Cystic Fibrosis Cases for NASPGHAN
Meet the Professor: Maria Mascharenhas, MD and Meghana Sathe, MD

Case 1:

A 10 year old girl with delta 508/V456A with history of pancreatic sufficiency presents to the CF Clinic for concern of poor weight gain over the last year. She has crossed percentiles by 2 standard deviations for weight and height over the last 1 year. Her lung health has been good with no changes in FEV. She has not been hospitalization for any pulmonary excaberation. She was hospitalized three times during the last 2 years for severe acute recurrent pancreatitis. She recently had an MRCP about 2 months ago that showed multiple strictures in the pancreatic duct.

What else do you want to know about patient?

What do you suspect is the cause of her poor weight gain and overall growth?

How would you confirm diagnosis?

Which patients with CF get pancreatitis?

How would you treat our patient?

Case 2:

You are called by the NICU that they were transferred a baby from a rural NICU who is an ex-34 week GA. He has an ileostomy – they are unable to decipher from notes why the ileostomy was done. They did find a newborn screen that showed a really high IRT and 1 positive delta 508 mutation. They need help with managing patient. In one transfer note, they were able to find that no bowel was resected. However, patient is not gaining weight and is currently on continuous feeds.

What do you suspect was the most likely cause of her ileostomy in which an ileostomy was created but no bowel resected?

What explains the high IRT? What is IRT and why is it used in newborn screening?

What is your recommendation to confirm diagnosis?

You confirm diagnosis of pancreatic insufficiency based on low fecal elastase – how would you treat this patient on continuous feeds?

4 years later, the same patient who was had meconium ileus presents to ER with abdominal distention, vomiting and no BM in 2 days. You haven't seen her in at

least 3 years. Currently, she is on Creon which mom opens and put in applesauce prior to each meal. She still does tube feeding at night – about 2-3 cans of Pediasure Peptide 1.5. Her lungs continue to be healthy. The ER resident is concerned about possible appendicitis as her pain is in RLQ.

What is your differential diagnosis?

What is treatment for DIOS?

What are risk factors for the development of DIOS?

2 years later, the same patient comes back to you with history of plateauing of weight at around the 25% percentile, height is at 50%. She has frequent abdominal discomfort/pain and feels bloated. Since her DIOS episode 2 years ago, she has been taking Miralax regularly and is quite complaint with her enzymes. When you check her dosing – she is taking 2500 lipase units/kg/meal and 1250 lipase units/kg/snack She is states that she is eating 4 meals and 4 snacks daily. Total enzyme dose per day 15,000. Despite this she describes occasional running stools. In addition, over the last 6 months, she has been hospitalization 3 times for pulmonary excaberation due to viral illnesses – she has tested positive for rhinovirus, RSV, and influenza A. She also complains of burning in her chest and feeling of food coming up to the back of her throat more often recently. This used to happen maybe once in awhile if she ate too much, now is happening on daily basis.

What is important to know about the history?

What is your differential diagnosis?

How would you treat small bowel bacterial overgrowth?

What is your thought of GERD and CF patient?

How would you treat GERD and Delayed Gastric Empyting?

Case 3:

A 12 year old male is referred to you by the CF pulmonologist due to newly appreciated hepatosplenomegaly. Patient is delta 508 homozygous. He has meconium ileus at birth with minimal resection. His lung function has decreased since his last visit to clinic which was about 2 years ago from FEV1 of 95% to 80% and has remained there for last 3 months. He has also lost weight and is malnourished. Family was without insurance for the last 1 year and so his access to medications including pancreatic enzymes has been limited. His parents also have noted more stumbling and running into furniture at night over the last 3 months.

What is the cause of his hepatosplenomegaly?

Who gets CFALD?

What is the treatment?

What do you think is cause of stumbling and running into things at night?

