Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients

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Abstract

Complete or incomplete intestinal obstruction by viscid faecal material in the terminal ileum and proximal colon – distal intestinal obstruction syndrome (DIOS) – is a common complication in cystic fibrosis. Estimates of prevalence range from 5 to 12 episodes per 1000 patients per year in children, with higher rates reported in adults. DIOS is mainly seen in patients with pancreatic insufficiency, positive history of meconium ileus and previous episodes of DIOS. DIOS is being described with increasing frequency following organ transplantation. Diagnosis is based on suggestive symptoms with a right lower quadrant mass confirmed on X-ray. The main differential is chronic constipation. Treatment consists of rehydration combined with stool softening laxatives or gut lavage with balanced electrolyte solutions. Rapid fluid shifts have been described following osmotic agents. Avoiding dehydration and optimizing pancreatic enzyme dosage may reduce the chance of further episodes. Prophylactic laxative therapy is widely used, but is not evidence-based.
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1. Introduction

Distal Intestinal Obstruction Syndrome (DIOS) is a common complication in Cystic Fibrosis (CF) patients [1,2].

It is characterized by the accumulation of viscid faecal material within the bowel lumen combined with sticky mucoid intestinal content adherent to the intestinal wall of the terminal ileum and caecum. This mass is strongly connected to the crypts and villi and difficult to remove. In many cases, this is a permanent condition, sometimes aggravated by new material which explains the intermittent course of the symptoms. It may present acutely with intestinal obstruction or, more commonly, sub-acutely with intermittent abdominal pain generally in combination with abdominal distension.

Characteristically, DIOS patients have a right lower quadrant mass which may be palpable and is usually seen on a plain abdominal X-ray. Consequently, DIOS is defined as a complete or incomplete intestinal obstruction with a faecal mass in the ileocaecum; presenting symptoms include abdominal pain, distension and vomiting [2].

An important differential diagnosis of DIOS is constipation, which is also common in patients with CF. Unlike DIOS, symptoms are usually of longer standing and faecal material is distributed throughout the colon on a plain abdominal X-ray.

The incidence of DIOS with complete intestinal obstruction was recently studied in children and found to be between 5 and 12 episodes per 1000 patients per year throughout

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Europe [2]. Rates for incomplete obstruction – impending DIOS – are likely to be higher; DIOS is seen more frequently in adult populations (35.5/1000 patient years) [3].

2. Pathophysiology

The intestinal epithelium shares the same secretory processes seen in the airway, where chloride secretion, together with an inhibition of sodium absorption, is the driving force for fluid secretion into the lumen [4–7].

In CF, defective cystic fibrosis transmembrane conductance regulator (CFTR) function leads to reduced chloride and fluid secretion. Moreover, an up-regulation of the epithelial sodium channel (ENaC) enhances sodium and fluid absorption from the luminal mucus [8]. In the lung, these anomalies combine to cause dehydration of mucus and plugging of the small airways; in the intestine they predispose to obstruction. In addition, in the CF intestine there are other factors that influence either the viscosity of luminal contents or gut motility [9], and may predispose to obstruction or account for the localization of the obstructive process to the terminal ileum (Table 1). For example, there is good evidence that gut transit is prolonged in CF: this affects gastric emptying and both ileal and colonic transit [10]. This may reflect an underlying inflammatory process resulting in enteric neuromuscular dysfunction [11]. Intestinal wall thickening is also seen [12]. This involves the muscularis mucosa, and may be a consequence of the dysmotility and/or an effect of viscid intestinal contents.

There is little evidence that pancreatic exocrine insufficiency is the primary event in causing obstruction since DIOS is also seen in patients with pancreatic sufficiency [13]. Nevertheless, poorly controlled fat absorption may contribute to DIOS by altering the viscosity of luminal contents and by activating the ileal brake [14].

Abnormalities in bile acid absorption may explain the location of the obstructive process. Normally bile acids are actively reabsorbed in the terminal ileum via a sodium gradient-driven co-transporter, the ileal bile acid transporter (IBAT) [15]. Bile acids also induce secretion via a CFTR-dependent mechanism [16]. Both these aspects of bile acid function in the intestine, their stimulation of secretion and their active re-uptake by the terminal ileum, are affected in CF and offer a possible mechanism for DIOS and an explanation for the site of involvement in the distal ileum.

Table 1
Events likely to predispose the bowel to obstruction

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

Table 2
Risk factors for DIOS

- Severe genotype
- Pancreatic insufficiency
- Dehydration
- Poorly controlled fat malabsorption
- History of meconium ileus
- History of DIOS
- Post organ transplantation
- CF related diabetes

3. Risk factors

Several factors have been identified as predisposing to DIOS (Table 2).

