.
- 1953 – Paul di Sant'Agnese M.D. connects the extra loss of salt by people with CF to the disease's underlying cellular problem, during a New York City heat wave.

History of CF & CF Foundation

- 1955 – CF Foundation (CFF) became incorporated as the National CF Research Foundation.
- 1961 – CFF established the accredited care center network by creating two centers devoted to treating CF. (Now over 110).
- 1982 – CFF created the Research Development Program, a network of research centers at universities and medical schools nationwide.

History of CF & CF Foundation

- 1989 – Single most important discovery in CF research
  - The discovery of the CF gene and it's protein product CFTR
  - CFTR – Cystic Fibrosis Transmembrane conductance Regulator
  - With this knowledge, researchers could make a healthy version of the faulty gene to study.
- 1993 – CF gene therapy was officially launched when the first gene therapy treatment was given to a CF patient. Also, research to correct the faulty protein product of the genes and discover new treatments for symptoms of CF
- 2000 - Scientists able to map entire genetic structure of *Pseudomonas aeruginosa* – most common cause of CF lung infections. Able to more accurately combat the bacteria

Medications

- 1993 – FDA approved Pulmozyme®, first drug developed for CF patients. Proven to thin the mucus.
- 1997 – The FDA approved TOBI®, the first aerosolized antibiotic designed for CF. Proven to reduce lung infections, and subsequently hospital stays. Also improved lung function.
- 2002 – Study showed long-term use of azithromycin improved health in CF patients. (Anti-inflammatory properties)

Medications

- 2004 – Studies in Australia showed that hypertonic saline (HTS) helps clear secretions in CF patients
  - Draws salt and water back into dehydrated airways, rehydrating them and aiding in secretion clearance
  - Adding HTS to regimen reduced hospital stays by 56%
  - Also showed that CF patients who live near the ocean (approx 15 miles) live an average of 10-20 years longer.
  - Subjective assessments by CF patients showed marked improvements and overall feeling “better”
  - My own experience with HTS and ocean

Medications

- 2010 – FDA approved Cayston®, inhaled antibiotic (aztreonam).
- 2012 – FDA approved ivacaftor (Kalydeco®) by Vertex Pharmaceuticals for people with G551D mutation, ages 6 and older.
  - First drug to attack the root cause of CF → CFTR
  - Works at the cellular level to open chloride channels
  - During clinical trials, patients showed highest increase in lung function ever seen in any clinical trial of a CF drug. Some as high as 30% increase in FEV1.
  - Approx 3% of CF patients have G551D mutation.

Medications

- 2014 - FDA approved ivacaftor to treat patients 2 and older for G551D and 9 other rare mutations. (8% U.S. CF population)
- 2015 – FDA approved ivacaftor/lumacaftor (Orkambi®) for CF patients 12 and older with two copies ΔF508. (1/3 U.S. CF population)
- 2016 – FDA approved Orkambi® for kids 6-11 (added 2,400 children to # being treated)

Medications/Delivery Devices

- TOBI podhaler®, Cayston®
- Portable devices allow for ease of travel and flexibility
- Neb machines/cups - better particle size and deposition leading to more effective treatments
- Better equipment/new technology leading to shorter treatment times
  - Focus now is reducing treatment times so patients can lead more “normal” lives.
  - As patents run out, it opens the door for competition. Lower costs. Competition drives results! Great news for patients!

Lung Transplantation

- Around 150-200 people with CF receive lung transplants every year. (>250 in 2015)
- Thanks to UNOS (United Network of Organ Sharing) more people are receiving transplants who need them most and less are passing away while on the list.
- Prior to 2005, patients were placed on the bottom of the list and rose to the top based on time spent on the list.

Lung Transplantation

- Now with UNOS, patients are given a "lung allocation score" based on how sick they are and how likely they are to stay healthy post transplant
- Scoring done every 6 months on a 0-100 scale
  - Health pre-transplant (physical, mental, emotional)
  - Projected health post-transplant (physical, mental, emotional)
  - Disease diagnosis (CF, IPF, COPD, etc.)
  - Health Factors (DM, use of Home O2 or Ventilator, etc.)

Lung Transplantation

- Success of transplantation is measured by average length of survival post-transplant
- CF patients
  - Over 80% alive after 1 year
  - Over 50% alive after 5 years
- Survival continues to climb as technology advances and more discoveries are made about why rejection occurs.