Vitamin/ Mineral	Absorption	Function	Deficiency	Toxicity	Laboratory Measurement
Vitamin A (retinoid)	- Upper small intestine	- Retinal in rhodopsin and iodopsin - Carbohydrate transfer to glycoprotein - Maintains epithetlial integrity - Required for cell proliferation	- Night blindness - Xerophthalmia - Bitot spots - Keratomalacia	- Alopecia - Ataxia - Muscle and bone pain - Cheilitis - Conjunctivitis - Headache - Hepatotoxicity - Hyperlipidemia	- Retinol - Retinol binding protein - Transthyretin
Vitamin D (Ergocalciferol = D2, Cholecalciferol = D3)	- Skin DIETARY - Rapid uptake in the duodenum and distal small intestine	- Regulates calcium and phosphate - Gut absorption, excretion by kidney, and bone resorption	- Rickets/osteomalacia - Dental caries - Hypocalcemia/hypophosphatemia - Increased alkaline phosphatase - Phosphaturia, aminoaciduria	- Hypercalcemia (N/V, weakness, fatigue, diarrhea, anorexia, headache, confusion, psychosis, and/or tremor) - Hypercalcuria	- 25-OH Vitamin D
Vitamin E	- Primarily jejunum by nonsaturable passive diffusion	- Cell membrane antioxidant - Inhibits polyunsaturated fatty acid oxidation	- Anemia/hemolysis - Neuroligic deficit (Ocular palsy, wide-based gait, decreased DTR's) - Altered prostaglandin synthesis	- Impaired neutrophil function - Abrogated granulocytopenic response to antigen - Thrombocytopenia - Cerebral hemorrhages	- Alpha-tocopherol
Vitamin K	- Jejunum by a saturable, energy-dependent process	- Carboxylation of clotting factors - Affects bone formation	- Coagulation/prolonged PT - Abnormal bone matrix synthesis	- Not well understood	- Most commonly used PT, INR

Reference:
Borowitz D, Baker R, Stallings V. "Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis." JPGN 2002. 35(3):246-259.

FDA Approved Enzyme Brands			
Product/Manufacturer/Dosage Form/Strength	Lipase USP units	Amylase USP units	Protease USP units
Creon® (AbbVie Inc.) Pancrelipase, delayed release capsule			
3,000	3,000	15,000	9,500
6,000	6,000	30,000	19,000
12,000	12,000	60,000	38,000
24,000	24,000	120,000	76,000
36,000	36,000	180,000	114,000
Pancreaze® (Janssen Pharmaceuticals), Pancrelipase, delayed release capsule			
4,200	4,200	17,500	10,000
10,500	10,500	43,750	25,000
16,800	16,800	70,000	40,000
21,000	21,000	61,000	37,000
Zenpep® (Actavis) Pancrelipase, delayed release capsule			
3,000	3,000	16,000	10,000
5,000	5,000	27,000	17,000
10,000	10,000	55,000	34,000
15,000	15,000	82,000	51,000
20,000	20,000	109,000	68,000
25,000	25,000	136,000	85,000
40,000	40,000	218,000	136,000
Ultresa® (Actavis) Pancrelipase, delayed release capsule			
13,800	13,800	27,600	27,600
20,700	20,700	41,400	41,400
23,000	23,000	46,000	46,000
Viokace™ (Activas) Tablet, porcine origin – unofficially crushable			
10,440	10,440	39,150	39,150
20,880	20,880	78,300	78,300
Pertzye® (Chiese) Pancrelipase, delayed release capsule – Bicarb Buffered, contains ursodiol			
8,000	8,000	30,250	28,750
16,000	16,000	60,500	57,500

Enzyme Dosing Guidelines:

Based on units of lipase/kg/meal

< 4 years of age: Begin with 1,000 units lipase/kg/meal

>4 years of age: Begin with 500 units lipase/kg/meal

Can increase up to 2,500 units lipase/kg/meal.

Use caution with doses > 2,500 units lipase/kg/meal. Usually ½ of meal dose is given with snacks

Total daily dose: 10,000 units lipase/kg/day

Based on units of lipase/grams of fat eaten

Infant formula or Breast milk: 2,000-4,000 units lipase/120mL Other solids and liquids: 500-4,000 units lipase/gm fat eaten Mean of 1,800 units lipase/gm fat eaten/day in divided doses. Use caution with > 4,000 units lipase/gm fat eaten.

