

CHAPTER 11 GASTROINTESTINAL & HEPATOBILIARY CONSIDERATIONS

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Gastrointestinal and hepatobiliary complications are important manifestations in people with CF. This chapter covers reflux, distal intestinal obstruction syndrome, constipation, screening for colon cancer and CF-related liver disease.

11.1 Gastro-oesophageal Reflux

Gastro-oesophageal reflux (herewith referred to as reflux) refers to the abnormal passage of gastric contents into the oesophagus⁵⁴¹. Reflux in CF can present as either symptomatic or asymptomatic⁵⁴². It has the potential to limit dietary intake and is therefore a risk factor for malnutrition^{543,544}. Reflux may impact quality of life and potentially impact lung disease severity by increasing the risk of aspiration and reflex bronchospasm^{545,546}.

Disease Aetiology

It has been suggested that the primary mechanism behind reflux in CF is the inappropriate transient relaxation of the lower oesophageal sphincter^{547,548}. Other potential contributing factors, specific to people with CF include:

- Increased gastro-oesophageal pressure gradient due to lower inspiratory intra-thoracic pressure⁵⁴⁷
- Delayed gastric emptying^{548,549}
- Chronic cough⁵⁴⁸
- Primary pulmonary disorders caused by the accumulation of intraluminal secretions and/or destruction of airway wall and bronchiolitis^{548,550}
- Medications including beta-agonists, alpha-blockers, aminophyllines, anticholinergics and benzodiazepines⁵⁵¹
- Postural drainage^{542,550}
- Post-transplantation complications such as vagal nerve damage, rejection or bronchiolitis obliterans syndrome^{542,548,552}

Reflux is common in children and adults with CF, particularly post lung transplantation. Prevalence has been reported to range between 20 and 100 percent^{548,550,553}.

Assessment

Reflux may impact dietary intake through decreased appetite and tolerance of food, oral nutritional supplements and/or enteral feeds^{543,544}. This in turn, may indirectly impact the individual's ability to meet their nutritional requirements.

DIET

Nutrition assessment should target volume, and frequency of meals and snacks, and if the individual receives enteral feed, the bed head elevation, feed volumes and rates of feeding.

CLINICAL

Signs and symptoms of reflux in CF include:

- Presence of heartburn, dyspepsia, acidic taste in the mouth or cough, chest pain, anorexia, nausea, vomiting, dysphagia, belching, frequent stomach gurgling, flatulence, early satiety, halitosis, pressure or a lump in the throat, hoarseness or bloating¹³⁸
- Food refusal, failure to thrive, frequent spitting up or vomiting and colic in younger children⁵⁵⁴

Other considerations:

- Nutrition status, weight and weight history
- Pulmonary function history (FEV₁, FVC), and exacerbation frequency



BIOCHEMICAL AND LABORATORY DATA

Invasive investigations are not always required for the assessment and diagnosis of reflux, but may include the following:

- 24-hour pH monitoring
- 24-hour combined Multiple Intraluminal Impedance (MII) and pH monitoring
- Oesophageal manometry
- Endoscopy and biopsies
- Barium swallow

Intervention

What are the nutrition considerations for the management of gastro-oesophageal reflux (GOR) in CF?

PICO 11.1.1

[Grade D] Specific dietary factors that influence the occurrence, severity and management of GOR in CF have not been identified. Further research into the impact of dietary factors on reflux in CF is warranted. ¹³⁶⁻¹³⁹

The following dietary and lifestyle factors may help to reduce reflux symptoms in some people with CF, although the evidence is limited:

- Performing physiotherapy treatments before meals or large snacks and in a more upright position ⁵⁴⁸
- Eating smaller volumes of food at regular intervals may be better tolerated
- Elevating the head during overnight enteral feeding
 - Supine positioning may exacerbate reflux, and so overnight enteral feeding may result in formula being regurgitated and aspirated into the lungs ¹
 - The elevation of the head of the bed during overnight feeding in a cross-over RCT of 15 people with reflux (non-CF) demonstrated a decreased time that oesophageal pH was <4 compared with a supine position (15 and 21 percent, respectively; $p < 0.05$) altering feed volumes and rate of feeding ⁵⁵⁵
- If overweight, aiming for gradual weight loss
 - Studies in the non-CF population demonstrate controlled weight loss in patients with a BMI > 25 kg/m² improves reflux symptoms and oesophageal pH ⁵⁵⁶
 - Avoiding high-fat meals within 2-3 hours of reclining to improve nocturnal gastric acidity ⁵⁵⁶
- Avoiding tight clothes ⁵⁵⁷
- Modification of postural drainage physiotherapy techniques ⁵⁵⁷

There have been no studies performed on the cessation of chocolate, caffeine, spicy foods, citrus and carbonated beverages and their impact on reflux symptoms. Individual elimination may be considered if patients identify an association with reflux symptoms and improvement when eliminated from the diet ⁵⁵⁶.

PHARMACOLOGICAL AND MEDICAL MANAGEMENT

Histamine receptor antagonists (H₂ antagonists) and proton pump inhibitors (PPIs) for acid suppression are often first choice for reflux treatment in CF. Surgical treatment of reflux in people with CF may be considered if symptoms have not been controlled by pharmacological, dietary or lifestyle interventions. In people with CF with worsening lung function and uncontrolled reflux, some studies have shown that a Nissen fundoplication may slow the decline in lung function, decrease the number exacerbations and lead to improvements in weight. ¹³⁶ The impact on pulmonary function decline remains controversial. It is important for the team to consider the potential risks and benefits of the surgery for each individual. There is an absence of long-term studies in CF, and those in the general population suggest 10% of fundoplication surgeries experience recurrent reflux symptoms ⁵⁵⁸. Nissen fundoplication is the most common treatment for the management of reflux in the post lung transplant group ⁵⁴⁸. Chapter 16 provides further information on the management of reflux in the context of lung transplant

Monitoring & Evaluation

No current consensus guidelines suggest formal screening for reflux disease. It is important to monitor for reflux symptoms and severity, and clinical and nutritional status as part of routine care, at all stages of the CF individual's lifespan. This should ideally occur as part of a interdisciplinary team.