Secretion Clearance

- Medications are only one piece of the puzzle

"It is like oatmeal that has been left on the stove too long. Their mucus becomes difficult to clear and, as a result, the lungs get obstructed, infected and inflamed."

-Dr. Preston Campbell III

Pediatric Pulmonologist at John Hopkins Hospital in Baltimore

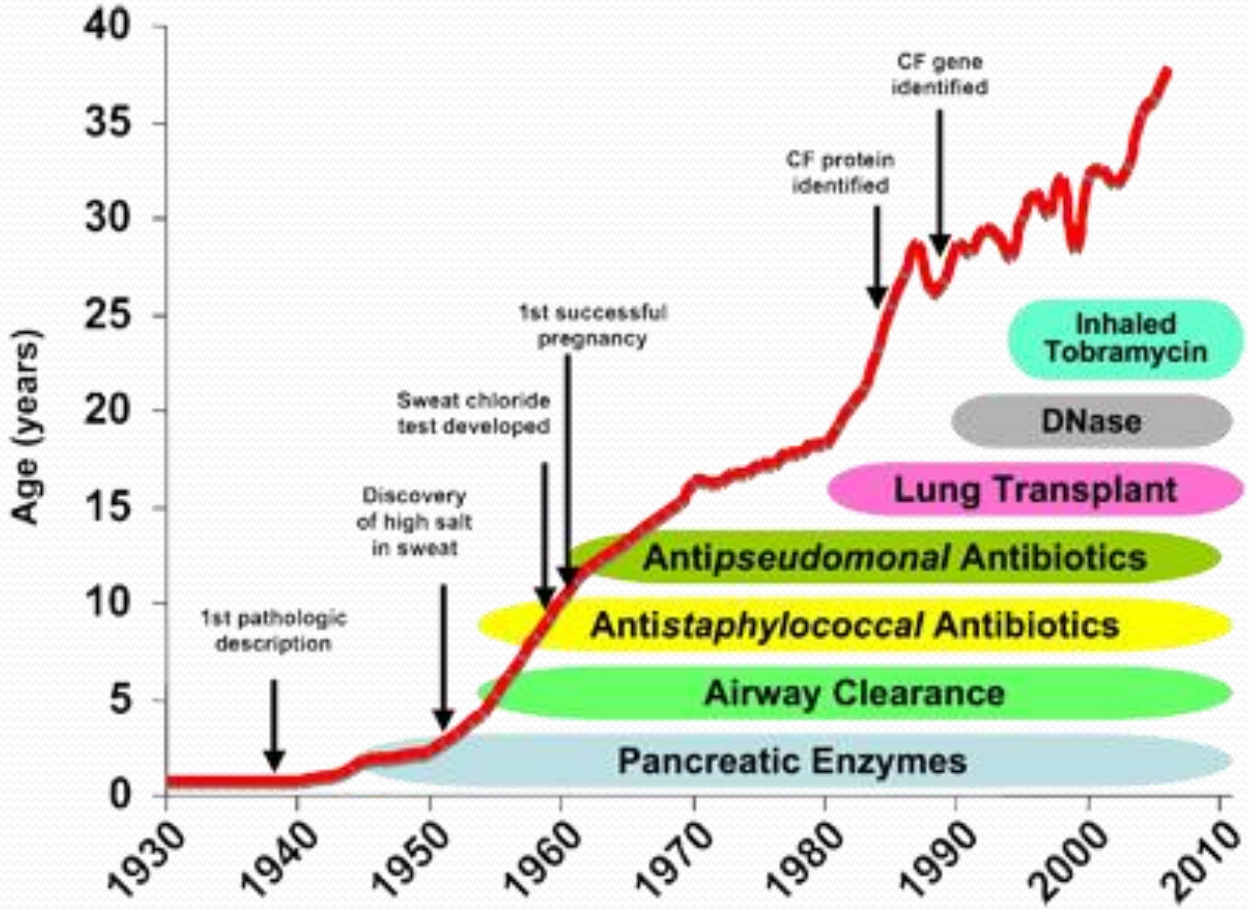
Secretion Clearance

- Many options:
  - Vest, IPV, PEP devices, etc.
- Now more portable options as well
  - Afflovest, Portable IPV, smaller machines that fit in carry-on space on planes
    - Allows for more flexibility, and more “normal” lives
- Exercise!!
  - We’ve learned is the BEST option for secretion clearance and overall health
  - Many non-profits give grants and offer other solutions to help CF patients become more active and exercise.
    - CysticLife, Rock CF Foundation, Cystic Fibrosis Lifestyle Foundation, etc.)

