Constipation in infants with Food Allergy and Cystic Fibrosis

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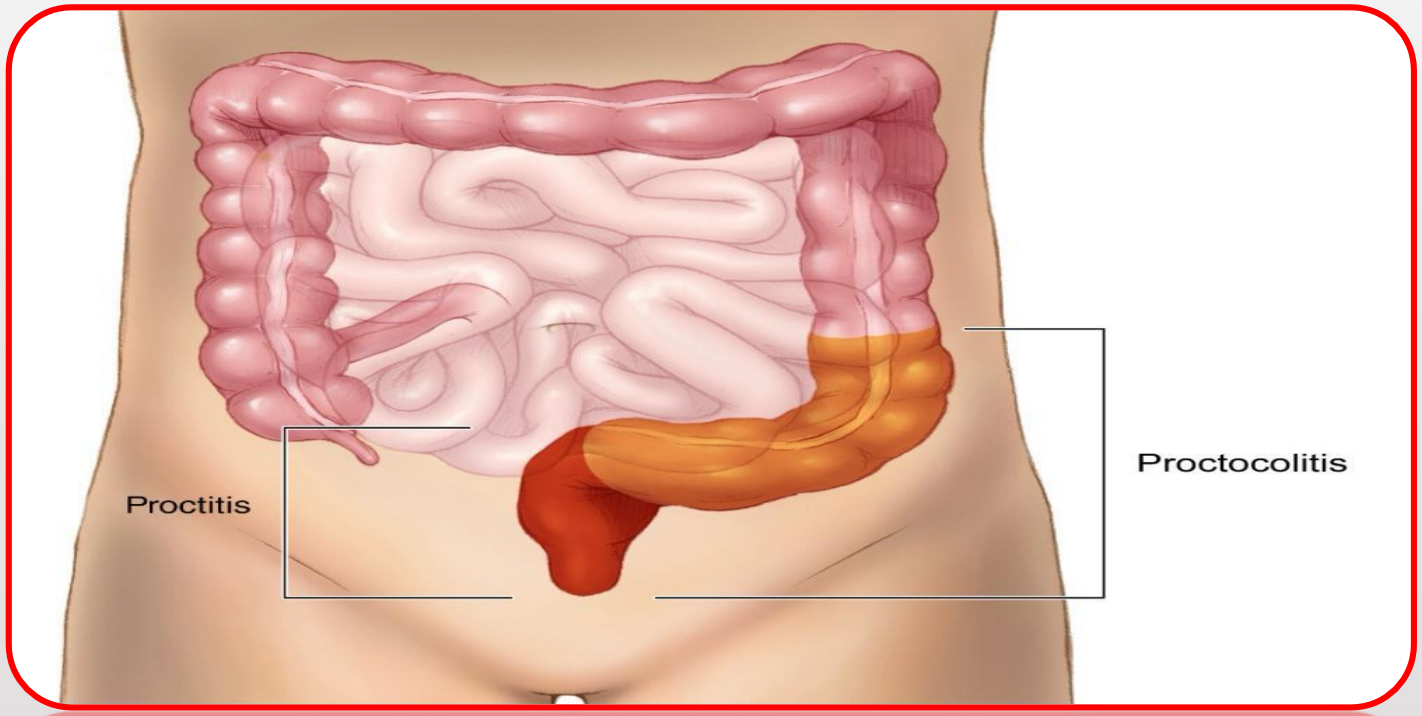
- Constipation in infancy is not merely a symptom , it can be a critical sign of an underlying serious condition
- Two major , and often overlapping , etiologies are :
  - Cow’s milk protein allergy (CMPA)
  - Cystic fibrosis (CF)
- Distinguishing between these two entities is the first and most crucial step in effective patient management

Constipation in food protein allergy (CMPA) :

- When evaluating infants with treatment-resistant constipation , while Cow's Milk Protein Allergy (CMPA) is the most prominent allergic cause , other food allergens can manifest through similar mechanism (primarily non-IgE mediated)
- Common Allergens :
  - Cow's milk protein
  - Soy
  - Egg
  - Wheat
  - Other Gluten-containing cereals
  - Nuts and Peanuts
  - Fish

