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Cystic Fibrosis & disorders of the large intestine: DIOS, constipation, and colorectal cancer

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Abstract

Since 1966 when the Cystic Fibrosis Foundation Patient Registry (CFFPR) was founded, clinicians have witnessed significant advances in both the quality and quantity of life for patients living with Cystic Fibrosis (CF). As patients with CF live longer and fuller lives, increasing encumbrances from gastrointestinal manifestations of CF will be observed. This article serves to discuss "below the diaphragm" concerns involving the large intestine (Distal Intestinal Obstruction Syndrome, Constipation, and Colorectal Cancer). Avenues for development and implementation of clinical care protocols, particularly regarding proactive management of known associated conditions and cancer screening, will continue to be refined in the coming years. It falls to the multidisciplinary CF care team to be actively engaged in addressing these concerns effectively as priority shifts from relative acuity (typically related to early nutrition and lung function) to the travails of longevity as the CF population continues to age.

Keywords: Distal intestinal obstruction syndrome; DIOS; Constipation; Colorectal cancer; Colon cancer; Colon; Colonoscopy; Cystic fibrosis; Gastroenterology

1. Introduction

Since 1966 when the Cystic Fibrosis Foundation Patient Registry (CFFPR) was founded, clinicians have witnessed significant advances in both the quality and quantity of life for patients living with Cystic Fibrosis (CF) – so much so, that per a recent survival estimate, patients born and diagnosed with CF in 2010 may reasonably expect to live well into their 4th decade (and quite possibly their 5th decade with expected ongoing improvements in care) [1,2]. As patients with CF continue to live longer and fuller lives, increasing encumbrances from other non-pulmonary issues "below the diaphragm" are observed. Some issues, particularly those involving the large intestine such as Constipation and Distal Intestinal Obstruction Syndrome (DIOS), are lifelong and well-described. Others, including attendant risks for Colorectal Cancer (CRC) development as patients age (and the role of the cystic fibrosis transmembrane conductance regulator (CFTR) mutation in this development), are not. This article serves to discuss "below the diaphragm" concerns involving the large intestine in both critical categories.

2. Distal intestinal obstruction syndrome & constipation

2.1. Background

Obstructive disease of the intestine is part of the CF phenotype [3]. This typically manifests as Meconium Ileus (MI) in infants, and as constipation or Distal Intestinal Obstruction Syndrome (DIOS) in older children and adults with CF [2,4,5]. Given the observed clinical overlap in symptoms and reported complaints in adult patients with constipation and DIOS, establishing clear definitions of each entity can be helpful in establishing the diagnosis and subsequent treatment plan (particularly as options for treatment of

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more acute/subacute presentations of constipation and DIOS will also significantly overlap as well). Prophylactic "bowel regimens", comprised of single or multimodal laxative therapies, are based on "best practices" rather than formal trial data; nevertheless, they are widely used for both conditions, but can be cumbersome and variably effective. We will discuss the approaches to diagnosis, treatment options, and prophylaxis further.

2.2. Clinical presentation of DIOS & constipation

The clinical manifestation of DIOS in the post-neonatal CF course, first described in 1941 by Rasor and Stevenson and given its name of "Meconium Ileus Equivalent" (MIE) in 1962 by Jensen [6], is a common complication in patients with CF over 15 years of age [5,7,8]. It is characterized by accumulation of inspissated fecal material in the distal ileum and proximal colon, and may present acutely or subacutely with varying severities of intestinal obstruction or intermittent abdominal pain (generally in conjunction with abdominal distention) [9,10]. However, a recent international prospective observational study by Munck and colleagues suggests the incidence of DIOS in children and adults with CF are roughly the same [11], with a prevalence of 10–15.8% among the CF population (though estimates within other selected CF populations may vary) [3,12].

Clinical symptoms may significantly overlap between patients with constipation and DIOS depending on the time course and severity/progression involved. There has been much confusion related to this overlap both in clinical practice and in the literature which may lead to overestimation (and sometimes underestimation) of the prevalence of these conditions; this has led to challenges in addressing patient symptoms efficiently and effectively. Recognizing this ongoing difficulty, and seeking to clear a pathway forward for the conversation and management of these disorders, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) CF Working Group published definitions for both DIOS and Constipation, upon which future work could be founded (Tables 1 and 2, respectively) [8].

It is important to recognize the key differences between DIOS and Constipation based upon these established working definitions. DIOS is defined the presence of partial or complete obstructive phenomena (abdominal pain and/or distention, nausea/vomiting, limited ability or inability to pass stool/flatus, etc.), usually with documented stool burden in the distal small bowel and/or proximal right colon on imaging (Image 1); symptoms of DIOS are usually also more acute in nature. In contrast, Constipation is typically associated with more gradual onset of symptoms, and is defined by improvement in symptoms with institution of appropriate laxative regimens. Although not required for diagnosis of Constipation, abdominal radiography (AXR) or Computed Tomography (CT) imaging, if performed, may demonstrate a more diffuse colonic stool burden throughout the entire colon (Image 2) [8,12].