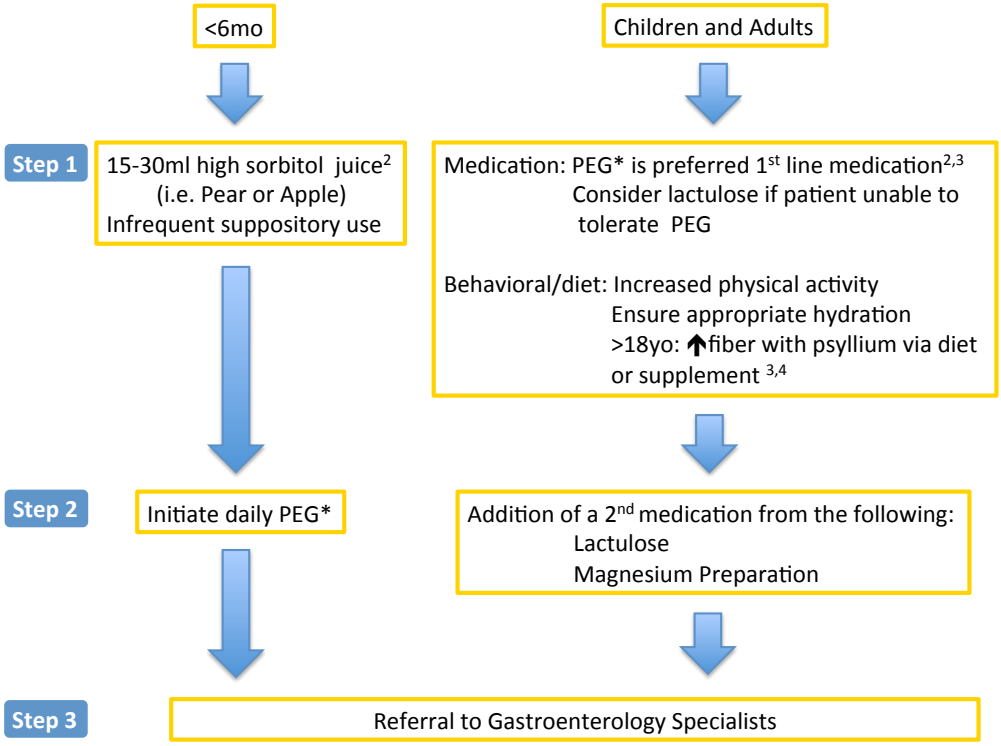
Management of Constipation in Children and Adults with Cystic Fibrosis

Constipation is a common reason for gastrointestinal problems in patients with cystic fibrosis (CF). Symptoms may include flatulence, poor appetite, abdominal pain, infrequent or difficult to pass stool, straining, hard/lumpy stools and prolonged time to stool. Daily bowel movements do not exclude the possible diagnosis of constipation. Untreated constipation can present in a number of ways including but not limited to: bloating, distention, bloody stools, poor weight gain and "overflow" diarrhea.

Diagnosis is made clinically and imaging is usually not warranted. Minimal evaluation includes a stooling history and physical exam, which may show palpable fecal mass in the pelvis (but its absence does not rule out constipation). Perirectal visual inspection can rule out fissures, abscess or rectal abnormality; if present, refer to a GI specialist. In most cases constipation can be managed in the outpatient setting with a plan that includes laxative use, dietary habits and behavioral modifications (see chart below).

Although often categorized together, distal intestinal obstruction syndrome (DIOS) and constipation are distinct diagnoses that are managed differently. DIOS is defined as complete or incomplete intestinal obstruction with fecal mass often in the ileocecum. Constipation with symptoms of obstruction, such as acute abdominal pain with nausea and vomiting warrant imaging to rule out DIOS. Although surgery is seldom indicated, DIOS requires a more intensive treatment regimen, often with inpatient hospital monitoring and advanced imaging[1].

Here we present a basic stepwise approach for providers caring for CF patients suspected of having constipation adapted from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) guidelines[2,3,4].



*See dosing table on next page

Other Considerations:

For some patients, gastroenterology referral may be warranted after failing step 1.

Avoid opiate use. Start concurrent bowel regimen if opiates are necessary.