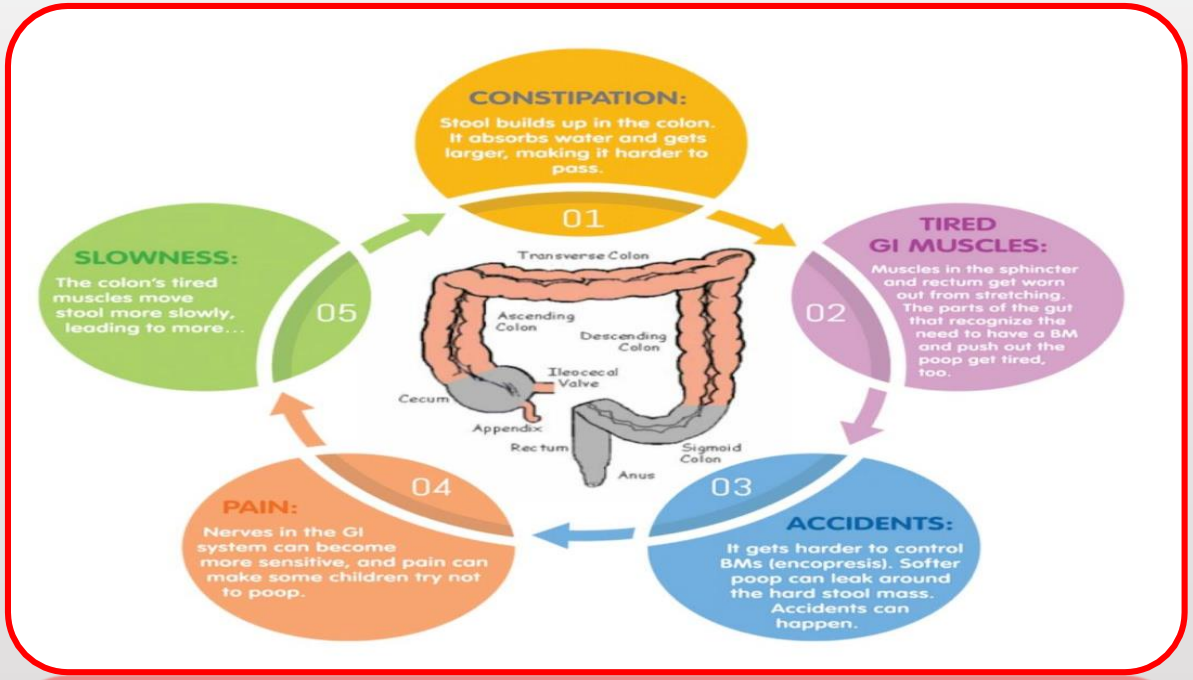
- Constipation can be the sole manifestation or one of the dominant symptoms of non-IgE mediated food allergy syndrome
- In non-IgE mediated CMPA , constipation is primarily a result of a delayed T-cell mediated inflammatory response to dietary proteins (most commonly cow's milk)
- This can lead to allergic proctocolitis , causing inflammation of the distal colon , resulting in painful defecation , anal fissures and functional stool retention



- Epidemiology :

- Overall prevalence of food allergy increasing globally , with a prevalence of 6-8% in children
- Studies show that up to 70% of infants with chronic constipation unresponsive to standard treatments have an underlying food allergy
- Therefore , correct diagnosis prevents wasted time , costs and psychological distress caused by chronic constipation and significantly improves the quality of life for the infant and family

- Pathophysiology :
- Predominant mechanism is : Cell mediated inflammation (non-IgE mediated)
  - Allergen contact with the Gut mucosa then activation of Lymphocytes and Mast cells then release of Cytokines and inflammatory mediators like such as IL , TNF
- Another mechanism is : Vicious cycle
  - Pain leads to withholding leads to constipation and further inflammation



- Pathophysiology :

- Cell mediated inflammation (non-IgE mediated) and its inflammatory consequences :
  - Impaired Gut motility (Dysmotility) :
  - Inflammatory mediators affect the neuromuscular function of the intestine , increasing transit time
  - Increased water absorption :
  - Delayed transit allows more time for water absorption from the colon
  - Visceral hypersensitivity :
  - Inflammation causes pain even with small amount of stool , leading to stool withholding

- Clinical presentation and differentiation from Functional constipation :