The Mayo GER questionnaire (GERQ) and the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS) are both validated self-administered questionnaires that have been used to record reflux symptoms and severity in the general population, and may be a useful tool in CF ¹³⁸.

Practice Points PICO 11.1.1

- GOR is common in children and adults with CF and can present as either symptomatic or asymptomatic.
- The Mayo GER questionnaire (GERQ) and the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS) are both validated self-administered questionnaires that have been used to record reflux symptoms and severity in the general population.
- There are no established guidelines for the diagnosis and treatments of GOR specific to CF. Use clinical judgment when applying GOR guidelines for general population to individuals with CF.
- Pharmacological therapy options to reduce the symptoms of GOR are often first choice of treatment. These include histamine receptor antagonists (H₂ antagonists) and protein pump inhibitors (PPIs).
- If dietary interventions are considered, take an individualised approach whereby nutritional adequacy is not compromised or unnecessarily restricted.
- Supine positioning may exacerbate GOR. Review bed head elevation, feed volumes and rate of feeding to optimise tolerance and reduce the risk of symptoms. Assess reflux symptoms prior to enteral feeding.
- Surgical intervention (fundoplication) may be explored if symptoms have not been controlled by pharmacological, dietary or lifestyle interventions. It is important for the interdisciplinary team to evaluate the potential risks and benefits of the surgery for each individual.

11.2 Distal Intestinal Obstruction Syndrome and Constipation

Distal intestinal obstruction syndrome (DIOS) and constipation are separate conditions, with DIOS having the potential for more severe acute implications including surgical intervention. DIOS, previously known as meconium ileus equivalent, is a known gastrointestinal complication in CF. The definitions of DIOS and constipation, according to the ESPGHAN guidelines are outlined in table 11a ⁵⁵⁹. DIOS is characterised by a complete or incomplete intestinal obstruction with faecal accumulation in the terminal ileum and proximal colon ⁵⁶⁰. Complete DIOS usually presents as bilious vomiting and/or fluid levels in the small intestine, abdominal pain and distension, and a faecal mass in the ileo-caecum ^{559,560}. Incomplete DIOS only differs by the absence of bilious vomiting on presentation ⁵⁶⁰.

Unlike the often acute presentation of DIOS, constipation usually presents with a more gradual onset of symptoms and is easily relieved with the use of aperients ⁵⁵⁹.

Table 11a. ESPGHAN CF Working Group definition for DIOS and constipation in Cystic Fibrosis ⁵⁵⁹

Condition	Physical definition	Symptoms
Complete DIOS	Faecal mass (ileo-caecum) Complete obstruction	Bilious vomiting +/- fluid levels in small intestine plus abdominal pain +/- distension
Incomplete DIOS	Faecal mass (ileo-caecum) Incomplete obstruction	Abdominal pain +/- distension
Constipation	No intestinal obstruction	Abdominal pain +/- distension. Less frequent bowel motions +/- increased stool consistency over a period of weeks to months. Symptoms relieved after commencing laxatives

Disease aetiology

DISTAL INTESTINAL OBSTRUCTION SYNDROME

DIOS is associated with more severe CF genotypes and pancreatic insufficiency, with 34-54% of all presentations occurring in homozygous F508del patients. Conversely, DIOS is rarely seen in pancreatic sufficient patients ^{141,559}.

Considerations for the pathophysiology of DIOS include:

- Dehydrated and thick secretions in the intestine predisposing a person with CF to obstruction ⁵⁶⁰
- Impaired cystic fibrosis transmembrane conductance regulator (CFTR) resulting in defective water and chloride secretion into the intestine ⁵⁶⁰
- Transluminal intestinal inflammation is thought to contribute to intestinal dysmotility and delayed intestinal transit time in CF ⁵⁶¹. As a result, intestinal inflammation is thought to indirectly contribute to the risk of DIOS in CF ⁵⁶¹



Additional factors which may increase the risk of DIOS include:

- **Meconium ileus** - Almost half of DIOS presentations are associated with a history of meconium ileus at birth ^{141,559,562}
- **Previous DIOS episode** - People with CF are up to 10 times more likely to develop recurrent DIOS post an initial episode ⁵⁵⁹
- **Organ transplantation** ⁵⁶³⁻⁵⁶⁶
- **CF-related diabetes and liver disease** – The relationship between these comorbidities is not a consistent finding across the literature ^{141,560}
- **Dehydration** - Most commonly associated with intercurrent illness. Ambient temperature peaks have also been found to play a potential role in the Australian context ²³⁴

Malabsorption related to inadequate enzyme replacement resulting in unabsorbed fat in the distal ileum has previously been thought to be a predisposing DIOS risk factor due to delayed gastric emptying and transit time in CF ⁵⁶⁰. However, recent studies have shown that this is unlikely to be the case ¹⁴⁰⁻¹⁴².

The incidence of DIOS was previously thought to be higher in adults than children ^{567,568}. Since the release of the 2005 ESPGHAN definitions for constipation and DIOS in CF, recent studies have shown a similar incidence of DIOS in both the paediatric (6.2–7.7 episodes per 1000 patient-years) and adult (7.8 episodes per 1000 patient-years) population ^{141,559}.

CONSTIPATION

Altered intestinal fluid composition, resulting from the primary CFTR defect is considered the main cause of constipation in CF ¹⁴³. Dysmotility and decreased water secretion in the intestine are also recognised as potential underlying mechanisms ⁵⁶⁹. Unlike DIOS, genetic factors, including the severity of the CFTR genotype, are not thought to contribute to the incidence of constipation in CF ^{142,143,570}.

