Advances in CF therapies and their effect on GI manifestations

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Presenter Disclosure

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Relationship related to this presentation

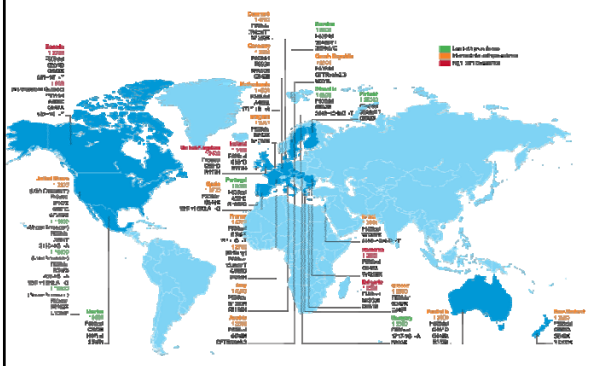
Cystic Fibrosis Foundation Therapeutics grant support
Vertex- Medical advisory board, consultant

Learning Objectives

- **Outline pathophysiology of CF and impact of CFTR on clinical manifestations**
- **Recognize gastrointestinal manifestations of CF and therapeutic interventions**
- **Outline recent development and advances in CF therapy targeting specific genetic mutations**
- **Discuss role of Wireless Motility Capsule (WMC) as gastrointestinal biomarker of CFTR activity**

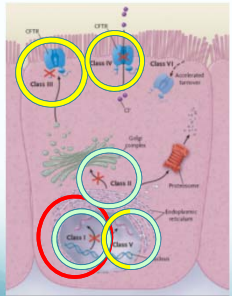
Pathophysiology of Cystic Fibrosis

- Cystic fibrosis (CF) is a disease of dysfunctional **C**ystic **F**ibrosis **T**ransmembrane **R**egulator protein (CFTR) inherited in autosomal recessive pattern (chromosome 7)
  - Channel controlling flow of Cl^-, H_2O, HCO_3^-
  - Dysregulation of fluid transport, increased viscocity in pulmonary, gastrointestinal (enteric, liver, pancreas) and reproductive organs
  - pH control through bicarbonate regulation
- ~ 2000 CFTR mutations identified
  - 127 are CF causing mutations (www.CFRT2.org)
    - (F508del ~88%)
  - 11 mutations in US with a frequency of >1%
  - 23 mutation with a frequency of >0.1%
- Severity of the mutations are based on the underlying mechanism causing CFTR dysfunction

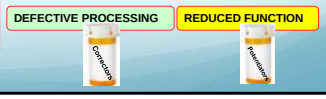


Adopted from www.cftrscience.com/?q=epidemiology

Classification of CFTR dysfunction



- Class I – Defective production
- Class II – Defective processing
  - F508del
- Class III – Defective Regulation (Gating defect)
  - G551D
- Class IV – Defective conductance
- Class V – Reduced amount



Adopted from Rowe SM et al., New Engl J Med 2005

How are organs affected by CFTR?

- Primary (luminal obstruction):
  - Skin (sweat gland)
  - **Lung** involvement with obstructive / restrictive respiratory disease

  - **Gut** involvement
    - CFTR present in a cephalad-caudal & crypt-villus gradient
  - Reproductive tract

- Scondary (parencymal involvement):
  - Alveoli, pancreatic acini
  - Hepatic tissue

CFTR drives bicarbonate (HCO_3^-) secretion

- Drives ionic content & fluid flux on epithelial surfaces
- Facilitates dense mucins secreted by goblet cells to unfold by changing pH and interfering with Ca^+ to become slippery
- Contribution to innate immunity
  - Trap microorganisms and facilitate defensins reaching the lumen
  - Antimicrobial protein activity is optimized at neutral pH
- Duodenum
  - large volume of bicarbonate secretions from mucosal epithelium, Brunners glands, ductal epithelium of pancreatic and biliary tracts is required to neutralize gastric acid
  - Pancreatic enzymes activity is pH dependent
  - Micelle formation is pH dependent

Borowitz, Pediatr Pulmonolo2015 Oct;50 Suppl 40:2S4-S30

Impact of CFTR defect on GI pH

- **Decreased bicarbonate secretion**

  Lack of gastric buffering, leading to:

  - ↓ Nutrient breakdown and absorption
    - ↓ Enzymatic activities
    - Precipitation of micelles
  - ↓ Hydration of the mucosa
  - Prolonged small bowel acidification
  - Immune dysregulation → altered microbiome