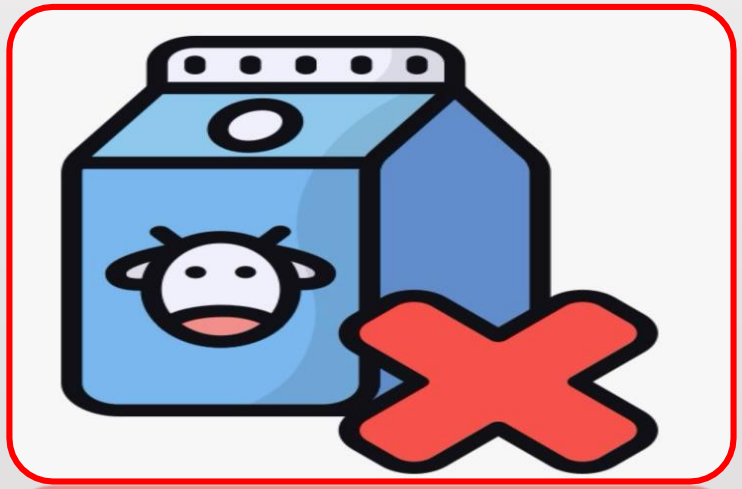
Functional constipation	**Food allergy-induced constipation**
Usually occurs after starting complementary feeding or toilet training	Onset even in the first weeks of life
Responds well to standard interventions (Dietary changes , laxatives)	Resistance to treatment with common laxatives
	Association with other non-IgE gastrointestinal symptoms , such as : resistant Reflux , severe colic , irritability and abdominal distension
	Presence of Occult blood or mucus in the stool
	Positive family history of Atopic disease

- Diagnostic approach :

- Step 1 : Detailed and targeted history taking :
  - Correlation between symptom onset and the introduction of new foods
  - Detailed recording of the infant’s and mother’s diet
- Step 2 : Use of Screening tools (CoMiSS) :
  - Although designed for CMPA , it provides a framework for systematic symptom assessment

SYMPTOM	SCORE		
Crying	0	≤ 1 hour/day	Score
	1	1 to 1.5 hours/day	
	2	1.5 to 2 hours/day	
	3	2 to 3 hours/day	
	4	3 to 4 hours/day	
	5	4 to 5 hours/day	
	6	≥ 5 hours/day	
Regurgitation	0	0 to 2 episodes/day	Score
	1	≥ 3 to ≤ 5 episodes of volume < 5ml	
	2	> 5 episodes of > 5ml	
	3	> 5 episodes of ± half of the feeds in < half of the feeds	
	4	Continuous regurgitations of small volumes > 30 min after each feed	
	5	Regurgitation of half to complete volume of a feed in at least half of the feeds	
	6	Regurgitation of the complete feed after each feeding	
Stools (Brussels Infant and Toddlers Stool Scale - BITSS)	4	Hard stools	Score
	0	Formed stools	
	3	Loose stools	
	6	Watery stools	
Atopic eczema: Head, neck and trunk	0	Absent	Score
	1	Mild	
	2	Moderate	
	3	Severe	
Atopic eczema: Arms, hands, legs and feet	0	Absent	Score
	1	Mild	
	2	Moderate	
	3	Severe	
(Acute) Urticaria* and/or angioedema*	6	Yes	Score
	0	No	
Respiratory	0	No respiratory symptoms	Score
	1	Slight symptoms	
	2	Mild symptoms	
	3	Severe symptoms	

- Diagnostic approach :
  - Step 3 : Elimination Diet is the cornerstone of diagnosis
  - Broad elimination of common allergens (cow's milk , egg , soy , wheat) for 2-4 w
  - In Breastfed infants : the mother eliminates all these allergens from her diet
  - In formula-fed infants : use of an amino acid-based formula as the Gold standard for complete allergen elimination or an eHF in milder cases
  - Step 4 : Food Challenge : after symptom improvement , a challenge with suspected allergens is performed singly and under medical supervision for final diagnosis confirmation