Additional factors thought to contribute to constipation in CF:

- Low total fat absorption ¹⁴³
- Meconium ileus at birth ¹⁴³
- High ambient temperatures – hypothesised to result in intestinal intraluminal dehydration, thus increasing the risk of constipation ²³⁴
- Medications - opiate analgesics, calcium and iron supplements and some antacids containing calcium or aluminum, list constipation as a common side effect

The impact of the following hypothesised risk factors for constipation in CF remains unclear:

- Poor fluid intake
- Inadequate fibre intake
- High dose pancreatic enzyme replacement therapy (PERT) - two papers report an association between high dose PERT and constipation ^{279,571} and one found no association ¹³⁰

While constipation is also a common occurrence in CF, only two studies have looked at constipation prevalence whereby it was found to range from 26-47% ^{143,572}. The incidence of constipation in CF is unknown.

Assessment

The potentially serious nature of DIOS should not be underestimated in CF. Differential diagnoses include constipation, appendicitis, appendicular abscess, Crohn's disease, adhesions, volvulus, intussusception, fibrosing colonopathy and malignancy ⁵⁶⁰. Diagnostic investigations for CF patients presenting with acute abdominal pain usually include an abdominal x-ray and ultrasound ⁵⁷⁰.

DIET

While evidence to support the role of dietary factors in the development of either DIOS or constipation in CF is lacking, nutrition assessment should include a review of dietary intake including recent changes to pancreatic enzyme replacement therapy and sodium, fluid and fibre intake. Overall there is inadequate evidence to determine the role of nutrition in the prevention and management of DIOS.

What are the nutrition considerations for the prevention and management of Distal Intestinal Obstruction Syndrome (DIOS) in CF? PICO 11.2.1

[Grade C] Inadequate PERT, including poor adherence and under-dosing, is unlikely to play a role in DIOS but should still be assessed as part of an overall dietetics review in CF.

The impact of diet, particularly fibre and fluid intake on DIOS is unclear.

Further research in the Australian and New Zealand context, particularly in regards to the impact of hydration on DIOS is required. While not examined in the current body of evidence, the impact of sodium intake on hydration and DIOS is warranted in future research. ¹⁴⁰⁻¹⁴²

What are the nutrition considerations for the prevention and management of constipation in Cystic CF?PICO 11.2.2

[Grade D] There is inadequate evidence to recommend nutrition considerations in the prevention and management of constipation in CF.

Until further evidence is available, complete a thorough diet history, including assessment of hydration (fluid and sodium intake) as well as fibre intake. Review PERT to optimise absorption.

Further research in the Australian and New Zealand context is warranted, particularly in regards to hydration (including sodium intake) and constipation in CF. ¹⁴³

While one study has found that sub-optimal fat absorption may contribute to constipation and that inadequate fluid and fibre intake do not, the evidence base is small and not applicable to the Australian and NZ context ¹⁴³. Overall there is inadequate evidence to determine the role of nutrition in the prevention and management of constipation in CF.

CLINICAL

Key nutrition related considerations for DIOS and constipation include:

- Nausea and vomiting
 - Distinguishing between bilious vs. non-bilious vomiting is important when differentiating between complete and incomplete DIOS
- Bowel patterns
 - Note any recent changes in frequency and/or consistency of bowel motions. A change in bowel habits, while usually present in constipation, may not always be a feature of DIOS
- Presence of overflow diarrhoea and/or faecal incontinence/soiling
- Presence of abdominal pain and distention
- Medications
 - Note medications with a known side effect of constipation (i.e. opiate analgesics and iron and calcium supplements)
 - Use of aperients (i.e. polyethylene glycol (PEG), Lactulose or Gastrografin)
 - PERT
 - Salt tablets
 - Adherence and any recent changes
- Recent intercurrent illnesses

The duration of all clinical symptoms should be noted.



BIOCHEMICAL & LABORATORY DATA

There are no routine biochemical markers for the assessment of constipation and DIOS in CF. In the event of DIOS, monitoring of electrolyte disturbances is warranted if dehydration occurs⁵⁷³. Renal function should also be monitored as the patient is vigorously rehydrated. In the event of persistent constipation, alternate causes such as coeliac disease should be considered.

Intervention

DISTAL INTESTINAL OBSTRUCTION SYNDROME

Medical intervention is a priority for a patient presenting with acute abdominal pain and suspected DIOS. While treatment protocols vary between centres, most follow a stepwise approach⁵⁶⁰. Surgical intervention (ranging from surgical decompression to open laparotomy and resection) is rarely required for the management of DIOS^{141,143,560,565}.

Examples of paediatric and adult DIOS management flowcharts are outlined in Figure 11a⁵⁷³ and Figure 11b⁵⁷⁴. These are site specific examples and practice may vary across sites, so it is important to refer to local guidelines.

CONSTIPATION

The treatment for constipation is usually intensive laxative treatment¹⁴³. Whilst the role of diet in the prevention of constipation in CF is unclear, optimisation of hydration (fluid and salt intake) and pancreatic enzyme dosing and adherence is recommended. While not routine practice, a small dose of PERT, usually third hourly may be prescribed to avoid further obstructions in patients who are initially nil by mouth.

Monitoring & Evaluation

DISTAL INTESTINAL OBSTRUCTION SYNDROME

Dehydration and fat malabsorption should be avoided to prevent recurrence of DIOS⁵⁷⁰. Close monitoring of bowel patterns, fluid and salt intake as well as pancreatic enzyme replacement dosing and adherence is recommended for people with a history of DIOS. The ongoing use of aperients after an acute DIOS episode is common and should also be reviewed regularly^{560,570}.

CONSTIPATION

Thorough clinical review, with focus on stool patterns and medications, particularly aperients, is important when monitoring the often chronic complication of constipation in CF. While conclusive evidence is lacking, hydration status^{234,572} and the prevention of fat malabsorption is recommended in the management of constipation¹⁴³.