Boomerang of CF related GI disease

- Clinical features of CFTR dysfunction in GI tract precedes respiratory manifestations
  - In-utero onset with pancreatic destruction, early onset malabsorption, meconium ileus
- Aggressive nutritional intervention, PERT
  - Patients no longer die of malnutrition
  - Respiratory disease - predominant cause of mortality
- Advancements in Respiratory therapy with antibiotics, new therapies → improved life expectancy
- With improved overall survival and optimization of pulmonary therapy emphasis changes to GI related complications of CF disease

Meconium Ileus (MI)

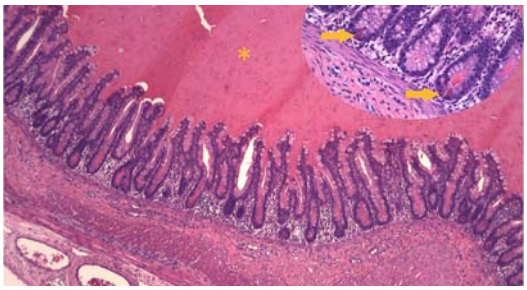
- Thick secretions in fetus → neonatal obstruction
- Incidence 13-17% among CF newborns*
  - More common common in infants with Class I-III mutations (F508del, G542X, W1282X, R553X, G551D)
  - Gene modifiers (4q35.1, 8p23.1, 11q25, 19q13) **
  - 53.5% of infants with MI are diagnosed with CF **
- Proposed pathophysiology:
  - Defective HCO_3^- excretion in utero likely causes acidic and dehydrated luminal environment
  - Not related to lack of pancreatic enzymes (CF mouse model with MI has normal pancreatic function)
- Treatment with enema irrigation vs. surgery

*Curr Gastroenterol Rep (2011) 13:265–270
Gorter, R, et. al. Journal of Pediatric Gastroenterology and Nutrition, 2010. **50(5): p. 569-572

Distal Intestinal Obstruction Syndrome (DIOS)

- Viscid fecal material with strong adhesion to villi and crypts of the mucosa in the TI
  - No gene modifiers as seen in MI
  - More common in patients with prior history of MI
  - Possible pathophysiology:
    - Combination of inherent deficiency of luminal bicarbonate along with altered motility and pancreatic insufficiency
- Prevalence 7-8% in children; 14-16% in adults

Intestinal segment of a CF patient with obstruction



* Viscid fecal material with strong adhesions to the mucosa and crypts
Yellow arrows = "constipated goblet cells"

DIOS

- Abdominal pain, vomiting and distention with palpable right sided mass and complete or partial obstruction
  - May mimic constipation & often occur concurrently
    - Chronicity and distribution of stool on imaging
  - May mimic appendicitis
    - Incidence of appendicitis is NOT greater in CF vs. control
- Treatment mostly with osmotic stool laxatives (PEG)
  - N-acetylcysteine may be used as a mucolytic PO / PR
  - Gastrografin enema refluxed to terminal ileum
- Prevention: adherence to PERT and osmotic stool laxatives

CF related Pancreatic disease

- Pancreatic Insufficiency (PI)
  - 85% of CF patients cared for in US
  - In utero destruction of the pancreas in ~60% of newborns
    - "Plasticity" of pancreatic function in others may be an opportunity to improve and recover function with early intervention
    - Basis of Immunoreactive trypsinogen (**IRT**) –newborn screening
  - Lifelong **P**ancreatic **E**nzyme **R**eplacement **T**herapy (PERT)
- Pancreatic sufficiency (PS)
  - 10-15% of CF subjects
    - Usually have at least 1 Class IV or V mutation
  - May develop PI
  - At risk of developing pancreatitis

Small Bowel Bacterial Overgrowth

- Increased predisposition in CF patients
  - Thick secretions
    - Provide media for bacterial growth
    - Obstrutc secretion of luminal defensins from Paneth cells
    - Adhere to epithelial mucosa
  - Malabsorbed nutrients
    - Bacteria deconjugate bile acids
  - Altered intestinal motility with slow transit in the small bowel = intestinal stasis
    - ↑# of bacterial organisms in the upper GI tract
  - Chronic use of antibiotics
- Therapy with enteric antibiotics, osmotic laxatives, (?probiotics)

Cystic Fibrosis Related Liver Disease (CFLD)

- Transient elevation of hepatic enzymes ≠ CFLD
  - 50% of young children and infants with CF
  - Normalizes within 2–3 years of age
- Spectrum of hepatobiliary disease
  - Cholelithiasis, biliary tract ductal stones, microgallbladder
  - Hepatic steatosis, nodular regenerative hyperplasia
  - Focal biliary cirrhosis and portal hypertension