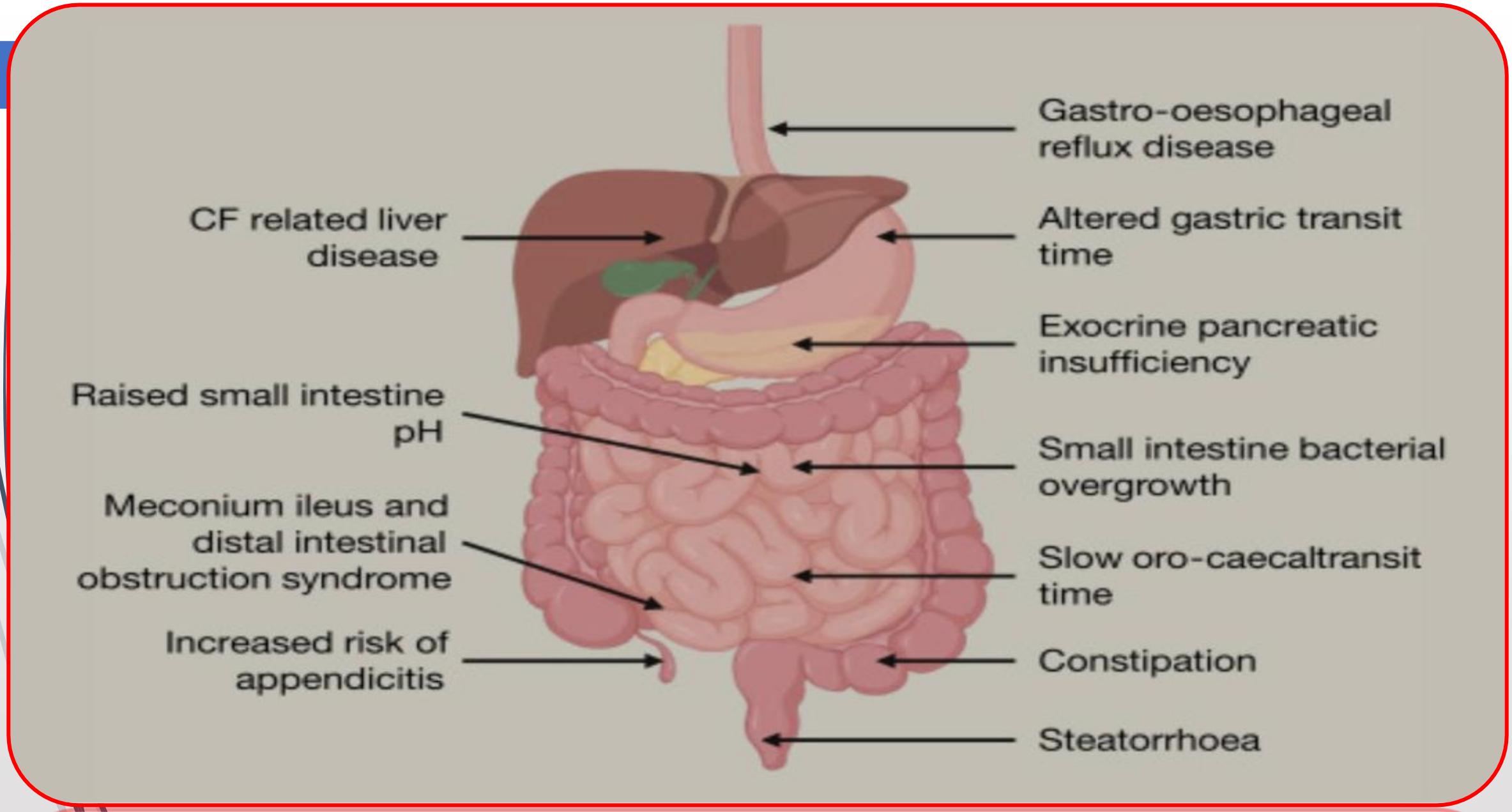


- Comprehensive management :
  - Strict avoidance of identified allergens :
  - Thorough education for families on reading food labels
  - Ensuring vital micronutrients (Ca , Iron , Vit D) through alternative sources or supplements
  - Constipation management :
  - After allergen elimination , short term use of laxatives may still be needed to break the cycle of withholding
  - Introduction of high-fiber foods
  - Growth monitoring :
  - Regular follow-up of weight , height and head circumference
  - Tolerance development :
  - Periodic Challenges (usually every 6-12 m) to assess the development of tolerance to the allergen

- Novel Evidence and Future Horizons :
  - Role of Gut Microbiota :
  - New studies show dysbiosis is evident in infants with food allergies
  - Probiotics :
  - Probiotics are being investigated as an adjunctive intervention to modulate the immune system and accelerate tolerance development
  - New Biomarkers :
  - Research is focused on finding specific biomarkers in stool or blood for the non-invasive diagnosis of non-IgE allergies
  - Oral Immunotherapy (OIT) :
  - Although currently not routine for constipation , it is an active research area for treating food allergy