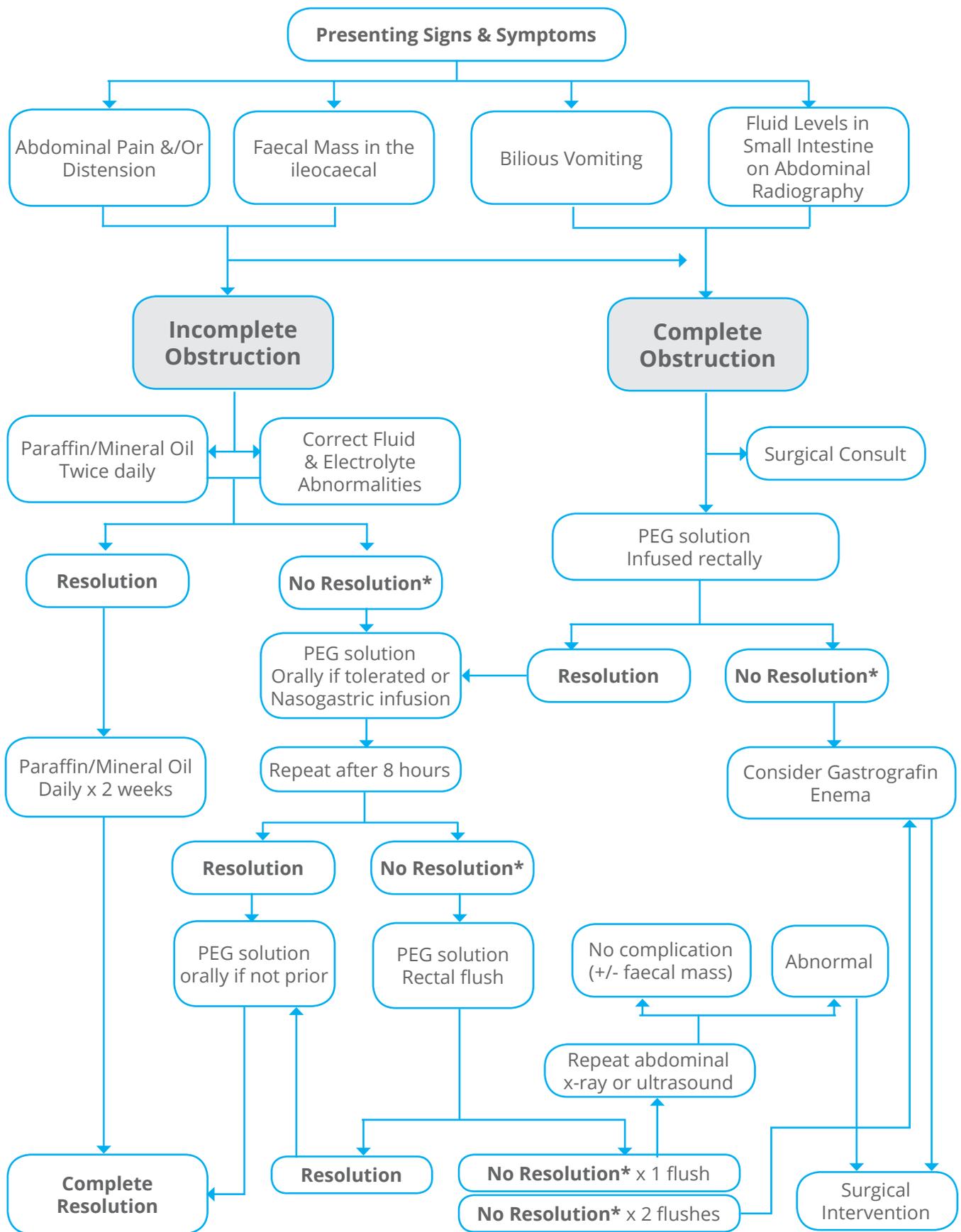


Figure 11a. Diagram outlining management recommendations at the Children’s Hospital Westmead (Westmead, NSW, Australia).

* Low threshold for further imaging (abdominal x-ray and ultrasound)

⁵⁷³ Note: Mineral oils should not be used for the treatment of DIOS & constipation in children less than 12 months of age.