Life Expectancy

- Median not average survival age
- 1955 – Median survival age 5 years old
- 1962 – 10 years old
- 1981 – 20 years old
- 1985 – 25 years old
- 2005 – 37 years old
- 2014 – 41 years old

Life Expectancy



Future of CF

- Goal: Make Cystic Fibrosis a controlled disease, like asthma.
- "We need to focus not only on developing therapies that treat the downstream effects of the disease but also on therapies that are further upstream – those that can intervene early and either improve complications that arise or prevent them entirely"

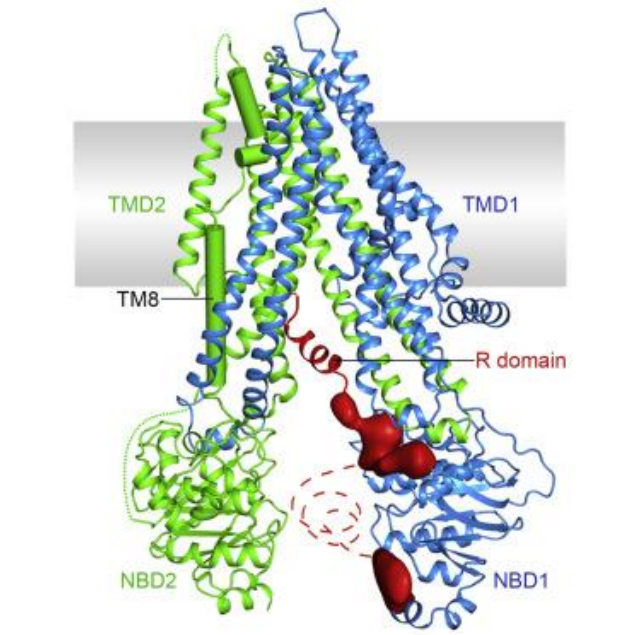
  - Dr. James Acton Cincinnati Children's Hospital
- CFTR Medications are where it's at! **GAME CHANGERS!**
  - Correctors/Modifiers – Correct the function of faulty CFTR protein
  - Potentiators – "Boost" the faulty CFTR protein

Future of CF

- Tezacaftor (VX-661) and ivacaftor (Kalydeco®)
  - Patients w/1 or 2 copies of ΔF508
  - Phase 3 trial showed 6.8% improvement in Fev_1
    - Double what Orkambi® showed
  - Has a more favorable safety profile
- CTP-656 (Vertex bought from Concert Pharmaceuticals)
  - Well tolerated in Phase 1 trial
  - Outperformed Kalydeco!
- QR-010 (ProQR Therapeutics)
  - Reported to <u>restore</u> CFTR function

Future of CF

- Researcher at Rockefeller University mapped the 3D structure of the CFTR Protein
  - Paves the way for further research
  - More focused medications to resolve problem with CFTR function



Future of CF

- CF Foundation sold rights to all future royalties for drugs developed and sold by Vertex for $3.3 Billion to Royalty Pharma in 2014.
  - CFF invested $150 million
  - Speaks volumes for the expected results from drugs in the pipeline.

CFTR Medications in Pipeline

PTI-428

Cavosonstat (N91115)

CTP-656 (Deuterated ivacaftor)

Riociguat

Editas

Tezacaftor (VX-661) + ivacaftor

VX-659 + tezacaftor + ivacaftor

Orkambi®

Kalydeco®

Genzyme/Sanofi

QR-010

QBW251

VX-152 + tezacaftor + ivacaftor

FDL169

VX-440 + tezacaftor + ivacaftor

Reata

GLPG2222

Pfizer

Southern Research Institutes

"It's not the same disease we saw years ago. The outlook for patients with cystic fibrosis has changed dramatically. There are a number of therapies on the horizon that will either lead to a cure or a very definitive control of the disease."

- Dr. Carlos Milla

Associate professor at Lucile Packard Children's Hospital

Stanford University

Krista Marie Parks

Jan. 26, 1982 – Sept. 2, 1982

33 year old CFer with his wife of 7 years, 4 yr old twins, and 2 year old son.

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