Table 1
ESPGHAN CF working group definition for DIOS in CF [8].
Adapted from R. Houwen et al. JPGN 2010; 50: 38–42.

1. Complete intestinal obstruction as evidenced by vomiting of bilious material and/or fluid levels in small intestine on abdominal radiography
2. Fecal mass in ileocecum
3. Abdominal pain and/or distention
Complete DIOS: 1 + 2 + 3
Incomplete/impending DIOS: 2 + 3, without 1

Table 2
ESPGHAN CF working group definition for constipation in CF [8].
Adapted from R. Houwen et al. JPGN 2010; 50: 38–42.

1. Abdominal pain and/or distention
2a. Reduced frequency of bowel movements in the last few weeks or months
2b. Increased consistency of stool in the last few weeks or months
3. Symptoms of 1 and 2 are relieved by the use of laxatives
Constipation: 1 + (2a or 2b) + 3

2.3. Differential diagnosis

Distinguishing between DIOS and severe constipation may be difficult, though typically the acuity of symptom onset as well as the presence of progressive obstructive symptoms may be more indicative of DIOS (when paired with suggestive physical exam and imaging findings). It is important to recognize that acute appendicitis or intestinal intussusception may mimic clinical features of DIOS; this should be considered carefully in appropriate patients. Intussusception (usually involving the ileocecum) has been described in approximately 1% of patients with CF, and may be self-limited/transient in nature; this may not always require directed medical or surgical management to resolve [10]. Inflammatory Bowel Disease (IBD), particularly ileocolonic Crohn's Disease, may also present acutely with obstructive symptoms, and should be considered in cases of presumed DIOS refractory to usual medical management. There is increased incidence of digestive cancers in CF as well [13], warranting appropriate consideration if other alarm features (unrelenting obstruction, unexplained weight loss, iron deficiency anemia, etc.) are present. These conditions do not represent the entirety of the differential diagnosis for symptoms involving the right lower quadrant of the abdomen; the critical importance of a detailed history and physical examination cannot be understated in establishing the correct diagnostic and treatment plan.

2.4. Risk factors for DIOS

Several secretory and intestinal motility-related factors may contribute to the pathophysiology of DIOS in patients with CF, including the role of CFTR in reduced chloride and water secretion into the intestinal lumen, reduced bile salt presence and triggering of ileal secretion, fat malabsorption and its induction of the ileal brake, prolongation of gut transit (briefly summarized in Table 3) [10]. In addition to the multiple pathophysiologic mechanisms at play, several clinical factors may also contribute to risk for (and recurrence of) DIOS (Table 4) [10]. DIOS is typically described in patients with a severe CFTR genotype and/or advanced pulmonary disease, although it can still be encountered in patients with less-severe CFTR genotypes as well [2,10]. Most patients with DIOS are