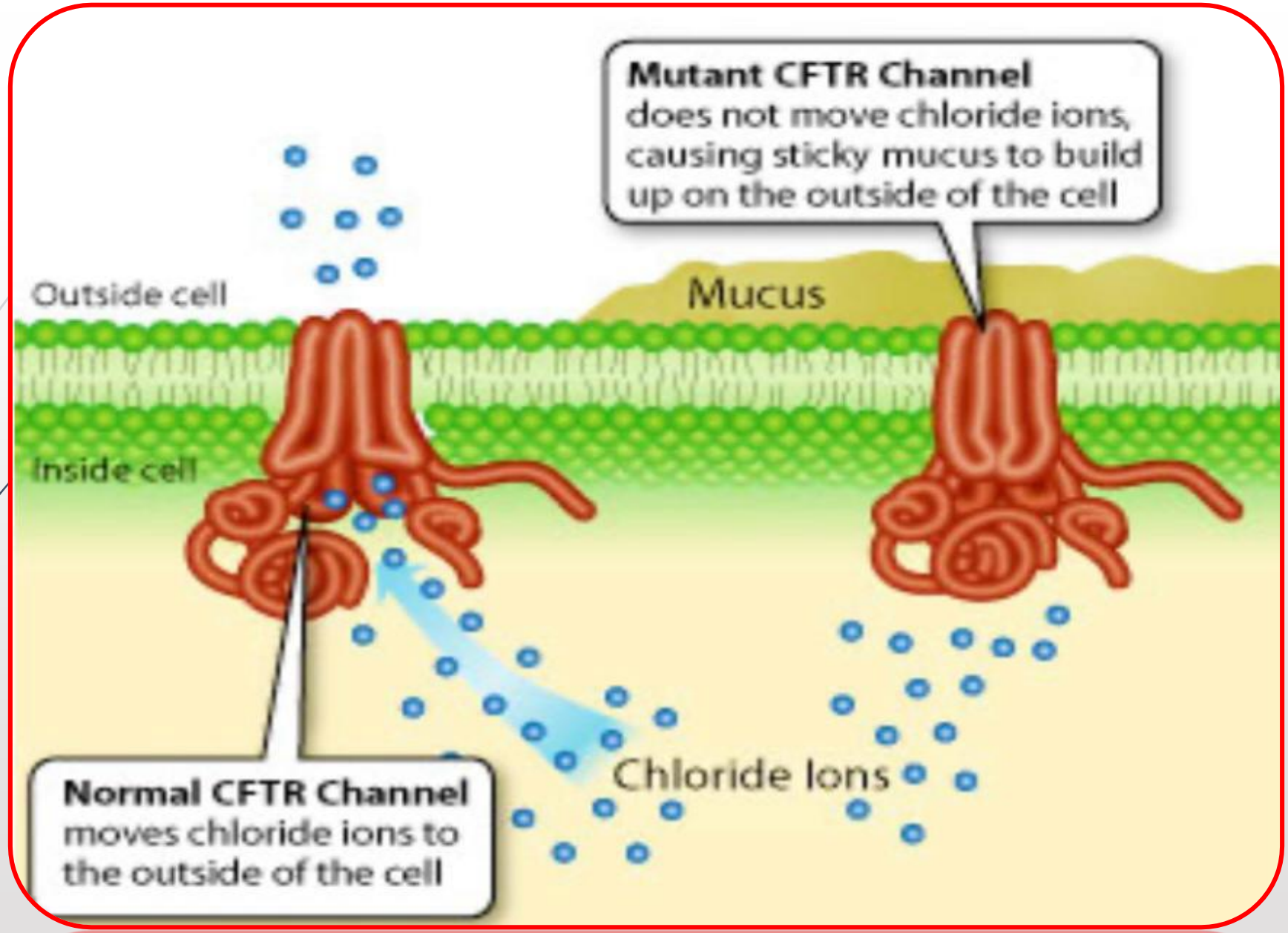
- See in and believe it :
- Constipation can be primary manifestation of food allergy (not just CMPA)
- Suspect in treatment-resistant cases :
- When facing resistant constipation , consider a broader list of food allergens (milk , soy , egg , wheat)
- Diagnosis is clinical :
- The diagnostic Gold standard is elimination and challenge , under medical supervision
- Amino acid Formula is the management hero :
- In severe or resistant cases , AAF is an effective and safe choice for complete allergen elimination
- Maintain a Long-term perspective :
- Managing these patients involves monitoring Growth , ensuring nutrition and periodic evaluation for tolerance development