DIOS is mainly seen in patients with genotypes associated with severe phenotypes [1,2,17], although it can be encountered in patients with genotypes associated with mild phenotypes. Indeed, the majority of patients with DIOS are pancreatic insufficient, with less than 10% of DIOS patients being pancreatic sufficient [2,18].

A previous history of meconium ileus is also a strong risk factor [19,20]. Almost half of the DIOS patients in a large European study had presented with meconium ileus at birth [2], as opposed to a frequency of 15% in the general CF population [17]. As both conditions probably share a similar pathophysiology, such as slow intestinal transit and impaired intestinal secretion, this association seems logical.

A previous DIOS episode will enhance the risk of subsequent episodes of DIOS. The chance of having a further episode was found to be more than 10 times higher in patients who had experienced a previous DIOS episode [2]. Poorly controlled fat malabsorption is also frequently reported in patients with DIOS. Unabsorbed fat entering the distal ileum will both inhibit gastric emptying and prolong intestinal transit [10,21], and could therefore induce DIOS.

Dehydration precipitated by intercurrent illnesses, such as respiratory exacerbation and hot weather might induce DIOS [1,22]. CF-related diabetes mellitus has also been suggested as a risk factor for DIOS; however there are no convincing data to corroborate this hypothesis [1,23].

The risk for DIOS appears to be increased after organ transplantation, particularly lung transplantation, with a reported incidence as high as 10–20% [24,25]. If not managed aggressively after transplantation, laparotomy may be required in the early postoperative period, with an associated poor outcome [26]. Specific predisposing factors after transplantation include adhesions due to previous surgery, transient postoperative adynamic ileus, adverse effects from pain relief drugs, and circulatory underfilling in the acute postoperative phase.

4. Establishing a diagnosis of DIOS

Patients with CF who experience an acute onset of abdominal pain and vomiting should be initially seen by a

Table 3
Differential diagnosis when DIOS is suspected

- Constipation (most common)
- Appendicitis
- Appendicular abscess
- Mucocele of the appendix
- Intussusception
- Crohn's disease
- Adhesions
- Volvulus
- Fibrosing colonopathy
- Malignancy

physician experienced with CF and its complications, rather than by a general paediatrician or surgeon. When considering DIOS, it is important to distinguish this diagnosis from other common causes of abdominal pain in CF (Table 3) [27,28] and rule out a surgical aetiology.

Both complete and impending DIOS are associated with a fairly acute onset of symptoms, with periumbilical and/or right lower quadrant abdominal pain. Vomiting of bilious material with progressive, colicky abdominal pain and/or fluid levels in the small intestine on abdominal radiography are signs of complete intestinal obstruction. Intermittent episodes of abdominal pain with nausea, or anorexia without vomiting are more typical of impending/incomplete DIOS. Radiographs of the abdomen usually reveal faecal loading in the right lower quadrant: sometimes multiple air-fluid levels in the dilated small bowel are seen [29]. In the majority of cases, the history combined with a palpable mass in the right lower quadrant, and supported by a characteristic plain abdominal film is sufficient to establish the diagnosis. It should be noted that a palpable mass in the right lower quadrant may persist for years without ileus symptoms and it is not per se an indication for intervention unless the plugs cause severe obstruction. Protracted or uncharacteristic symptoms or an atypical radiograph should prompt re-evaluation of the diagnosis, as should failure to respond to treatment. In such cases sonography [30] or, if needed, an abdominal computed tomography (CT) should clarify the diagnosis and may assist in ruling out an appendiceal abscess which may be missed on ultrasound.

In DIOS, a CT scan of the abdomen will show significant proximal small-bowel dilatation, with inspissated faecal material in the distal ileum (soft-tissue mass) [31,32]. Magnetic Resonance Imaging (MRI) is rarely used to establish a diagnosis, but Magnetic Resonance enterography may be applied more widely in the future, especially when it is necessary to repeat examinations [33].

5. Differential diagnosis

In DIOS, there is an acute onset of symptoms versus a gradual onset of symptoms in constipation. In clinical practice, the differential diagnosis between impending DIOS and severe constipation may not always be possible, although an abdominal radiograph may clarify the diagnosis by showing faecal accumulation throughout the colon in constipation. However, this might not be an important issue, as the initial approach to treatment, i.e. laxatives, is similar.

Appendicitis and intussusception both mimic DIOS. Diagnosis in the former is sometimes delayed leading to an increased rate of appendiceal perforation and abscess formation in CF [34]. Both diagnoses should be ruled out by clinical examination and abdominal ultrasonography [30,35,36]. However, differentiating acute appendicitis from chronically distended, swollen, mucoid appendix caused by inspissated mucoid contents with imaging may be difficult [37].