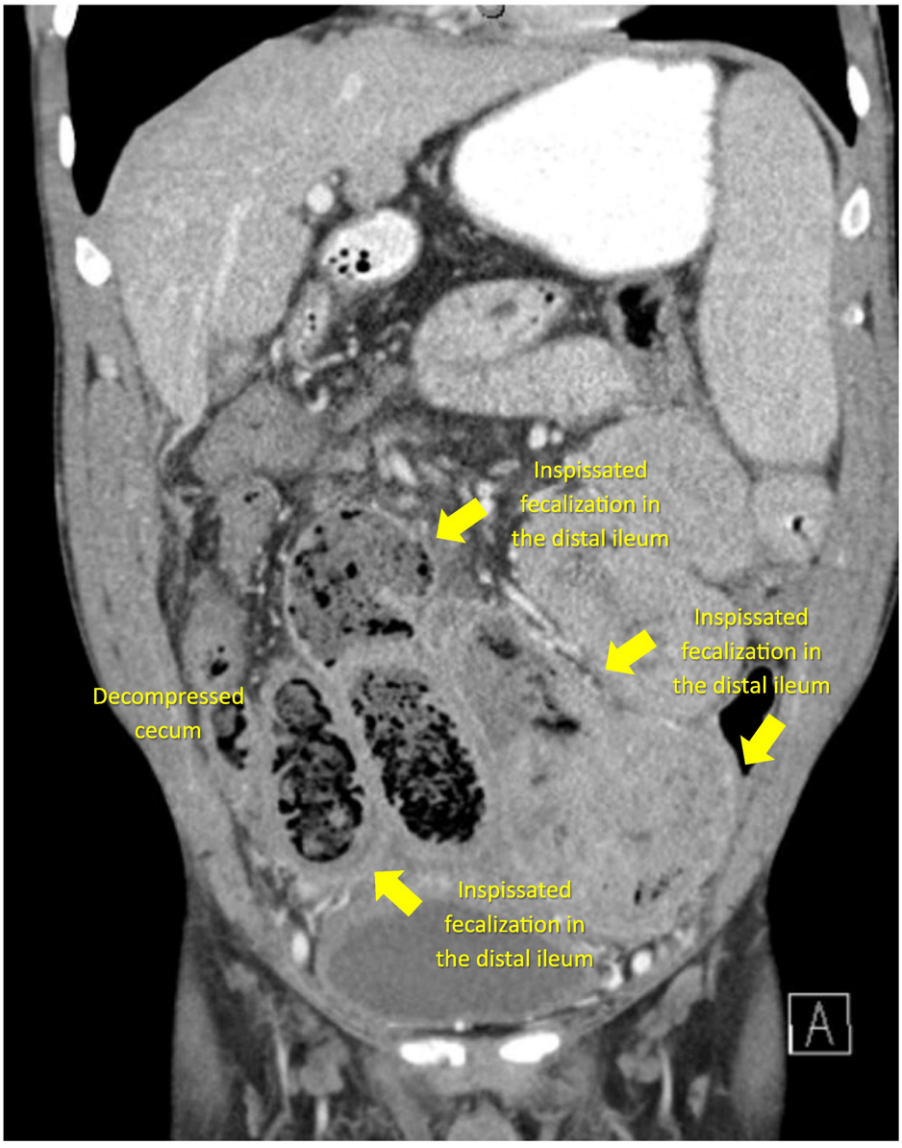

Image 1. Recurrent DIOS in an adult patient with CF. Characterized by inspissated fecalization within the distal ileum with a decompressed cecum on CT scan (though the proximal right colon may also be involved in some cases), extending proximally into the small bowel with associated small bowel dilation. (denoted by arrows). Image courtesy of James M. Abraham, MD (University of Minnesota, Minneapolis, MN, USA).

pancreas-insufficient (PI), with <10% of DIOS patients being pancreas-sufficient (PS) [2,8,10].

Previous history of MI appears to be a fairly strong predictive risk factor in several studies, as well as history of prior surgery for MI [8,11,14]. Nearly 50% of patients with CF diagnosed with DIOS had presented with MI at birth in a large European study, compared to an estimated prevalence of 10–15.8% among all patients with CF. [3,8,12].

Organ transplantation in patients with CF, notably after lung transplantation [6], appears to increase risk for DIOS; several international studies have identified an incidence of 10–20% in the post-operative period [15,16]. Among all-comers undergoing lung transplantation, risk for mortality is high with laparotomy when non-surgical therapies for intra-abdominal complications have failed [17]. Previous literature has described that up to 10% of CF patients experiencing DIOS following lung transplantation may require laparotomy [12]. Post-operative factors which may play a role include post-operative ileus, bowel dysmotility due to narcotic pain medication use, prolonged immobility/deconditioning, adhesions from prior surgery, and vascular depletion in the acute post-operative period [10].

Patients with DIOS often report or experience symptoms of worsened fat malabsorption that may precede an episode; the presence of steatorrhea, weight instability, or progressive declines in key nutritional biomarkers (fat-soluble vitamins, albumin) should warrant concern for clinicians caring for patients with history of DIOS and assessment of pancreatic enzyme replacement therapy (PERT) dosage/adherence. Increases in unabsorbed fat entering the distal ileum may activate the ileal brake, potentially inducing risk for DIOS by promoting fecal stasis and worsening gastric and intestinal dysmotility [5,18].

Increased insensible fluid losses, sometimes brought about by concomitant illness or environmental factors (i.e. CF pulmonary exacerbation, other febrile illness, increased ambient temperature),

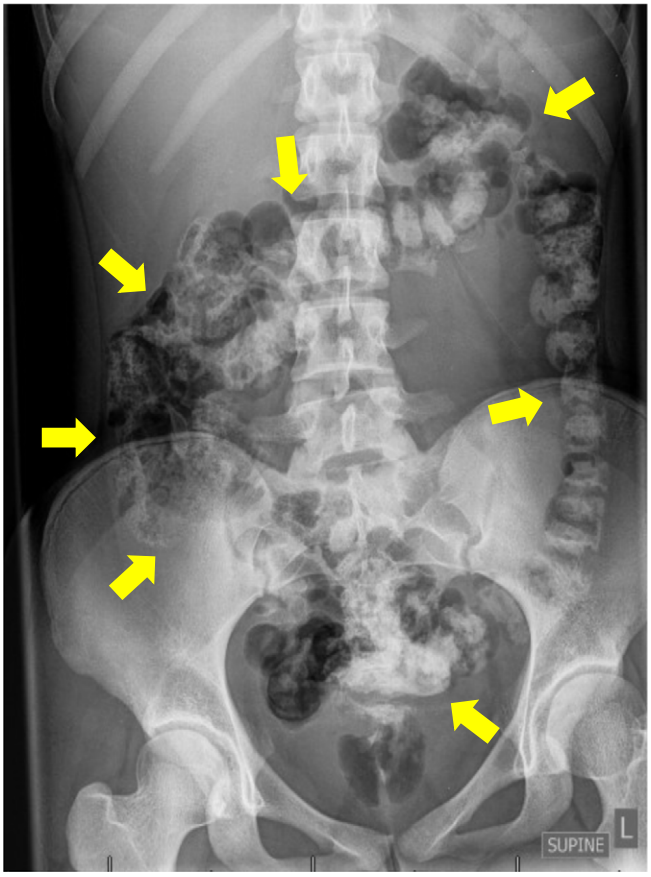

Image 2. Constipation in an adult patient with CF. Characterized by diffuse stool and gas pattern throughout the entire colon on AXR (denoted by arrows). Image courtesy of James M. Abraham, MD (University of Minnesota, Minneapolis, MN, USA).

and relative dehydration may contribute to DIOS [10,19]; the impacts of these factors may be overestimated, however, as inadequate fluid intake may be a more likely contributing cause when prospectively assessed [11]. CF-related Diabetes Mellitus (CFRD) may be a possible risk factor for DIOS, but this has not yet been objectively corroborated [11].