Constipation and Cystic Fibrosis :


Gastro-oesophageal reflux disease
CF related liver disease
Altered gastric transit time
Exocrine pancreatic insufficiency
Raised small intestine pH
Small intestine bacterial overgrowth
Meconium ileus and distal intestinal obstruction syndrome
Slow oro-caecaltransit time
Increased risk of appendicitis
Constipation
Steatorrhoea

➢ Constipation and Cystic Fibrosis :

- Cystic Fibrosis transmembrane conductance regulator (CFTR) is a critical chloride and bicarbonate channel expressed in epithelial cells , including the entire GI Tract
- Dysfunctional CFTR leads to :
  - Reduced chloride secretion and increased sodium absorption leads to : dehydrated intestinal luminal contents
  - Impaired bicarbonate secretion leads to : acidic and viscous mucus
  - Altered mucin composition and function leads to : thick , adherent mucus plaques
  - Therefore , Gut environment predisposed to dysmotility , Bacterial overgrowth and Luminal inspissation creating a constipation and its severe counterpart , DIOS


Mutant CFTR Channel
does not move chloride ions, causing sticky mucus to build up on the outside of the cell
Outside cell
Mucus
Inside cell
Chloride Ions
Normal CFTR Channel
moves chloride ions to the outside of the cell

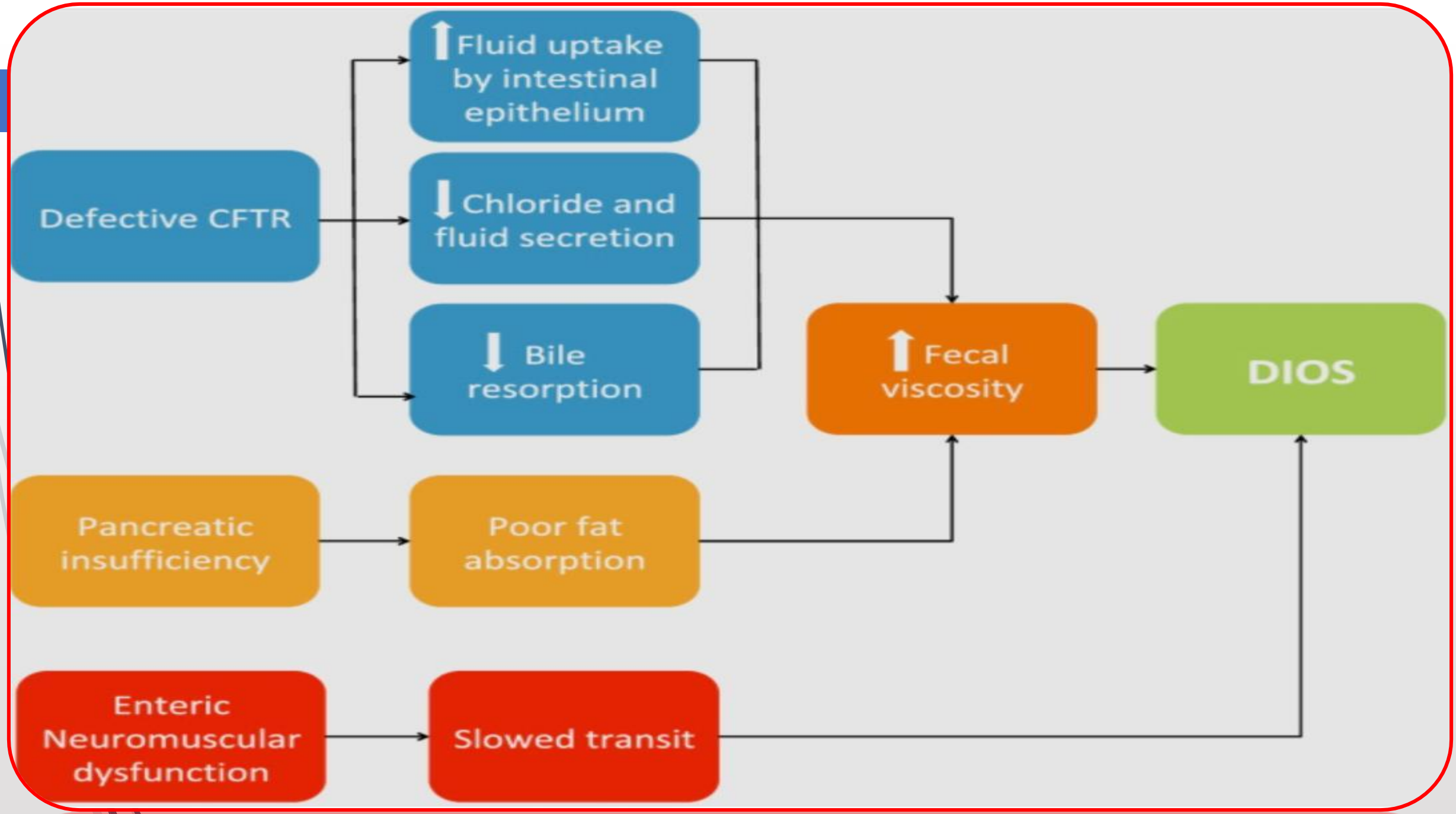
➢ Constipation and Cystic Fibrosis :

