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Intractable Diarrhea and Steatorrhea after Initiation of Ivacaftor/ Lumacaftor in a Child with Cystic Fibrosis and a History of Meconium Ileus and Small Bowel Resection

Christopher M. Oermann

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Christopher M Oermann, MD
Division Director, Pulmonary and Sleep Medicine
Center Director, Cystic Fibrosis Care Center
Children's Mercy Kansas City
Kansas City, Missouri

NORTH AMERICAN CYSTIC FIBROSIS CONFERENCE
CYSTIC FIBROSIS FOUNDATION

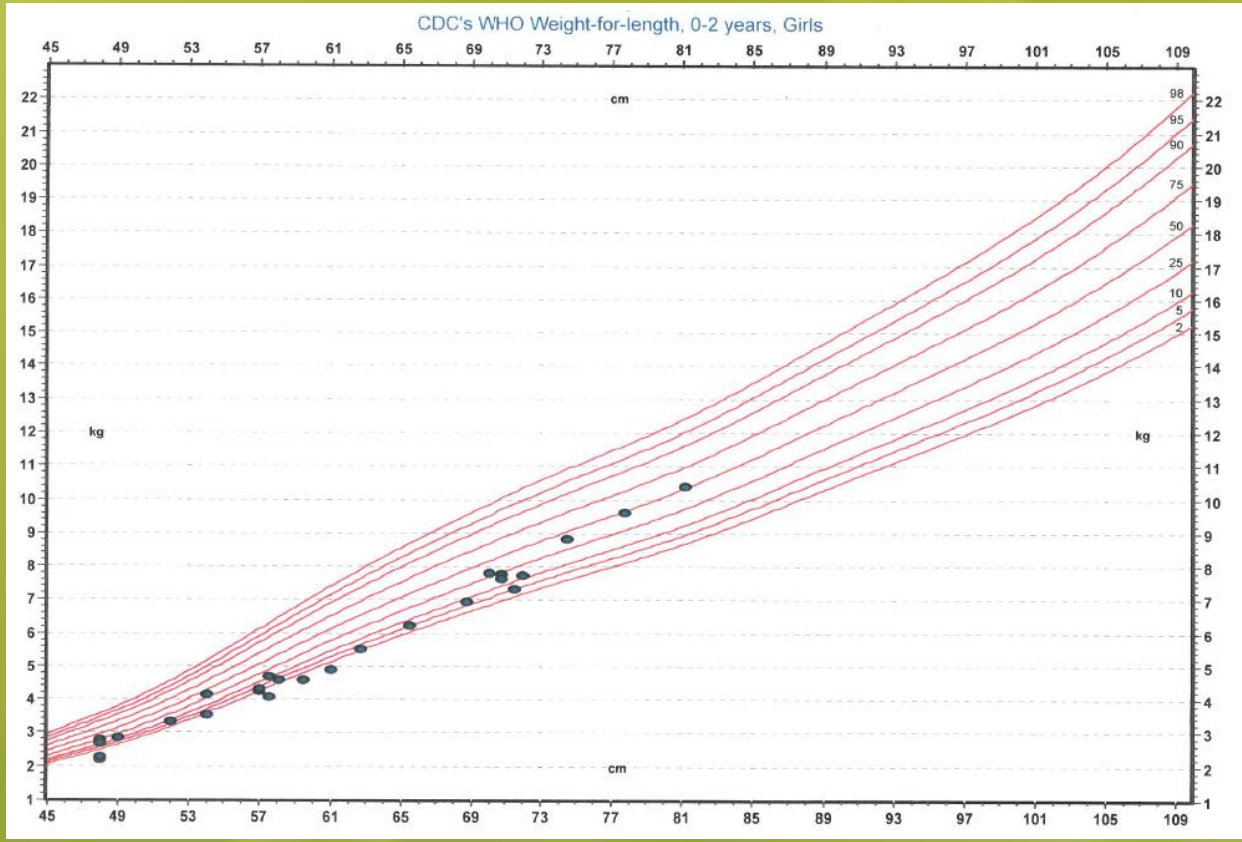
Presenter Disclosure

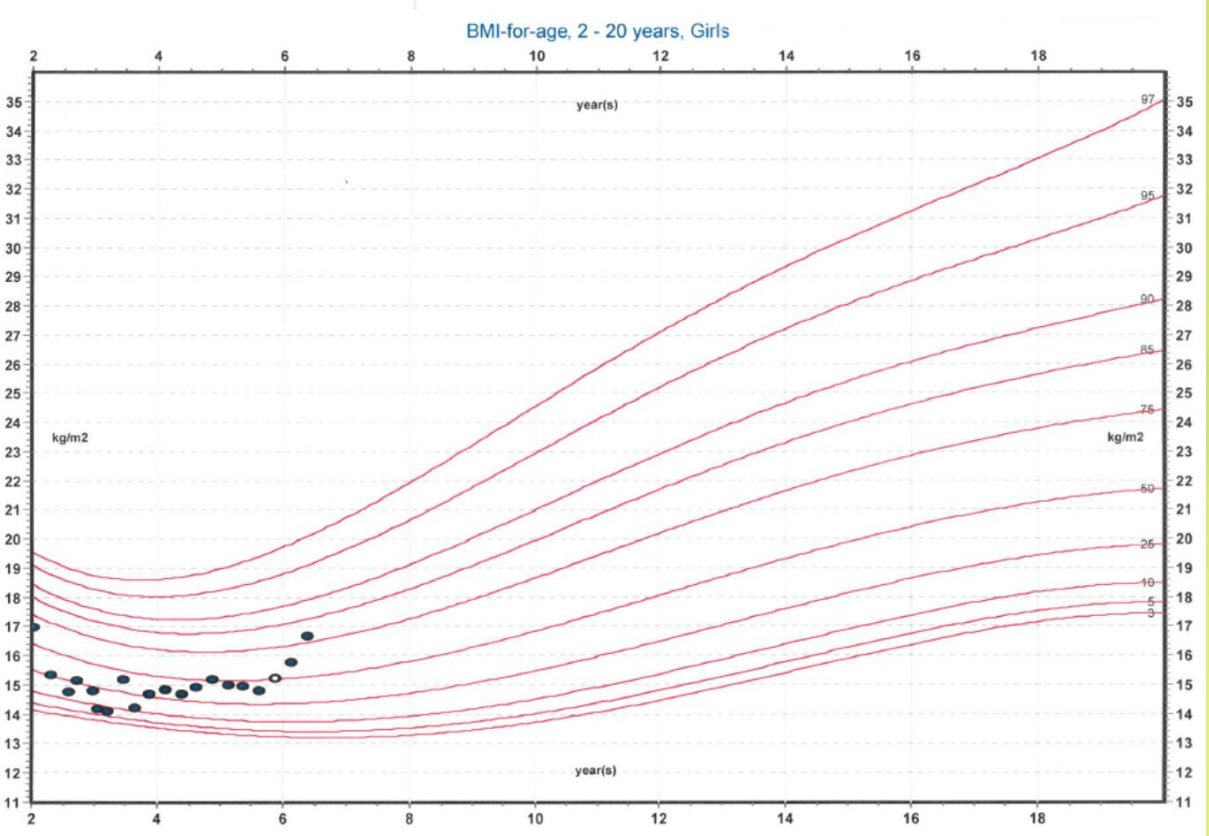
Christopher M Oermann, M.D.

There are no relationships to disclose related to this presentation.