Of particular importance for the clinician to remember, is that "***DIOS begets DIOS***". Patients with prior episodes of DIOS may be 10 times more likely to experience another episode [10]. While not yet validated by robust evidence, this may have clinical implications for symptom screening and proactive initiation of "bowel regimen prophylaxis" with an appropriate scheduled laxative regimen in selected patients with CF.

Table 3
Pathophysiology of DIOS [10].
Adapted from C. Colombo et al. Journal of Cystic Fibrosis 2011; 10: S24–S28.

- *Secretory*
  - Defective chloride and water secretion into gut lumen via CFTR
  - Enhanced fluid uptake via epithelial sodium channels
  - Loss of bile salt-triggered secretion in terminal ileum
- *Impaired motility*
  - Enteric neuromuscular dysfunction
  - Muscular hypertrophy
  - Fat malabsorption

Table 4
Risk factors for DIOS [10].
Adapted from C. Colombo et al. Journal of Cystic Fibrosis 2011; 10: S24–S28.

- Severe genotype
- Pancreatic insufficiency
- Dehydration
- Poorly controlled fat malabsorption
- History of Meconium Ileus (MI)
- History of DIOS
- Post-organ transplantation
- CF-related Diabetes (CFRD)

2.5. Management of DIOS & constipation

There is no single validated strategy for treatment of DIOS or constipation in the setting of CF. For constipation, gradual step-up therapy (typically using non-stimulant stool softeners, fiber, or polyethylene glycol (PEG)-based solutions first) have been used safely and effectively for short- and long-term use in patients with CF. [20] To a certain extent, a similar approach to diagnostic evaluation (when necessary) and gradual therapeutic escalation used in non-CF patients may be utilized by the clinician based on anecdotal experience [21,22]; consideration for specialty consultation with a gastroenterologist familiar with CF may be indicated when response to initial conservative treatment has not yielded timely resolution of symptoms.

Approaches to treatment of DIOS are still largely empiric based on a combination of available evidence, individual center experience, and proposed best practices. In fact, individual protocols for DIOS treatment widely varied among the centers participating in the ESPGHAN Working Group's multi-center study (utilizing oral lavage, rectal/enema-based lavage, or both); each center's preferred protocols appeared to be equally effective [8]. In 2016, the Cystic Fibrosis Foundation DIOS Task Force published a Clinical Pathway to aid assessment and management decisions in patients with subacutely and acutely symptomatic DIOS [23]. When symptoms of complete DIOS are present (i.e. bilious vomiting, inability to pass stool or flatus, severe abdominal pain and distention), hospitalization with bowel rest and urgent nasogastric decompression are recommended; subspecialty consultation with Gastroenterology (and possibly Surgery if peritoneal abdominal symptoms are present) may be advisable for management during the acute episode and to aid in DIOS risk reduction management following discharge (discussed later in *Prevention of DIOS & Constipation*) [23].

2.5.1. Osmotic laxatives

Osmotic non-stimulant laxatives remain the backbone of bowel regimens used for management of DIOS & Constipation. Polyethylene glycol (PEG) remains the most commonly used in both children and adults, and can be utilized in several forms for oral lavage (by nasogastric tube if needed) in patients without vomiting or symptoms of complete obstruction. PEG is available in several preparations, including an isoosmotic solution that may help to reduce severe fluid shifts during use. An isoosmotic PEG solution (Go-Lytely®, Movicol®, etc.) may be administered at a dose of 20–40 mL/kg/h, up to a maximum of 1 L/h for a total of 8 h; therapeutic success is

determined by achievement of clear fecal effluent with improvement in abdominal pain, distention, and vomiting [10,24]. Imaging (usually an AXR) may be advisable after therapeutic lavage to objectively document response [23]. Lactulose and sorbitol have also been used as alternative osmotic laxatives, typically in patients intolerant of PEG; their role in DIOS management has been limited due to common associated side effects of bothersome bloating and abdominal discomfort. Magnesium citrate preparations have also been used for intermittent oral lavage in patients intolerant to PEG solutions; this may be center- and practice-specific when used.