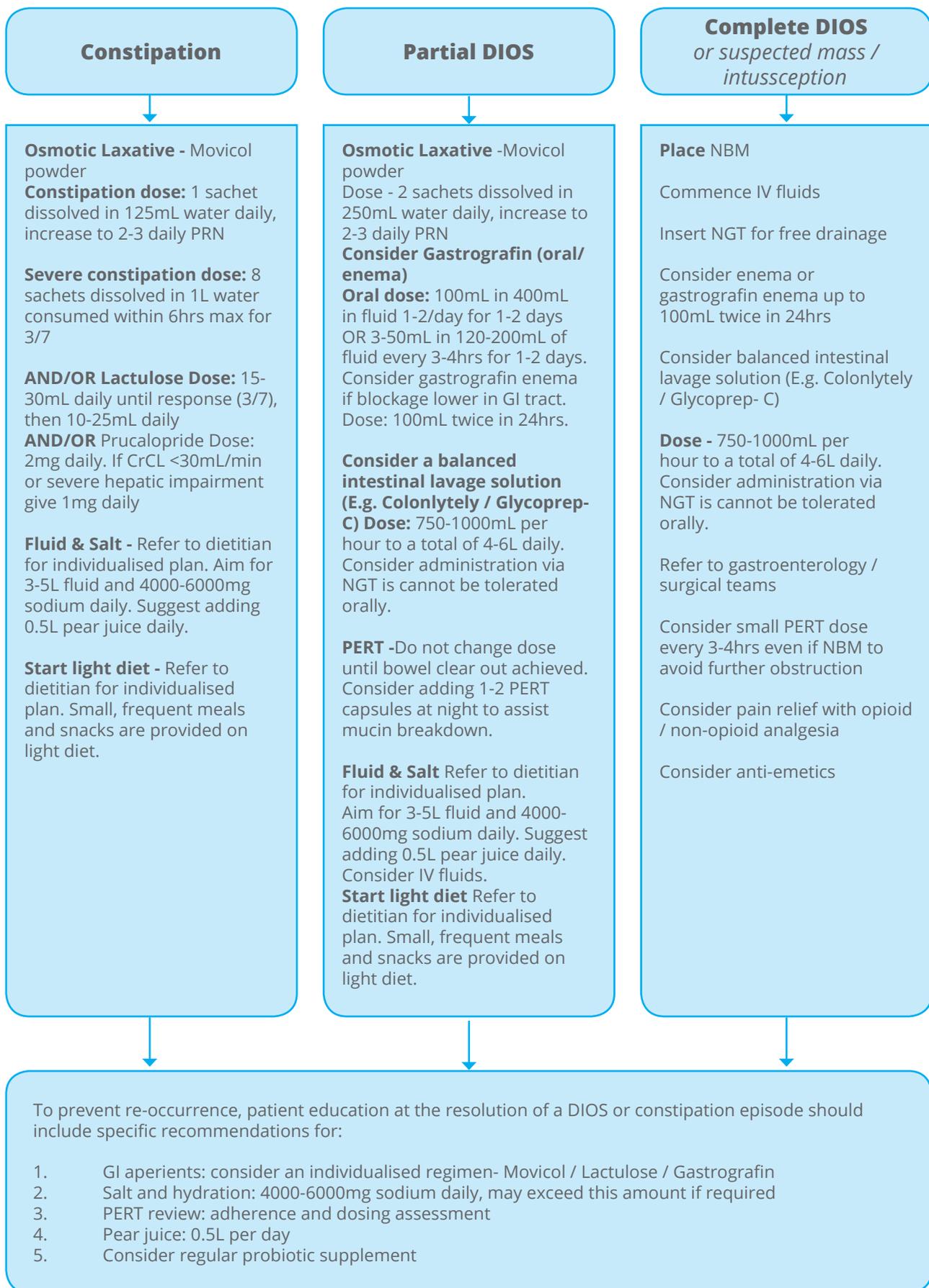


Figure 11b. Management recommendations at the The Prince Charles Hospital (Chermside, QLD, Australia) ⁵⁷⁴.

Practice Points PICO 11.2.1 and 11.2.2

- Medical treatment is a priority, particularly for the diagnosis and management of DIOS.
- Surgical intervention is rarely required.
- Polyethylene glycol (PEG) laxatives are usually used for the treatment of constipation and are often a first line treatment for DIOS. Many patients continue on laxatives after the resolution of DIOS.
- Optimise fluid and salt intake as well as fat absorption in those who present with or have a history of constipation and DIOS.
- Patients with complete DIOS may be fasted during initial treatment. In most cases this is short term, however, monitor patients for risk of malnutrition. Total parenteral nutrition (TPN) may be required for more complex cases that do not resolve in a few days.
- The Bristol stool chart can be used when assessing bowel patterns in CF. A paediatric version is also available when trying to engage younger children.

Laxatives:

- Insufficient evidence to assess the relative effectiveness or tolerability of different classes of laxatives. Considerations when choosing an agent should include hardness of the stool, potential adverse effects, effectiveness of previous treatments and patient preference.
- Adjust laxative regimens according to response and tolerability.
- Osmotic laxatives draw water into the stool to help soften the stool and washout the colon. The active ingredient in most osmotic laxatives is usually Polyethylene glycol (PEG). Lactulose, a non-absorbable sugar, is another osmotic laxative used in CF but is often associated increased abdominal pain/cramping.
- Stool lubricants help lubricate the bowel wall & soften faecal mass to allow the faecal mass to transit through the colon.

NOTE - Mineral oils should not be used for the treatment of DIOS & constipation in children less than 12 months of age. Potential side effects of longer term use in children greater than 12 months of age include:

- Possibility of reduced fat soluble vitamins.
- Abdominal cramps

Risk of aspiration if used during period of respiratory exacerbation or if the child is fighting the dose.

Translating into Practice

Tools used to assess gastrointestinal (GI) symptoms in CF may include:

- The Bristol stool chart
 - Stool form scale used to assess changes in intestinal function ⁵⁷⁵
 - A modified version of the tool is readily available on the internet for the paediatric population
 - Not validated for the CF population so should be used in combination with other GI assessment tools or questions
- GI symptom trackers

There is currently insufficient evidence to assess the relative effectiveness or tolerability of different classes of laxatives. In practice, the choice of agent depends on symptoms, required onset of action, hardness of stool, potential adverse effects, effectiveness of previous treatments and patient preference. Regimens are then adjusted according to response and tolerability. Some examples of commonly used laxatives are as follows:

- Osmotic laxatives draw water into the stool to help soften the stool and washout the colon. The active ingredient in most osmotic laxatives is usually Polyethylene glycol (PEG). Products commonly used in CF include Movicol®, Osmolax® and GoLYTELY® in Australia or Kleanprep® in New Zealand. Lactulose, a non-absorbable sugar, is another osmotic laxative used in CF but is often associated with increased abdominal pain/cramping
- Stool lubricants, such as mineral oil (Parachoc® and Paraffin Oil®) help lubricate the bowel wall and soften faecal mass to allow the faecal mass to slide along easily

NOTE - Mineral oils should not be used for the treatment of DIOS and constipation in children less than 12 months of age. Potential side effects of longer term use in children greater than 12 months of age include:

- Possibility of reduced fat soluble vitamins
- Abdominal cramps
- Risk of aspiration if used during period of respiratory exacerbation or if the child is fighting the administration of the mineral oil



11.3 Colon Cancer Screening

Advancements in treatment options, early diagnosis and organ transplantation have led to an increased survival rate for people with CF. In turn, complications such as gastrointestinal malignancies have emerged. Colon cancer represents the highest risk in comparison with all other GI cancers for people with CF post transplantation⁵⁷⁶.

Disease Aetiology

A recent study showed that people with CF had a higher rate of adenomatous polyps and a greater risk of developing colon cancer than the general population⁵⁷⁷. In all patients who had follow-up colonoscopies within one to three years, multiple polyps were found. The mechanism underlying the increased incidence of polyps has not been established. It has been suggested that it may be related to increased epithelial cell proliferation and turnover, and/or the altered composition of intestinal mucous, but further research is required⁵⁷⁸.