- Constipation is exceedingly common in CF , affecting up to 50% of patients
- Spectrum of disease :
  - Simple , mild constipation that responsive to standard laxatives
  - Chronic , severe constipation that resistant to conventional therapy
  - Distal Intestinal Obstruction Syndrome (DIOS) that a medical emergency unique to CF , characterized by complete or incomplete intestinal obstruction by viscid fecal material in the terminal ileum and cecum

➢ Pathophysiology :

- The development of constipation in CF is multifactorial , driven by the core CFTR defect and its sequelae :
  - Dehydrated intestinal contents :
  - The primary defect leading to hard and difficult to pass stools
  - Exocrine pancreatic insufficiency (EPI) :
  - Present in approximately 85% of CF patients
  - Inadequate pancreatic enzyme replacement therapy (PERT) leads to maldigestion , which can paradoxically cause both Steatorrhea and the formation of sticky , bulky stool that is hard evacuate

- Pathophysiology :
  - Abnormal intestinal motility :
  - Thick mucus and altered fluidity may disrupt normal peristalsis
  - Microbiome Dysbiosis :
  - CF patients have a distinct Gut microbiome , which may further influence Gut motility and immune function
  - Medications :
  - Some drugs used in CF care such as Opioids for pain or some antibiotics can contribute to constipation
  - Dietary factors :
  - Despite high-calorie needs , sometimes diets are low in fiber , which can be a contributing factor


Fluid uptake by intestinal epithelium
Defective CFTR
Chloride and fluid secretion
Bile resorption
Fecal viscosity
DIOS
Pancreatic insufficiency
Poor fat absorption
Enteric Neuromuscular dysfunction
Slowed transit

feature	Chronic constipation in CF	DIOS	Simple Functional constipation
pain	Colicky , intermittent , often generalized	Acute , severe , often in RLQ	Variable , often suprapubic
Abdominal Exam	May be distended , palpable stool in colon	Distended , Tender , often a palpable mass in RLQ	Non-tender
Vomiting	Uncommon	a Cardinal feature (may be bilious)	Rare
Radiology	Stool throughout colon	Air-fluid levels , Bubbly fecal mass in ileocecal region	Stool in rectum/colon
Response to laxatives	Often slow/partial	Requires aggressive medical intervention , may fail	Good

- Diagnostic workup :
  - Detailed History :
  - Stool frequency , consistency (Bristol Stool Scale) and caliber
  - Abdominal pain location , severity and timing
  - Associated symptoms such as vomiting , bloating , weight loss
  - Review of PERT dosing and adherence
  - Review of medications
  - Physical Examination :
  - Abdominal inspection for distention
  - Palpation for tenderness and fecal mass
  - DRE for assessment of fecal impaction , stool consistency and anal tone

- Diagnostic workup :
  - Imaging :
  - Abdominal X-Ray :
  - First line
  - Assesses stool burden , distribution and sign of obstruction
  - A fecal mass in the Ileocecal area is suggestive of DIOS
  - Abdominal Ultrasound :
  - Can help visualize the terminal ileum and cecum and Rule out other pathologies
  - CT scan :
  - Reserved for complex cases where diagnosis in unclear or complications are suspected