2.5.2. Sodium meglumine diatrizoate (Gastrografin)

Sodium meglumine diatrizoate (Gastrografin) is a hyperton-ic radio-opaque contrast medium that has been observed to be efficacious in relieving an acute DIOS episode when used in oral or enema applications as required [7]. Use of this hypertonic solution orally is not completely without risk; while relatively rare, cases of hypovolemic shock (due to rapid severe fluid shifting), necrotizing enterocolitis (in neonates), and bowel perforation have been described [25,26]. When performed by an experienced care team, however, therapeutic enema with diluted Gastrografin (defined as rectal instillation of Gastrografin with visualization of the terminal ileum) has had demonstrable success when used in children and adult patients with CF. This may be considered a potential preferred first-line therapy (either prior to or subsequent to PEG lavage) once the diagnosis of acute partial or complete DIOS requiring urgent hospitalization has been established [7,10,23].

2.5.3. N-acetyl cysteine (Mucomyst®)

N-acetyl cysteine (NAC) has been a mainstay mucolytic treatment in CF pulmonary disease; oral NAC formulations have been used for similar effect in management of refractory constipation and DIOS in patients with CF for many years. Its use has been relegated to an adjunct maintenance therapy with the more predominant use of PEG lavage and Gastrografin enema in first-line treatment of acute DIOS [10,11].

2.5.4. Lubiprostone (Amitiza®)

Lubiprostone is a Type 2 chloride channel (ClC-2) activator that induces intestinal chloride secretion and decreases transit time via prostanoid receptor signaling; a pathway which is of interest in the management of patients with CF experiencing refractory constipation, or for adjunct management in patients with DIOS [27]. Studies are conflicting regarding the role of CFTR in intestinal chloride secretion (most pertinent in patients with CF) as lubiprostone appears to work by an unrelated chloride activating pathway, but recent data would suggest that such induced secretion only results in the presence of functional CFTR. As such, efficacy in patients with CF for management of constipation (or use as an adjunct agent for multimodal maintenance treatment of DIOS) may be limited [28]. In the United States, lubiprostone is currently only approved for use in non-CF adults [29]. While some studies have demonstrated safety and tolerance for management of functional constipation in non-CF children [30], due to limited available data, lubiprostone is not yet approved for use in the pediatric population. This agent may have a role as an adjunct component of a multimodal bowel regimen in selected patients with CF.

2.5.5. Linaclotide (Linzess®)

Linaclotide is a guanylate cyclase-C (GC-C) ligand agonist which binds to the GC-C receptor located on the luminal surface of intestinal enterocytes. This binding increases intracellular levels of cyclic guanosine monophosphate (cGMP) and stimulates intestinal fluid secretion, most notably through phosphorylation and activation of CFTR. Activation of CFTR results in secretion of chloride and bicarbonate into the intestinal lumen as well as decreased transit time [31]. Linaclotide, unlike lubiprostone, has not yet been formally studied in CF; efficacy in patients with CF has been variable per anecdotal experience (possibly related to its similar indirect reliance on retained CFTR function). In the United States, linaclotide has not been approved for use in the pediatric population. This agent may have a role as an adjunct component of a multimodal bowel regimen in selected patients with CF.

2.5.6. Endoscopic and surgical approaches

Endoscopic management of DIOS may be considered in very highly-selected cases. Anecdotal reports of Gastrografin delivery to the cecum via colonoscopy [32], as well as aggressive colonic irrigation under colonoscopic visualization [33], have been described as potential therapeutic approaches in non-surgical candidates with refractory acute DIOS. These procedures are often quite technically demanding, and do need to be performed with experienced Gastroenterology and Surgery teams given the potential for serious harm (i.e. chiefly respiratory complications or bowel perforation). Surgical management for refractory DIOS is often fraught with significant morbidity and mortality, and may vary depending on the clinical urgency, pulmonary status, and extent of surgery planned (ileocolonic lavage and manual disimpaction, colonic lavage via appendicostomy tube, ileal diversion with or without bowel resection, modified antegrade continence enema procedure) [34,35]. Thankfully, with prompt recognition and initiation of treatment with PEG lavage and/or Gastrografin enema, most episodes of acute severe DIOS may be managed non-surgically.

2.6. Prevention of DIOS & constipation

As with treatment, there is no single validated strategy for prevention of DIOS recurrence; an individualized step-wise multidisciplinary approach is recommended. Factors important to both patients and the multidisciplinary CF Clinical team include maintenance of adequate hydration and adequate exercise. The role of fiber supplementation in CF is unclear; given the inherent propensity for slow transit and stool viscosity, fiber supplementation may worsen symptoms of bloating, flatulence, and constipation in some patients. Unopposed fat malabsorption may contribute to worsening slow transit and stool viscosity as well; multidisciplinary efforts by the CF Clinical Team (Pulmonology, Gastroenterology, Nutrition, Social Work, etc.) focused on ensuring access and

adherence to pancreatic enzyme replacement therapy (PERT) is critical for these patients to thrive.

As discussed above, it is important to remember that "***DIOS begets DIOS***". Given the known significant risk of recurrence associated with a prior episode of DIOS, consideration for proactive initiation of a scheduled bowel regimen may be needed in affected patients. Often this requires scheduled use of PEG-based solutions (typically Miralax® mixed into 8–10 oz of water or juice) as a first-line preventive agent, used at least 1–3 times daily as tolerated to ensure adequately soft stool consistency and antegrade throughput. For escalating symptoms occurring without vomiting, experience at individual centers may warrant consideration for oral PEG lavage performed at home (if tolerated) as a strategy to potentially avoid hospitalization. A "rescue regimen" consisting of a 2–4 L of isoosmotic PEG solution (typically Go-Lytely® or an equivalent) ingested over 4 h, repeated once depending on response has been used to varying effect [23].