There is limited evidence specific to colon cancer screening in CF. Further research is required into the type of preparation used. The standard bowel preparation used for the general population may result in inadequate clearance, poor gastrointestinal visualisation and lower detection rates in people with CF due to the intestinal secretions^{578,579}. The optimal length and aggressiveness of CF-specific bowel preparations have yet to be agreed on.

Assessment

DIET

CF-specific colonoscopy preparation and recommendations (medications, doses and length of preparation) may vary. The preparation regimen, a decreased appetite and/or loose stools may impact the individual's ability to meet their nutritional requirements. This should be more closely assessed in the malnourished individual.

CLINICAL

Key points to consider as part of a clinical assessment include:

- Unexplained weight loss
- Unexplained abdominal pain
- Bowel obstruction unrelated to DIOS
- Rectal bleeding
- Family history of colorectal cancer

A colonoscopy is recommended as part of the screening process for colon cancer.

BIOCHEMICAL & LABORATORY DATA

The medical assessment and diagnosis of colon cancer involves a colonoscopy. CT colonography has not been assessed in the setting of CF.

Intervention

What are the nutrition considerations for colon cancer screening in CF? PICO 11.3.1

[Ungraded] There is insufficient evidence available regarding nutrition considerations for colon cancer screening in CF.

The following factors should be considered during preparation for colonoscopy:

- People at risk of malnutrition or diagnosed with malnutrition may consume clear fluid oral nutrition supplements containing protein
- Cordial, high energy cordial, lemonade or clear oral nutrition supplements may assist tolerance of the colonoscopy preparation. Alternatively, preparation administered via the nasogastric tube may be considered
- Monitor blood glucose levels and insulin requirements (especially in those people with CF-related or frequent hypoglycaemic episodes)
- Monitor hydration status and renal function

Monitoring and Evaluation

There is currently no consensus with regards to the age at which colon cancer screening may be warranted. After initial colonoscopy, gastroenterologists may recommend further surveillance every 1-5 years based on initial results, risk profile and the general population guidelines.

An increased survival rate in people with CF suggests that earlier colon cancer screening may be warranted. The Minnesota Cystic Fibrosis Centre screens all patients aged ≥ 40 years old ⁵⁷⁷. Local CF centres should consider individualised colon cancer screening until further research and consensus is available.

A few reports have identified poor gastrointestinal visualisation ^{577,579} with standard colon preparation in CF compared to the general population. Further research is required to optimise colonic preparation solutions in this specific patient group.

Practice Points PICO 11.3.1

People with CF have a greater risk of developing colon cancer than the general population. Individual centres need to develop local guidelines with regard to screening older adults to assess risk of colorectal cancer

More extensive colonoscopy preparation may be required and further research is required.

11.4 Liver Considerations

There is a wide spectrum of manifestations that affect the hepatobiliary system in CF, including involvement of the liver, gallbladder and biliary tree ²³⁶. CF-related liver disease is the third leading cause of death in CF ⁵⁸⁰. While there is no universally accepted definition available, CF-related liver disease may present with neonatal cholestasis, asymptomatic elevation of liver enzymes, through to hepatic steatosis and focal biliary cirrhosis to the clinically relevant and more severe complication of multilobular cirrhosis ²³⁶. The majority of people with CF do not go on to develop this severe complication of cirrhosis with portal hypertension ⁵⁸¹, but those affected are at risk of variceal bleeding and progression to liver failure and need for transplantation, which increases the risk of morbidity and mortality ^{581,582}. Liver disease can have serious implications for the nutritional status of people with CF, i.e. increased risk of malabsorption, undernutrition/malnutrition and fat soluble vitamin deficiencies ²³³.

Disease Aetiology

CF-related liver disease often develops before or during adolescence, with ninety percent of severe disease being diagnosed by 20 years of age ⁵⁸¹⁻⁵⁸³. Liver disease almost universally affects people with CF who are pancreatic insufficient and have severe CF genotypes ^{581,584}. Male gender has also been suggested as a risk factor ^{581,582}.

The cause of CF-related liver disease remains largely unidentified, although it is thought to be related to the CFTR gene which is expressed in the epithelium of the bile ducts ⁵⁸⁰. Absence or dysfunction of CFTR likely causes the retention and accumulation of bile acids ⁵⁸⁰. Accumulation of bile acids leads to hepatocyte injury, which in turn increases fibrogenic and pro-inflammatory cytokines expression, eventually resulting in peribiliary fibrogenesis ^{580,585,586}. Ongoing inflammation and hepatocyte damage results in fibrogenesis, progressing over time to multilobular cirrhosis ²³⁶.

The prevalence of CF-related liver disease is poorly described, partly due to the absence of a universally accepted definition and the lack of sensitive non-invasive diagnostic tests. Development of cirrhosis and portal hypertension occurs in five percent of patients with CF with clinically significant hepatobiliary manifestations reported to occur in 15 to 30 percent of children and adolescents ⁵⁸². Upon death, autopsy has revealed that approximately 70 percent of adults with CF have severe liver disease and in many cases this was not recognised antemortum ⁵⁸⁷.

Assessment

DIET

Assess dietary intake of energy, protein and essential fatty acids

- Cirrhosis leads to increased basal metabolic rate and energy requirements ⁵⁸⁸
- Steatosis has been associated with malnutrition, and deficiencies of essential fatty acids, carnitine and choline ⁵⁸⁸



- Large ascites can cause early satiety ⁵⁸⁹
- Reduced appetites are common ⁵⁸⁹
- Dietary intake is often over-reported by those with liver disease ⁵⁸⁹
- Review fat soluble vitamin supplementation and pancreatic enzyme replacement therapy
- Liver disease may exacerbate the severity of malabsorption as a consequence of diminished bile acid secretion and/or circulation (i.e. cholestasis) ¹⁴⁴. Further increasing the risk of fat soluble vitamin deficiencies.
- People with CF can develop cholestasis, otherwise known as conjugated hyperbilirubinaemia (e.g. during infancy, and at end stage of decompensated chronic liver disease)