- Management strategy :
  - Foundation and laxatives
  - Advanced and DIOS specific

- Foundation and laxatives :
  - Re-evaluated and Optimize PERT :
  - Ensure the patient is on an adequate dose
  - Undertreated EPI is a major contributor
  - Check Fecal Elastase level if unsure
  - Dietary interventions :
  - Fluids , Fluids , Fluids . Aggressive oral hydration is paramount
  - Soluble Fiber such as Psyllium and Pectin that must be accompanied by massive fluid intake or it can worsen obstruction

- Foundation and laxatives :
  - First line pharmacotherapy :
  - Osmotic laxatives that are the cornerstone of treatment :
    - Polyethylene Glycol (PEG) : First-line , High doses are often required and well-tolerated
    - Lactulose : An alternative but can cause more bloating
  - Stimulant laxatives :
    - Senna , Bisacodyl that are useful for short-term use in severe cases

- Advanced and DIOS specific :
  - For chronic severe constipation :
  - Combination therapy :
    - High dose PEG + Stimulant laxative
  - Prokinetic Agents :
    - Consider drugs like prucalopride (5-HT4 agonist) in refractory cases
  - Rectal therapies :
    - Phosphate or Salin Enemas for rectal impaction

- Advanced and DIOS specific :
  - For Acute DIOS :
  - NPO + IV Fluids +NGT :
    - For decompression if vomiting is present
  - Aggressive Lavage :
    - Gastrografin Enema can be both diagnostic and therapeutic
    - Oral/NG balanced lavage solutions : High-volume PEG solutions are often first line
  - Surgical consultation :
    - Mandatory for all cases of DIOS
    - Surgery (Laparotomy and Manual disimpaction) is reserved for failed medical management or signs of perforation

- The impact of CFTR Modulators:
  - A paradigm shift :
  - Elexacaftor/ Tazacaftor/Vacaftor correct the underlying CFTR defect
  - Emerging GI Data :
  - Improved pancreatic function : some patients show improved fecal elastase levels , reducing the burden of EPI
  - Reduced GI Symptoms :significant improvements in abdominal pain , constipation and DIOS incidence have been reported in clinical trials and real-world studies
  - Altered Gut PH and Microbiome : early evidence suggests modulator use normalizes intestinal PH and may shift the microbiome towards a healthier state
  - Clinical implication :
  - As modulator use becomes universal , the prevalence and severity of CF-related constipation may decrease . However , it will not eliminate the problem entirely and clinicians must remain vigilant

- A long-term management Algorithm :
  - Prevention :
  - Daily , proactive use of osmotic laxatives (PEG) in patients with a history of constipation
  - Education :
  - Empower patients and families to recognize early signs and adjust laxatives within a prescribed range
  - Regular monitoring :
  - Ask about Bowel habits at every clinic visit
  - Multidisciplinary team (MDT) approach

- Multidisciplinary team (MDT) approach :
  - Gastroenterologist :
  - Manage complex constipation/DIOS
  - CF Dietitian :
  - Optimizes nutrition and PERT
  - Physiotherapist :
  - Techniques like abdominal percussion/postural drainage may help stimulate motility
  - Psychologist :
  - Addresses anxiety and adherence issues

- Constipation in CF is primarily a disease of dehydration at the intestinal level , not just a functional disorder
- Differentiate meticulously between chronic constipation and DIOS , as the latter is a medical emergency
- Management is proactive and aggressive , High-dose PEG is the first-line pharmacologic cornerstone
- Always reassess PERT adequacy that is reversible and common contributing factor
- CFTR modulators are changing the landscape of GI disease in CF , offering hope for a fundamental improvement in this comorbidity

- Practical clinical guide :

feature	CMPA	CF
Primary mechanism	Immune mediated inflammatory reaction to allergen	Genetic defect in CFTR protein that leads to thick mucus and pancreatic insufficiency
Constipation pattern	Often resolves with allergen elimination	Chronic , refractory and can progress to DIOS
Key GI symptoms	Hard stools , straining , blood in stool , anal fissures	Fatty , bulky , foul-smelling stools (Steatorrhea) , FTT
Systemic symptoms	Eczema and other atopic manifestations	Recurrent pulmonary infections , chronic cough , salty sweat , nasal polyps
Diagnostic Gold standard	Elimination diet and challenge	Sweat chloride test , genetic testing


Thank You