The role of intestinal secretogogues (i.e. lubiprostone and linaclotide) as adjunct preventive agents may have a role in some selected patients with CF and subsequently documented clinical response. The interaction of oral NAC, either alone or in addition to secretogogue use, has not been studied extensively from the standpoint of prevention of DIOS recurrence, but may have some limited utility per anecdotal experience.

As discussed above, previous literature has described that up to 10% of CF patients experiencing DIOS following lung transplantation may require laparotomy [12]. As such, proactive pre-operative bowel lavage and a post-operative bowel regimen may be need to be implemented in patients with CF undergoing lung transplantation [15,36].

2.7. Potential clinical trial endpoints & future directions

There is no single validated strategy for treatment or prevention of DIOS or Constipation in patients with CF, though individual centers may have employed several center- and practice-specific modalities to help care for these complications as they occur. Institution of common clinical practices for acute DIOS could be studied in multiple centers, potentially utilizing "Clinical Pathways" or decision-making models already available to allow for mindful refinement of the current best-practice (but individual center-based) approaches. Future study could also be directed at comparing time to discharge in hospitalized patients with DIOS depending on initial presenting symptoms and use of PEG lavage vs. early Gastrografin enema, as well as assessing time to next recurrence in these same patients with or without institution of a standardized bowel regimens (retrospectively and prospectively).

3. Cystic fibrosis & colorectal cancer

3.1. Background

Colorectal Cancer (CRC) currently ranks as the second leading cause of cancer-related death in the United States. Approximately 134,000 new cases of CRC are anticipated in 2016 with an estimate of approximately 49,000 CRC-related deaths [37,38]. Among European patients, CRC ranks second only to lung cancer as the leading cause of cancer-related death; in 2012 alone, 400,000 cases of CRC were estimated with over 200,000 deaths recorded [39]. In the general US population, CRC is most commonly diagnosed in adults over the age of 65 with a median age of 68 for CRC-related deaths [38], though more recent data of increasing CRC incidence in patients younger than age 50 may warrant reconsideration of this typically-accepted age risk profile in the future [40].

3.2. Cystic fibrosis as a hereditary colon cancer syndrome?

Within this context, it is important to recognize the increasing awareness and relevance of these common malignancies in Cystic Fibrosis (CF) patients, particularly as these cancers appear to arise at a much younger age in comparison. In a seminal article published in the *New England Journal of Medicine* in 1995, Neglia and colleagues, as part of the Cystic Fibrosis and Cancer Study Group (CFCSG), delved further into the anecdotal evidence suggesting a trend towards certain cancers among patients with CF. In their retrospective cohort analysis of 28,511 CF patients from the US and Canada from the period of 1985–1992, of 37 total cancers identified in 164,764 person-years of follow-up, 13 cancers were noted to arise within the digestive tract with a Standardized Incidence Ratio (SIR) of observed-to-expected cancers of 6.5 (95% Confidence Interval, 3.5–11.1). The average age at diagnosis of these digestive cancers was 32.5 ± 9 years [13]. In the following years after this original publication, the CFCSG revisited and expanded this database twice to describe granular cancer trends in CF over a 10-year [41] and 20-year study period [42]. Regarding the risk of digestive organ cancer development over the periods of 1990–1999 and 2000–2009, the group reported an SIR of 5 (95% CI, 3.3–7.3) and an SIR of 2.6 (95% CI, 1.7–4), respectively for each 10-year time period. Within these subsets, an SIR of 7.8 (95% CI, 4.2–13,3) and SIR of 5.3 (95% CI, 3–8.7) for colon cancer was observed respectively within each 10-year period [42].

When the risk of digestive organ cancer in CF was assessed over the entire 20-year period (1990–2009), an SIR of 3.5 (95% CI, 2.6–4.7) with an Absolute Excess Risk (AER) of 7.3 more cases than expected per 100,000 person-years was described. Of these digestive cancers, an SIR for colon cancer was 6.2 (95% CI, 4.2–9) with an AER of 4.9 more cases than expected per 100,000 person-years was described; colorectal cancer represented the preponderance of digestive cancers identified in the 20-year cohort – far and away, more than the esophageal, stomach, small bowel, hepatobiliary/pancreatic, and miscellaneous digestive malignancies combined. In keeping with prior anecdotal experience and data, risk for bowel cancer was more likely to be associated with male sex, severe functional CF genotype, F508del homozygosity, and age >30 years [42]. These trends towards increased risk for digestive cancers, particularly of the colon and rectum, were only magnified in patients who had undergone lung transplantation [42,43].

