Advances in CF therapies and their effect on GI manifestations

Daniel Gelfond, MD
University of Rochester
WNY Pediatric Gastroenterology

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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 Cystic Fibrosis Transmembrane Regulator protein (CFTR) inherited in autosomal recessive pattern (chromosome 7)
  - Channel controlling flow of Cl-, H2O, HCO3-
  - Dysregulation of fluid transport, increased viscosity in pulmonary, gastrointestinal (enteric, liver, pancreas) and reproductive organs
  - pH control through bicarbonate regulation
- ~ 2000 CFTR mutations identified
  - 127 are CF causing mutations (www.CFTR2.org)
  - 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

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
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
- **Secondary (parenchymal involvement):**
  - Alveoli, pancreatic acini
  - Hepatic tissue

CFTR drives bicarbonate (HCO₃⁻) secretion

- Drives ionic content & fluid flux on epithelial surfaces
- Facilitates dense mucins secreted by goblet cells to unfold by changing pH and interfering with Ca²⁺ 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, Brunner’s 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

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

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**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 HCO3⁻ 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

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**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 Pancreatic Enzyme Replacement Therapy (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
- Obstruct 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

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


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


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

Adapted from Rosen SB et al., New Eng J Med 2005
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

Sample Test

- Rise in the temperature
- pH drop (delayed contractions)
- Capsule evacuation = 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 through Ileo-cecal valve into ascending colon Ph 7.6

Adopted and modified from Jack Semler WMC Tracing
Small bowel pH profile in CF vs. Healthy controls
- Deficient neutralization of gastric acid in CF subject
- Difference between mean pH values
  - 2-22 min (p<0.05)
- Time required to reach and sustain pH 5.5 and 6.0 (p<0.01)
  - pH value needed for dissolution of enteric coating of PERT
- 12.6 min
- 42.2 min

Normalization of intestinal pH with ivacaftor therapy
- Improvement of proximal SB pH [8-24 min] (p<0.05)
- Time required to reach and sustain pH>5.5
  - Pre Ivacaftor – 40 min; Post Ivacaftor – 8 min (p=0.002)
- Average 1.1 kg 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 (HCO₃⁻) 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