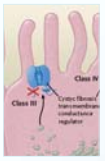
Common GI diseases in CF patients

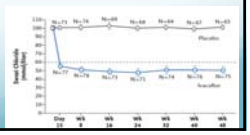
- GERD
  - 6-8 fold greater in CF population
  - Conventional therapy with acid suppression or more aggressive surgical interventions in complex disease
  - Long term therapy to improve PERT availability
- Constipation
  - Common in CF
- Increased incidence in CF population
  - Inflammatory Bowel Disease (second hit hypothesis)
  - Celiac disease 2-3 fold increase* (TTG might be false positive)
  - Gastrointestinal cancer in organs with higher CFTR expression

* Fluge G., Co-morbidity of cystic fibrosis and celiac disease in Scandinavian cystic fibrosis patients. J Cyst Fibros 2009;8:198–202

Therapeutic approach to Class III Gating mutations

- Ivacaftor first mutation specific drug for CF (Approved by FDA Jan'12 for treatment of G551D, label now expanded to include other mutations)
  - CFTR potentiator that improves ion channel activity
    - ↓ Sweat Cl^-
    - ↑Lung function and ↓pulmonary exacerbations
    - Improved nutritional status





Ramsey et al., N Engl J Med. 2011 Nov 3;365(18):1663-72

Therapeutic approach to Class II Folding mutations

- Lumacaftor + Ivacaftor – first combination therapy (approved by FDA July'15 for treatment of F508del/F508del)
- CFTR corrector + potentiator that improves ion channel activity
  - ↑ lung function and ↓ pulmonary exacerbations
  - No effect on sweat chloride
  - Modest improvement in nutritional status

Wainwright et al., N Engl J Med. N Engl J Med. 2015 Jul 16;373(3):220-31

Adopted from Rowe SM et al., New Engl J Med 2005

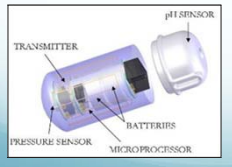
GOAL Study

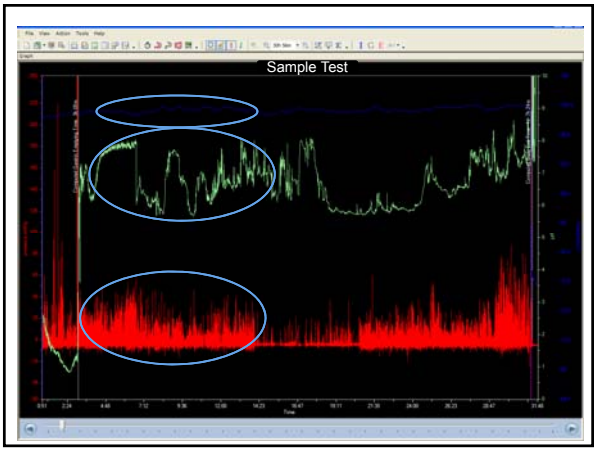
- Multicenter observational study of CF patients with G551D mutation before and after taking ivocaftor
  - Clinical and QOL outcomes, biomarker collection
  - Multiple sub-studies
- Nested study of Intestinal pH and motility
  - Evaluate intestinal pH parameters (indirect measure of luminal bicarbonate) before and one month after therapy with ivacaftor
  - Improvement of CFTR function hypothesized to improve CFTR dependent bicarbonate secretion

Wireless Motility Capsule (WMC)

Ingestible capsule system that measures:

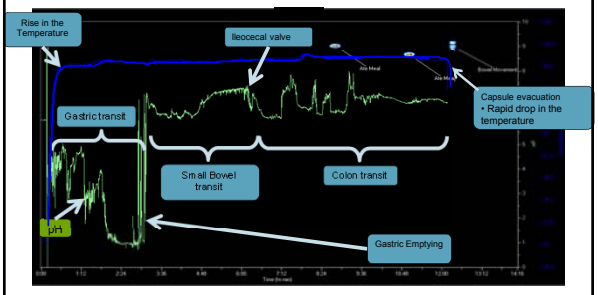
- pH
- Pressure
- Temperature
- Regional GI transit (Motility)
  - Gastric (GET)
  - Small Bowel (SBTT)
  - Colonic (CTT)
  - Whole Gut (WGTT)



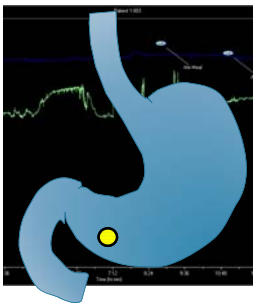


Wireless Motility Capsule Study

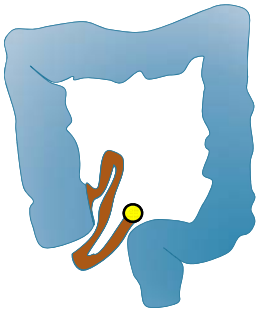
- Ingestion = increased temperature
- Gastric emptying = Increased pH
- Ileocecal transit = pH drop (delayed contractions)
- Capsule exit = Loss of signal ± temperature drop