Considering that cancers of the digestive tract (particularly CRC) appear to typically arise at an older age in the general population, one might surmise from the data thus far that this might occur similarly in patients with CF as well (relatively speaking); alas, this is not always the case as CRC has been reported in younger patients with CF under the age of 25 as well [44]. This warrants consideration as to whether there are other factors specific to CF that may play a role in the risk for earlier development of digestive cancers, particularly of the colon and rectum.

While inflammatory and non-inflammatory mechanisms and their speculated contributions to risk for CRC require serious consideration (Table 5), they fail to fully account for the inherent malignancy risk associated with CFTR mutations alone, particularly with regard to cancers of the digestive organs [49]. In recent years, increasing evidence has arisen that implicates CFTR as one of 77 potential genetic drivers for CRC development [50]; furthermore, loss of expression of CFTR in patients with early-stage CRC has been associated with poorer disease-free outcomes [51].

In light of well-established CRC screening efforts for the general non-CF population, these discoveries beg several important questions of clinicians caring for their aging patients with CF: 1) Should CF be considered a form of hereditary colon cancer syndrome?; 2) Should CF clinicians be taking more proactive steps to screen for CRC?; 3) If screening should be performed, when and how should it start in CF patients, given the inherent genetic risk, to avoid the natural progression of CRC from adenomatous precursors?; and 4) Can we accurately extrapolate experiences and data from non-CF populations to make screening decisions going forward? [52].

3.3. Colorectal cancer screening & surveillance in cystic fibrosis

When considering screening strategies for the CF population, particularly in those CF patients with severely compromised lung function, the role for non-invasive vs. more-invasive testing remains an important consideration. Non-invasive studies might include guaiac Fecal Occult Blood Testing (gFOBT), Fecal Immunohistochemical Testing (FIT), or imaging modalities such as Air-Contrast Barium Enema (ACBE) or Computed Tomography Colonography (CT Colonography or "Virtual Colonoscopy"). FIT has been proven to be a more sensitive screening modality in stratifying patients more likely to have lesions detected on colonoscopy in the general population [53], and may be a reasonable screening tool to utilize in CF patients with more tenuous pulmonary status. More-invasive testing with direct white-light optical colonoscopy remains the current primary strategy for reducing risk of CRC mortality in higher-risk individuals (and may have pertinent bearing on those with CF if this is considered a hereditary CRC syndrome) [54,55]. As yet, there is not yet a single validated strategy for CRC screening in the CF population, but several studies have been published in recent years which may provide some clues towards future care.

Table 5
Speculated contributing factors for colorectal cancer in CF.

Inflammatory risk factors
- Chronic intestinal inflammation
  - Host-gut interaction in setting of disrupted intestinal microbiome [45,46]
  - Role of repeated and/or chronic insults to intestinal microbiome (via disease or antimicrobial pressure)?

Non-inflammatory risk factors
- Chronicity and severity of intestinal cell turnover [20,47]
- Alterations in mucin gene expression (and intestinal mucus composition) [41,45]
- Native bile acid composition, differences/alterations in bile acid exposure [13,48]
- Chronic nutritional deficiencies [13]
- (Transplanted patients) Intensity, duration, and/or type of immunosuppressive exposure [42,43]

CF-specific risk factors
- Role of CFTR as oncogene? [49–51]

In 2010, the University of Minnesota Cystic Fibrosis Center began systematically screening all eligible adult CF patients via white-light optical colonoscopy [45]. Screening colonoscopy was recommended to eligible patients under the following inclusion criteria: age ≥ 40, FEV1 (Forced Expiratory Volume in 1 s) $\geq 40\%$ of predicted value, and no colonoscopy in the preceding 5 years. Patients were primarily asymptomatic (34 out of 45 patients total), though the results of diagnostic and surveillance exams (presence/number of adenomatous polyps) performed during the study period were also recorded. Colonoscopies performed through the University of Minnesota were completed by a single gastroenterologist, and utilized a rigorous bowel preparation to improve visualization at the time of the procedure. Several patients had undergone colonoscopy outside of the University of Minnesota; these were also included in the database if inclusion criteria were met during the study period. Several patients had also undergone follow-up colonoscopies (surveillance and diagnostic exams) during the study period. In total, colonoscopy results from 45 CF patients was reviewed and reported. Median age of males included in the study was 46.4 ± 6.3 years of age; median age of females included in the study was 44.2 ± 5.8 years of age. Notably, of the 36 total colonoscopies performed in non-transplant CF patients, 12 examinations were positive with findings of adenomatous polyps. Males represented the bulk of the positive examinations, even when exams done purely for screening were separated out from the total exams performed. Six cases with identified advanced adenomas (defined as polyps >1 cm in size or with villous features) were reported exclusively among the males with positive exams in this study. This study would suggest that the prevalence of advanced and non-advanced adenomas is increased among patients with CF, and these appear to occur much earlier in comparison to non-CF patients of similar age [56].