CLINICAL

Presentation of CF-related liver disease is often subclinical with many remaining asymptomatic until the pathological changes are diffuse and pronounced ¹⁴⁴. Signs and symptoms of people with portal hypertension^{2*} and multilobular cirrhosis include ⁵⁹⁰

HYPERSPLENISM

- Oesophageal or gastric varices
- Ascites
- Synthetic liver failure^{3*} (rare) ⁵⁹¹
- Difficulty in gaining and maintaining weight

Clinical presentation of severe liver disease may include ⁵⁹⁰

- Fatigue
- Nausea
- Abdominal distension and/or pain

ANTHROPOMETRY

The presence of ascites will confound anthropometric data with regards to measurement of weight and BMI, potentially causing overestimation of nutritional status ⁵⁸⁹. Use of mid arm circumference and skin fold measurements may be more appropriate anthropometric variables for people with severe liver disease as they do not require adjustment or interpretation for hydration ⁵⁸⁹. Hand-grip strength can also be a good functional assessment tool for liver patients, however this has not been validated in CF ⁵⁸⁹.

MEDICAL SCREENING AND DIAGNOSIS

Screening consists of annual liver transaminase measurement; if the levels are elevated, an abdominal ultrasound is obtained and done annually thereafter if cystic fibrosis-related liver disease is suspected. The risk of gallstones is also higher in cystic fibrosis ⁵⁹². Liver biopsies are not routinely obtained in CF-related liver disease unless another diagnosis is being considered that would change management ²³⁶. Furthermore, cystic fibrosis-related liver disease is patchy and can be missed on routine liver biopsy ⁵⁹².

BIOCHEMICAL & LABORATORY DATA

ELEVATIONS IN LIVER FUNCTION TESTS

Biochemical abnormalities are common in patients with CF. Results vary over time and may be absent even in those with advanced cirrhosis ⁵⁸⁰. Elevated alanine aminotransferase (ALT), aspartate aminotransferase (AAT) or gamma-glutamyl transferase (GGT) may be seen but none are predicative or indicative of severe CF-related liver disease ⁵⁹³.

FAT-SOLUBLE VITAMINS

The presence of liver disease can make accurate assessment of fat soluble vitamin levels challenging and less clear, because it is the liver that is responsible for producing the biochemical markers used in assessment, and it also is the primary location where large amounts of fat soluble vitamins are stored. Chapter 8 describes management of fat soluble vitamins in more detail.

- **Vitamin A:** Monitor serum retinol together with retinol-binding protein (RBP) to ensure appropriate therapy to prevent deficiency, as well as fasting serum retinyl ester concentration to assess for toxicity ^{78,144,202,252}. Calculation of retinol : retinol binding protein ratio will provide further insight into vitamin A status and the appropriateness of management. Calculation is outlined in Chapter 8.

2 * Portal hypertension may predate the onset of cirrhosis in some people with CF.

3 * Only 10 percent of people with CF will progress to loss of synthetic liver function characterised by a high bilirubin and vitamin K resistant coagulopathy.

- **Vitamin D:** Assess serum 25-hydroxyvitamin D
- **Vitamin E:** Including a serum vitamin E : total lipid ratio is particularly important when interpreting vitamin E status in liver disease ^{363,365,402} . Vitamin E deficiency may be missed if lipids are not considered ⁴⁰² .
- **Vitamin K:** The risk of vitamin K deficiency is increased in people with CF-related liver disease. Prothrombin time is an insensitive measure of vitamin K, and is generally only indicative of severe deficiency. The PIVKA-II (protein induced vitamin K absence-II/CF-related liver disease) test is a more sensitive measure of detecting vitamin K deficiency than prothrombin time and reflects vitamin K deficiency of the liver, however is not readily available ^{365,408} .

Intervention

Interdisciplinary input into the management of CF-related liver disease is essential (physician, dietitian, and pharmacist), ideally being overseen by a gastroenterologist. Treatments for liver disease remain supportive in nature; namely, optimisation of nutritional status and early identification/management of complications.

NUTRITIONAL SUPPORT

Should vitamin K supplementation be recommended for all people with CF-related liver disease? PICO 11.4.1

[Ungraded] Insufficient evidence to make a recommendation – follow recent consensus guidelines. ¹⁴⁴

Practitioners should be guided by the most recent recommendations for vitamin K supplementation in CF. The European consensus guidelines for the management of CF-related liver disease, suggest that daily supplementation of Vitamin K for children and adults is recommended ^{78,144}. Routine daily supplementation for people with pancreatic insufficiency is as follows:

- Infants: 300-1000 µg/d
- Children (>1year): 1000-10 000 µg/d
- Adults: 1000-10 000 µg/d

What are the requirements for effective supplementation in episodes of vitamin A deficiency in people with CF-related liver disease? PICO 11.4.2

[Ungraded] Insufficient evidence to make a recommendation – follow recent consensus guidelines. ¹⁴⁴

In the absence of evidence clinicians should be guided by the most recent consensus guidelines which suggest that high oral doses (5000 to 15 000IU/day) of vitamin A may be required to attain adequate vitamin A status in people with CF-related liver disease ¹⁴⁴. Careful monitoring of biochemical data to prevent vitamin A toxicity or deficiency is also recommended ¹⁴⁴.

The following nutrition strategies are highlighted in a recent expert-opinion based guideline ¹⁴⁴:

- Use nutritional support interventions to achieve optimal growth in children and weight in adults with CF-related liver disease :
 - Increase the proportion of fat in the diet and/or supplementary enteral feed to 40 to 50 percent of total energy intake.
 - Supplementation with medium chain triglycerides and use of polyunsaturated fatty acids may provide benefit to some people with CF-related liver disease
 - Caution with excessive use of carbohydrate supplements (e.g. glucose polymers) due to the risk of development of CF-related diabetes ⁵⁹⁴
- The supply of protein should not be routinely restricted, unless there are signs of decompensated liver failure and hepatic encephalopathy.
- Optimise use of pancreatic enzyme replacement therapy to enhance absorption of long-chain triglycerides and essential fatty acids.
- Avoid excess supplementation of salt in the presence of cirrhosis and portal hypertension to reduce the development of ascites.