Background

- LB is a 6-year old with pancreatic insufficient CF
- Delivered at 35 weeks EGA and diagnosed with meconium ileus
  - Segmental resection of 7 cm of the distal ileum and ileostomy
  - Ileostomy take-down at 8 weeks of age
- Intermittent use of TPN but discharged from NICU at 3 ½ months of age on full oral feedings
- Intermittent gastrointestinal issues and poor growth early in life





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Ivacaftor/Lumacaftor Therapy

- Medications
  - Pancreatic enzyme replacement therapy (16,000 lipase units/capsule; 4 capsules with meals and snacks [3,200 lipase units/kg/meal])
  - H_2 blocker
  - Fat-soluble vitamin supplementation
  - Bronchodilator therapy prior to assisted airway clearance BID
  - 7% saline BID
  - Dornase alfa QD
- BMI at the 63rd percentile
- FEV_1 was 95% of predicted
- Ivacaftor/Lumacaftor (100mg/125mg), 2 tablets BID, started

- Day 2: increased cough; increased number of stools with steatorrhea, abdominal distension, mild discomfort
- Day 5: cough resolved; number of stools, steatorrhea, and GI symptoms did not improve
- Day 14: bowel prep with polyethylene glycol without improvement
- Day 21: ivacaftor/lumacaftor (100mg/125mg) dose changed to 1 tablet BID; improvement in symptoms but continued increased stools and steatorrhea
- Day 28: PERT increased to 5 capsules with meals (4210 lipase units/kg/meal) without improvement

- Day 56: H_2 blocker changed to PPI without change in symptoms
- Stools studies sent for comprehensive infectious diarrhea panel
  - Shiga toxin and *Campylobacter* antigen negative
  - *Giardia*, *Cryptococcus*, and *Entamoeba* tests negative
  - *Salmonella* and *Shigella* cultures negative
- Day 70: ivacaftor/lumacaftor therapy discontinued following long conversation with the family

Discontinuation of Therapy

- Stooling pattern returned to normal within 48 hours of discontinuation of ivacaftor/lumacaftor therapy
  - Normal number of stools
  - Complete resolution of steatorrhea
- No change in normal stooling pattern after return to routine PERT dosing and H_2 blocker

Discussion Points

- What are the physiologic effects of CFTR modulators on the GI system?
- Is there something about patients with a history of MI and small bowel resection that places them at increased risk for poor gastrointestinal tolerance of CFTR modulators?
- What are therapeutic options for this child moving forward?

Effects of CFTR Modulators on the GI Track

- Improved HCO_3^- secretion and intestinal pH[1,2]
- Fecal elastase increases[3,4]
- Discontinuation of PERT (2 case reports)
- Biliary function?
- Alteration in GI microbiome?

1. Gelfond et al. Clin Transl Gastroenterol. 2017 Mar 16;8(3):e81. doi: 10.1038/ctg.2017.10.
2. Borowitz et al. Dig Dis Sci. 2016 Jan;61(1):198-207. doi: 10.1007/s10620-015-3834-2.
3. Rosenfeld et al. Lancet Respir Med. 2018 Jul;6(7):545-553. doi: 10.1016/S2213-2600(18)30202-9.
4. Ratjen et al. Lancet Respir Med. 2017 Jul;5(7):557-567. doi: 10.1016/S2213-2600(17)30215-1.

Meconium Ileus, Bowel Resection, and CFTR Modulators

- The Theory
  - MI with resection resulted in "anatomic short gut"
  - CF resulted in abnormal luminal contents and decreased motility ("physiologically slow gut")
    - **"anatomic short gut" + "physiologically slow gut" = "functionally normal gut"**
  - Treatment with ivacaftor/lumacaftor resulted in normalized luminal contents and improved motility ("physiologically normal gut")
    - **"anatomic short gut" + "physiologically normal gut" = "functionally short gut syndrome"**

Where do we go from here?

- Reintroduce ivacaftor/lumacaftor with motility or biliary modulating agent
- Reintroduce ivacaftor/lumacaftor or other modulator when GI effects are more acceptable
- Other?

Thank You!

Questions?