Gory and colleagues at the Alfred Hospital in Melbourne, Australia, found similar concerning trends for an increased prevalence of colonic adenomas and malignancy in their matched case-control study involving a cohort of 50 adult CF patients and 100 non-CF patients who had undergone colonoscopy for any reason during the study period of 2007–2012. They documented 5 cases of CRC (10%), 13 cases with non-advanced adenomas

(26%), and 16 with advanced adenomas (26%) in their adult CF patients; only 1 case of CRC (1%), 11 cases of non-advanced adenomas (11%), and 6 cases of advanced adenomas (6%) in the non-CF control group. Compared to the control group, CRC risk was increased 10-fold (OR 10.0, 95% CI 1.2–85.6; $p = 0.03$), adenoma risk was increased 3-fold (OR 3.34, 95% CI 1.23–9.08; $p = 0.018$), and advanced adenoma risk was increased approximately 7-fold (OR 6.95, 95% CI 2.3–21.01; $p = 0.001$) among patients with CF. [57].

In an update to their report from 2014, the Minnesota CF Center published a report of their systematic recording of colonoscopy results from 2008 to 2015 in patients ≥ age 40 (noting that formal screening recommendations were provided to eligible adult patients from the CF Center starting in 2010). This data included results from initial screening, re-screening, and surveillance colonoscopies performed. Adenomas were identified in 43 of 88 initial screening colonoscopies performed (49%). Of 15 patients with a negative initial screening colonoscopy, re-screening was performed within 5 years; seven re-screening examinations revealed adenomas, and three revealed advanced adenomas that had arisen within the interval screening period. Overall, lesions with advanced adenomatous features were identified in 20/88 patients screened (23%). The presence of three or more adenomatous lesions and/or advanced adenomas were identified in 28/88 patients (32%), with carcinomas identified in 3/88 patients [58]. The prevalence of adenomas, as well as presence of advanced adenoma on initial screening or re-screening, is significantly increased in comparison to non-CF age-matched cohorts (and may, in certain circumstances, equate to risk seen in non-CF nonagenarians) [59,60].

Regarding risk factors associated with polyp formation in these patients, Cystic Fibrosis-related Diabetes (CFRD) and F508del homozygosity were found to be statistically significant risk factors. Additionally, while not statistically significant, a trend towards statistical significance was found in patients with history of lung transplantation. In assessing risk factors associated with multiple polyp formation or advanced polyp features, male sex and lung transplantation were identified as statistically significant factors. Of the three patients in the cohort that were diagnosed with colonic malignancy, all three were F508del homozygotes with documented CFRD [58].

Interestingly, of 16 patients with any adenoma(s) identified on initial screening colonoscopy who had also undergone surveillance colonoscopy within 1–2 years of screening (as per center recommendations), 13/16 (81%) were noted to have persistent findings of adenomatous lesions with ongoing surveillance; of this group, 6/16 (38%) were found to have advanced features histologically on subsequent exams [58]. This study suggests that starting routine CRC screening at an earlier age than the general population, with shorter intervals for re-screening or surveillance, may need to be strongly considered in the future care of adult patients with CF. Currently, a single CRC screening strategy has not yet been implemented, but guidance from national and international CF organizations may be forthcoming; in the United States, screening/surveillance recommendations from the Cystic Fibrosis Foundation (Bethesda, MD, USA) for transplant and non-transplant patients with CF are anticipated later this year. Until that time, individual CF centers will need to assess their specific CF populations to determine if a single center-based strategy would be sustainable and effective per their local practices and available resources.

3.4. Potential clinical trial endpoints & future directions

A single CRC screening strategy has not yet been widely implemented, though guidance from national and international CF organizations may be forthcoming. As individual centers begin to establish CRC screening programs, further multi-center study should be directed at determining incidence of adenomas and advanced pathology on the index screening exam (helping to better target the optimal screening age for patients with CF), as well as time to emergence of adenomas and advanced pathology thereafter (helping to better target recommended surveillance intervals).

4. Clinical practice points

- Distal Intestinal Obstruction Syndrome (DIOS) and Constipation are common gastrointestinal complications of Cystic Fibrosis (CF); providers should actively inquire if patients are experiencing symptoms suggestive of these conditions.
- DIOS increases risk for future episodes of DIOS; gentle implementation of a step-up bowel regimen (in addition to encouraging adherence to dietary/lifestyle factors) titrated to symptom control may be required in long-term management.
- There is an increased risk for digestive cancers, particularly Colorectal Cancer (CRC), in patients with CF.
- As CF may have features akin to a hereditary CRC syndrome, institution of proactive CRC screening and surveillance protocols within individual centers may need to be considered as CF lifespans continue to expand.

5. Summary

As patients with CF live longer and fuller lives, increasing encumbrances from the GI manifestations of CF will be observed. Avenues for development and implementation of clinical care protocols, particularly regarding proactive management of known associated conditions and cancer screening, will continue to be refined in the coming years. It falls to the multidisciplinary CF care team to be actively engaged in addressing these concerns effectively as priority shifts from relative acuity (typically related to early nutrition and lung function) to the travails of longevity as the CF population continues to age. The need for efficient transitions within the multidisciplinary team – particularly from Pediatric to Adult Gastroenterology providers accustomed to the multisystemic nuances of CF – becomes ever more important as the overlap of increasingly complex adult comorbidities evolves across the extended CF lifespan.

Conflict of interest

Authors declare no conflict of interest.

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