PHARMACOLOGICAL AND MEDICAL INTERVENTIONS

Ursodeoxycholic acid is often used to treat CF-related liver disease and can result in normalisation of liver transaminases, but there is currently no evidence to support its use for the treatment or prevention of cirrhosis with portal hypertension in CF⁵⁹⁵. Concerns about its safety have also been raised⁵⁹⁶. As such, this is not a routinely recommended treatment.

LIVER TRANSPLANT

The best practice guidelines for the diagnosis and management of CF-related liver disease outline indications for liver transplantation in CF¹⁴⁴. The 2014 Australian Data Registry report describes one person with CF being accepted for a liver transplant in 2014¹⁸⁸. Close liaison between the CF team and the liver transplant team is essential to ensure optimal patient management.

Monitoring & Evaluation

Weight, body mass index, lung function, and vitamin status should be monitored regularly. All CF patients with liver disease require annual follow-up by gastroenterologist to evaluate the progression to cirrhosis and monitor for development of portal hypertension and other complications¹⁴⁴.

Practice Points PICO 11.4.1

The risk of vitamin K deficiency is increased in people with CF-related liver disease. Clinicians should base supplementation on the most recent recommendations for vitamin K supplementation in CF^{78,144}:

- Routine daily supplementation for all PI patients
- Infants: 300 – 1000µg/d
- Children (>1year) and adults: 1000 - 10 000 µg/d

Practice Points PICO 11.4.2

Supplement with high oral doses between 5000 – 15 000IU/day (1500ug - 4500 µg/d) with the aim of achieving the normal range of serum retinol for healthy individuals.

Use caution when giving doses above 20 000 IU/d (6000 µg/d) preformed vitamin A if RBP is low. A low retinol : RBP molar ratio may indicate deficiency but further increase in supplementation of preformed vitamin A may be toxic to the liver. Although not routinely available we recommend increased supplementation with β-carotene in these circumstances.

Monitor serum retinol and retinol binding protein to ensure the adequacy of therapy to prevent deficiency as well as fasting serum retinyl ester concentration to assess for toxicity.

11.5 Additional GI considerations & the role of the Gastroenterologist

Cystic fibrosis has wide-ranging effects on the gastrointestinal tract. In addition to the conditions described above, other common conditions and/or clinical manifestations of CF should also be considered. These include delayed gastric emptying, intestinal dysbiosis and infection, intestinal inflammation, intussusception and appendiceal disease.

GASTROPARESIS

The dysmotility that affects the gastrointestinal tract in CF may also involve the stomach. However, delayed gastric emptying (or gastroparesis) is not a consistent finding, with gastric emptying reported to be accelerated⁴⁹⁵, normal⁴⁹⁶ and delayed⁴⁹⁷ in patients with CF when compared to general population controls. Patients may report

symptoms of reduced appetite, nausea or early satiety. Affected patients may also present with symptoms similar to gastroesophageal reflux (e.g. recurrent vomiting). Gastroparesis may impact on oral caloric intake and nutritional status, glycaemic control, and also interfere with efficacy of pancreatic enzyme replacement therapy ¹¹¹. There is currently no “gold” standard for the diagnosis of gastroparesis. Various techniques have been used to measure gastric emptying (e.g. technetium scintigraphy ⁴⁹⁵, C-Octanoic breath test) ¹¹¹ and different test meals (solid vs. liquid) have been used. There is also a lack of validated reference ranges in certain age groups for the various techniques and test meals. Prokinetics and dietary modification is recommended for the management of gastroparesis ^{597,598}. In terms of dietary modifications, fat and fibre are known to delay gastric emptying, so limiting these sources may be beneficial ⁵⁹⁷. Enteral nutrition support should be considered if oral intake is found to be insufficient. An initial trial of continuous or small volume bolus gastric feeding (nasogastric or gastrostomy) should be considered. Failing this, continuous transpyloric feeding (jejunostomy or naso-jejunal feeding) is the next consideration ⁵⁹⁷.

INTESTINAL DYSBIOSIS

Intestinal dysbiosis, historically referred to as small bowel bacterial overgrowth (SBBO), is another well-reported complication of CF ²³⁶. SBBO may present with non-specific symptoms of abdominal pain, bloating, weight loss, diarrhoea and steatorrhoea. In addition, SBBO has been implicated with the development of intestinal inflammation in CF ²³⁶. Treatment of SBBO involves the use of enteric antibiotics, with different antibiotic regimens proposed ⁵⁹⁹. The role of probiotics in restoring the gut microbiota remains to be fully explored ([Chapter 15](#)).

INTUSSUSCEPTION

Intussusception occurs 10-20 times more frequently in patients with CF compared to the general population ⁶⁰⁰, however cases in CF remain uncommon. It is hypothesised that the adherent inspissated muco-faeculent material on the intestinal mucosa acts as lead point. Intussusception may present with symptoms of bowel obstruction, abdominal mass on abdominal palpation and poses the risk of intestinal ischaemia in the affected intestinal segment if missed. The differential diagnoses of DIOS, appendicitis and gastrointestinal cancer should also be considered. Similarly, a delayed diagnosis of appendicitis is reported in patients with CF ⁶⁰⁰.

OTHER GASTROINTESTINAL ENTEROPATHIES

Whether there is an increased prevalence of co-existing enteropathies such as inflammatory bowel disease (IBD) and coeliac disease among patients with CF is controversial. Previous reports indicate up to 17- and 3-fold increase in prevalence of Crohn’s disease and coeliac disease respectively in the CF population ^{601,602}. However, none of these studies have been replicated elsewhere. It remains unclear whether the initial reports of increased prevalence of IBD in CF were related to fibrosing colonopathy rather than true IBD ⁶⁰³. Nonetheless, refractory gastrointestinal symptoms should prompt a referral to gastroenterologist for further evaluation.