Intussusception is seen in approximately 1% of CF patients; it is usually ileocolic, and can subside spontaneously. Transient asymptomatic small-bowel intussusception, chiefly seen in the jejunum, is not uncommon. Possible pathological lead points for ileocolic intussusception include inspissated secretions, enlarged lymphoid follicles or a distended appendix. Intussusception may also occur as a complication of DIOS. Plain abdominal radiographs are often non-specific, but may show evidence of small bowel obstruction. Sonography is the primary method of diagnosis in this circumstance, showing a "doughnut sign" on transverse imaging or a "pseudokidney" on longitudinal imaging. In adults, clinically significant intussusception is rare.

The clinical presentation of fibrosing colonopathy may be quite similar to DIOS, with abdominal pain, distension, vomiting and constipation. However, these symptoms do not respond to usual medical management of DIOS and the patient may progress to subacute and later acute obstruction. Symptoms of colitis with diarrhoea sometimes containing blood and mucus may also be present [38].

An association between Crohn's disease and CF has been suggested in the older literature and should be considered in atypical cases [39,40].

Small bowel, liver and pancreatic malignancies are being reported with increasing frequency in CF adults and should be considered in patients with uncharacteristic or recurrent symptoms [41].

6. Treatment of acute episode

Treatment of DIOS is still largely empirical as there are few randomized controlled trials to guide therapy, thus the following reflects best practice. Patients with incomplete DIOS usually respond to oral rehydration combined with stool softeners (osmotic laxative containing polyethylene glycol (PEG). There are several available preparations containing PEG, which have water and electrolyte concentrations that are iso-osmotic to avoid significant fluid shifts on administration (Klean-Prep®, Golytely®, Movicol®).

PEG can be given at the dose of 2 g/kg/day, maximum 80–100 g/day, or as a ready to use iso-osmotic PEG solution, at a dose of 20–40 ml/kg/h up to a maximum of 1 L/h over 8 hours. The aim of such treatment is to achieve fecal effluent consisting of clear fluid and resolution of pain, abdominal distension and vomiting.

Alternatively, sodium meglumine diatrizoate (Gastrografin)

can be administered orally or by naso-gastric tube, at a dose of 50 ml in 200 ml of water or juice for children <6 years and 100 ml diluted in 400 ml for older patients on day 1, and half doses on subsequent days should this be required [16]. The use of N-acetyl cysteine administered orally has been superseded by the above medication. Prokinetics have shown some efficacy in post operativeileus and pseudo-obstruction, however, there is no evidence base to support their use in DIOS [42].

In patients with complete DIOS, a stepwise approach is usually employed. In cases of moderate obstruction, in patients who do not vomit, PEG can be used as above. The efficacy of intestinal lavage with a balanced electrolyte osmotic solution either orally or via nasogastric tube was firstly reported in 1989 by Koletzko et al. [43]. When DIOS presents with more severe intestinal obstruction characterised by bilious vomiting, or when washout therapy has failed, hospitalisation should be recommended and IV rehydration and nasogastric aspiration commenced. Gastrografin can be used by enema (100 ml diluted four times with water) [44]. The advantage is that it is radio opaque, so the procedure of choice is to give it as retrograde lavage with hydrostatic pressure under direct vision until the terminal ileum is reached. However, gastrografin may cause considerable fluid shift from the circulation to the bowel and serious complications have been reported, including, shock, perforation and necrotizing entero-colitis [44]. This procedure is only safely performed by an experienced radiologist. The local installation of diatrizoate in the caecum by colonoscopy has recently been described as an alternative approach [45].

With early aggressive medical management, surgery is seldom required. Laparotomy with washout via enterostomy should be tried before considering resection of the ileocaecum [46]. It should be emphasized that comorbidity and even mortality from surgery are not infrequent.

7. Prophylaxis

As a previous episode of DIOS is a risk factor for recurrence, maintenance laxative therapy can be considered, with avoidance of dehydration and reassessment of adequate pancreatic enzyme dosage. These steps seem logical, although there is no evidence base. Oral PEG, 0.5–1 g/kg/day to a maximum of 40 g/day for 6–12 months, is probably the best choice. Lactulose is also widely used, but it may cause abdominal pain and flatulence, especially in high doses. The role of increasing dietary fibre in preventing a subsequent DIOS episode is unclear.

Suggested preventive measures for patients undergoing organ transplantation include pretransplant bowel preparation, early postoperative bowel lavage and enteral feeding with immediate introduction of pancreatic enzymes [24].

8. Conclusions

These good practice guidelines will assist CF caregivers to diagnose and treat DIOS promptly and efficiently. A multinational study is currently underway (ESPGHAN and ECFS) to study DIOS prospectively.

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Conflict of interest

The authors state that there is no conflict of interest.

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