Both pancreatic insufficient and sufficient patients are at risk for constipation.

There is no evidence to suggest that increased pancreatic enzyme supplementation increases constipation risk.[5]

Prepared for the CFF by Dr. A Jay Freeman and Dr. Monika Kowalczyk

Summary of Medications Commonly Used to Treat Constipation in Children and Adults with Cystic Fibrosis

Generic Name	Trade Name Examples	Dosage	Comments/Side Effects
Glycerin	Pedia-Lax	1 pediatric suppository (only in <6months)	No more than 1x per week
Sorbitol in fruit juice	Apple juice Prune juice Pear juice	15-30 mL once or twice daily	First line therapy in patients < 6 months Abdominal cramps, bloating, flatulence
Polyethylene Glycol (PEG)	Miralax Colyte	<6 months: 1 tsp in 4oz fluid daily <10kg: 1/2 cap in 4 oz of fluid daily 10-22kg: 1 cap in 8oz of fluid daily >22kg and adult: 1 cap in 8oz of fluid up to three times daily	First line therapy in patients > 6 months May see incontinence due to potency Dosing frequency may vary from patient to patient
Lactulose		<6 months: not recommended <10 kg: 1-2g once daily 10-22 kg: 1-2g once daily (max 40g) >22kg to adult: 15-30 mL once or twice daily	Abdominal cramps, bloating, flatulence Decreased Na^+ and increased glucose levels
Magnesium	Milk of Magnesia	<10kg: not recommended 10-22kg: 5 mL daily before bed >22kg and adults: 15-30 mL once or twice daily -or- 2-4 tablets once or twice daily	One to two doses may be sufficient Should not be used continuously > 14 days Caution in renal insufficiency (magnesium toxicity)

References:

1. Colombo C et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. *J Cyst Fibros.* 2011 Jun;10 Suppl 2:S24-8.
2. Tabbers MM et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014 Feb;58(2):258-74.
3. Chang L, Lembo A, Sultan S. American Gastroenterological Association Institute Technical Review on the pharmacological management of irritable bowel syndrome. *Gastroenterology.* 2014 Nov;147(5):1149-72.e2.
4. Ford AC et al. American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation. *Am J Gastroenterol* 2014; 109:S2 – S26.
5. Baker SS et al. Pancreatic Enzyme Therapy and Clinical Outcomes in Patients with Cystic Fibrosis. *J Pediatr*. 2005 Feb; 146(2):189-93.

Cystic Fibrosis Tip Sheet
Meet the Professor: Maria Mascharenhas, MD and Meghana Sathe, MD

IRT (immunoreactive trypsinogen) – basis of newborn screening	• Trypsinogen is a secretory product of pancreas. • Presumably in CF, HIGH levels are observed ONLY in infancy due to leakage of trypsinogen protein into circulation as a result of exocrine pancreatic injury. • Elevated screen MUST be repeated after 7 days of life and prior to 6 weeks. • Once patient has pancreatic insufficiency, IRT level is LOW. Therefore this is not a good screening test outside of the neonatal period. • False negative: Patients with meconium ileus may have low IRT • False positive: Patients with significant prenatal stress or low APGARS • If IRT is persistently elevated, it MUST be further evaluated with sweat chloride or gene screen • If patient has meconium ileus, this MUST be further evaluated with sweat chloride or gene screen • Of note patients with pancreatic sufficiency will not have an abnormal IRT. Sweat chloride is still gold standard if you are suspicious of diagnosis.
GERD	• High risk of GERD due to physiologic increased hyperacidity and physical increase in intra abdominal and intrathoracic pressures from constant coughing. • Treatment is aggressive acidic suppression, sometime lifelong with consideration of promotility agents as these patients are also high risk for gastroparesis. • One thought is that Nissen fundoplication should be avoided if possible as it often comes loose or results in constant retching due to constant coughing.
Gastroparesis	• High risk of gastroparesis, especially post-viral. • Promotility agents should be utilized in management. For post-viral gastroparesis can be utilized temporarily. For chronic gastroparesis, more long-term.
Small bowel bacterial overgrowth (SIBO):	• Increased incidence of SIBO due to following risk factors: frequent and sometimes chronic antibiotic use, malabsorption of nutrients due to pancreatic insufficiency, and previous small bowel surgeries (meconium ileus) leading to some form chronic dysmotility. • Should be considered in patient with increase in gas and bloating. • Treated with metronidazole or rifaximin as frequently as qmonth • Probiotics should be used with caution in patients with ports as bacterial translocation and lactobacillus sepsis has been described in populations with central lines.