Gastric Emptying



Delineation of Ileo-cecal transit

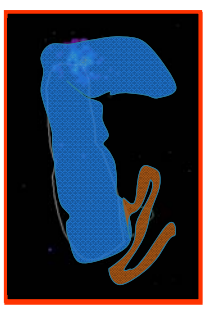


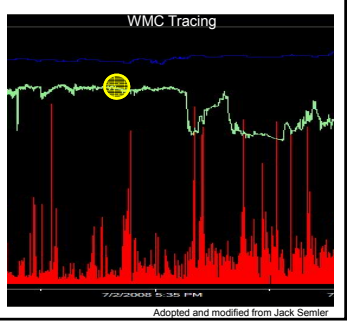
- With capsule entering colon:
  - Change in pH (-1)
  - Change in frequency of contractions (↓)

Confirmation of Ileo-cecal transit

Location: Pill in [illegible] into ascending colon Ph 7.6

7.5

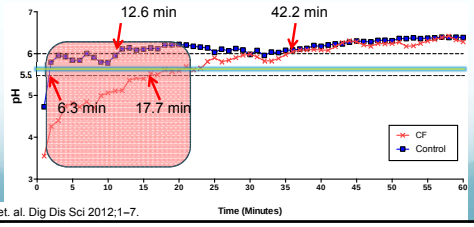




Adopted and modified from Jack Semler

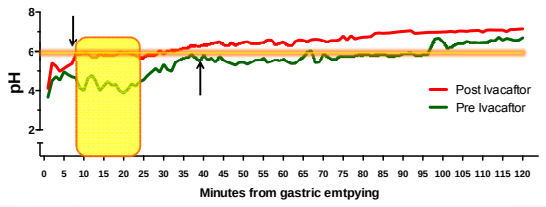
Small bowel pH profile in CF vs. Healthy controls

- Deficient neutralization of gastric acid in CF subject
- Difference between mean pH values
  - 2-22min (p<0.05)
- Time required to reach and sustain pH 5.5 and 6.0 (p<0.01)
  - pH valued needed for dissolution of enteric coating of PERT



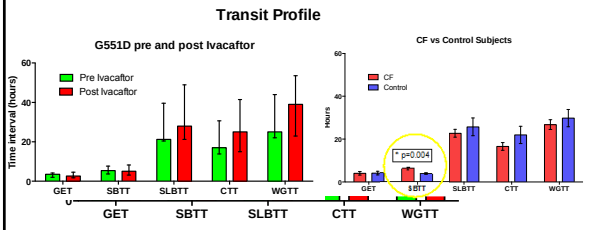
Gelfond et. al. Dig Dis Sci 2012;1–7.

Normalization of intestinal pH with ivacaftor therapy



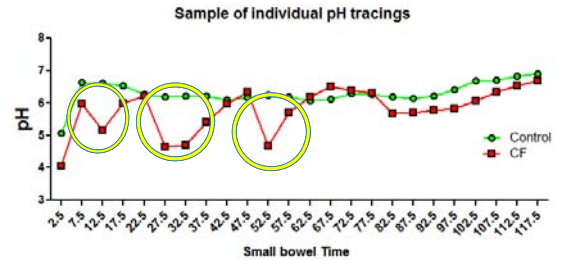
- Improvement of proximal SB pH [8-24min] (p<0.05)
- Time require to reach and sustain pH>5.5
  - Pre Ivacaftor – 40 min; - Post Ivacaftor - 8 min (p<0.002)
- Average 1.1kg of weight gain (1 month) (p=0.08)

Transit profiles in G551D subjects



- No change in transit profiles pre and post therapy (1 m)
- In contrast to CF vs Control observations with SB delay
- Longer duration of therapy?

Can intestinal pH evaluate or predict SBBO?



- Regional acidification of the luminal contents in the small bowel
  - Bacterial fermentation
  - Carbohydrate malabsorption
  - ?Role of probiotics / Antibiotics

Future directions

- Evaluate new modalities in the GI testing to guide clinical care and future research
  - In vivo measurement of intestinal pH (HCO_3^-) as a biomarker of CFTR activity
    - Verified in Patients with G551D on ivacaftor
    - To be evaluated in F508del homozygotes on lumacaftor +ivacaftor
- Roles of CFTR therapy in non CF diseases
  - Pancreatitis
  - Intestinal dysmotility
- Translate lessons learned from CF animal models to patients