Pancreatitis	• Seen in patients with heterozygous mutations for Cystic Fibrosis with 1 severe CFTR mutation and 1 milder mutation. Patients are initially pancreatic sufficient. • Develop chronic recurrent pancreatitis that can result in "burnout" of the pancreas, resulting in pancreatic insufficiency (PI). • Signs and symptoms of PI include increase in stool frequency, steatorrhea, foul smelling stools, weight loss. • Patients with signs and symptoms of PI should be assessed with fecal elastase (easier and quicker than 72 fecal fat test). • Pancreatic enzyme therapy should be initiated for patients with new onset PI. • Patients with 2 severe CFTR mutations already have "burnout" of pancreas and are not likely to develop pancreatitis.
Pancreatic enzymes	• *See enzyme sheet attached for type of enzymes and current dosage forms.* • Pancreatic enzymes contain: Lipase to breakdown fat, Protease to breakdown protein, and Amylase to breakdown carbohydrate. • Two DIFFERENT enzymes: Viokase is a TABLET as is crushable – given either in bicarbonate or mixed in with formula. Pertyze contains Ursodiol and bicarbonate. • All other enzymes are very similar: Creon, Zenpep, Pancrease • If pancreatic enzymes are opened – microspheres should be placed into acidic medium (apple sauce, jelly, ketchup, etc.) to protect the microspheres through the stomach into the basic environment of the proximal small intestine where we want them to be activated. • It is thought that due to hyperacidity in the stomach, that proximal pH of small intestine can sometimes be too acidic to optimize the function of pancreatic enzymes. It is recommended that if enzyme dose is maximized and patients are still exhibiting symptoms of PI (poor growth, steatorrhea) a trial of acid suppression with either H2 blocker or PPI be tried in order improve efficacy of pancreatic enzymes. • Pancreatic enzyme dosing by lipase units/kg/meal OR by lipase units/g of fat eaten. • Overdose of enzymes, mainly based on lipase component, has been associated with the development of fibrosis colonopathy. • Important fact: Increasing dose of pancreatic enzymes does not result in constipation as such, but may result in perceived increase in constipation.
Fat-soluble vitamin management	• *See attached vitamin sheet on how to detect deficiencies and overdoses as well as how to test for.* • Water-soluble vitamin formulations are available on the market, however, none of them contain enough of each individual vitamin. So

	often the best way to supplement is individually. • You should follow vitamins more regularly than on annual labs if you are increasing supplements to treat deficiencies. • Of note, most insurance companies do not cover vitamins. Many of the enzymes companies have some coverage for enzymes.
Constipation/DIOS	• *See DIGEST constipation and DIOS guidelines attached* • High risk of constipation and DIOS or distal intestinal obstruction syndrome. • Thick secretions within the GI tract and malabsorption of nutrients, especially fat can contribute. • Differential diagnosis should include both constipation and DIOS, but also anastomotic stricture, appendicitis, and adhesions.
CFALD (Cystic Fibrosis Associated Liver Disease)	• Spectrum of disease – most common is transient elevations in liver enzymes and fatty liver disease. • Fatty liver disease can be due to malnutrition or innate to cystic fibrosis. Treatment is to optimize nutritional status. • More severe – focal biliary cirrhosis and multilobular cirrhosis. • Focal biliary cirrhosis is where certain areas of the liver are scared, but overall function is preserved and portal hypertension does not occur. This diagnosis most often made on autopsy. • Multilobular cirrhosis most commonly results in portal hypertension. Synthetic function of liver is usually preserved. • Complications of portal hypertension such as GI bleeding from varices or ascites may necessitate TIPs, surgical shunt, or even liver transplantation.