Gastrointestinal complications therapy

Fibrosing colonopathy in cystic fibrosis / DIOS

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Background

Fibrosing colonopathy (FC) is a rare usually iatrogenic disease associated to shortening and fibrosis of the colon, which almost exclusively occurs as a gastrointestinal complication in pwCF. FC is characterized by severe submucosal thickening in distal caecum and ascending colon with mild or negligible signs of inflammation and absence of other lesions evocative of Crohn's disease. Small bowel is never involved. Epithelium border is intact.

The pathogenic mechanisms leading to FC remain unclear. Previous studies have suggested that this complication is prevalent among people receiving large doses of high-strength pancreatin preparations (>50000 IU lipase per Kilogram per day), regardless of formulation. Since updated guidelines agree to reccomend restrictions on PERT dose, FC has virtually disappeared after 2000.

Other predisposing factors have been discussed, including young age (2-13 years) at the fisrt episode, history of gastrointestinal complications (DIOS, meconium ileus), previous intestinal surgery, HdPE and use of histamine H2-receptor blockers, corticosteroids or recombinant human deoxyribonuclease (dNase). Therefore a causal relationship is still debated.

Clinical manifestations of FC include abdominal pain, diarrhea, bloody stools, and in some cases partial or complete abdominal obstruction as the result of narrowing or colon strictures. Treatment of FC ranges from reduction of pancreatic enzyme supplementation to surgery, consisting of either partial or total colonic resection.

FC is a complication quite different from constipation (a gradual faecal impaction of the colon) and distal intestinal obstruction syndrome (DIOS), a well-recognised complication in CF that may share with FC similar symptoms, e.g. abdominal pain, at least at the onset (Munck A et al. 2016). DIOS is considered as both incomplete or complete accumulation of faeces and sticky mucus, forming a mass in the distal part of the small intestine. DIOS affects adults more than children; risk factors include a genotype, with minimal function of CFTR protein, deydration, high ambient temperature, history of meconium ileus, organ transplantation and CF related diabetes. Many different strategies are used in clinical practice, but no consent has yet been reached for treatment of DIOS. An update on DIOS has been published (Mavilia M. 2019).

Issues

- to define risks factors of FC and/or DIOS
- to evaluate therapeutical options

What is known

FC

No CDSR are available.

No clinical trials have bene performed.

A recent large prospective cohort study (Chiuve ES et al. 2023) included eligible pwCF enrolled iwith history of FC n the Cystic Fibrosis Foundation Patient Registry with ?1 clinic visit in 2012-2014 and follow-up through 2020. Data on PERT exposure, demographics, and medical history were collected. Clinical data, imaging, and histopathology of suspected cases were examined by an independent adjudication panel of physicians familiar with this complication. Main results showed that on a base Study Population including 26,025 pwCF who contributed 155,814 person-years [mean (SD) 6.0 (2.0) years] of follow-up over 7.8 years, 29 pwCF had suspected FC; three cases were confirmed by adjudication, 22 cases were confirmed as not FC, and four cases were indeterminate. There were 22,161 pwCF exposed to any PERT, with mean PERT use time of 5.583 person-years and mean daily dose of 8328 U lipase per kg per day. All three confirmed cases and four indeterminate cases of FC occurred during current use of PERT. Incidence rates per 1000 person-years exposed were 0.0242 (95 % CI [0.0050, 0.0709]) for confirmed FC and 0.0566 (95 % CI [0.0227, 0.1166]) for indeterminate or confirmed FC. These data confirm that in the era of current treatment guidelines incidence of FC is very low.

DIOS

1 CDSR (Carroll W. 2021) was performed in order to evaluate trials comparing laxative therapy for preventing DIOS (including osmotic agents, stimulants, mucolytics and substances with more than one action) at any dose to placebo, no treatment or an alternative laxative therapy, in people of any age with sufficient or insufficient exocrine pancreas and any stage of lung disease. Only 1 cross?over trial with a duration of 12 months, including 17 patients, was selected in which participants were randomly allocated to either cisapride (a gastro?prokinetic agent) or placebo for 6 months each. No significant differences were registered at 6 months between cisapride and placebo for abdominal distension, MD ?0.90 (95% CI ?2.39 to 0.59) or abdominal pain, MD ?0.4 (95% CI ?2.05 to 1.25). The global symptom scores (whether individuals felt better or worse) were reported in the paper to favour cisapride and be statistically significant (P

< 0.05). The Authors concluded that there is an absence of evidence for interventions for the prevention of DIOS. Furthermore, cisapride is no longer licensed for use in several countries due to the risk of serious cardiac events. Therefore, the limited findings from the trial are not applicable in current clinical practice.

1 CDSR (Gilghrist FJ, 2021) was performed in order to evaluate the effectiveness and safety of different treatment regimens prior onset of DIOS (complete and incomplete) in children and adults with CF. Only 1 double?blinded, randomised cross?over trial performed in 1993, which had a duration of 12 months, included 20 subjects (16 females, mean age 13.1 years) that were randomly given either high?dose or low?dose pancreatic enzymes for six months each. Trial investigators measured the difference in acute episodes of DIOS, presence of an abdominal mass and abdominal pain. Other outcomes measured in the trial included the coefficient for fat absorption and weight gain. There were no numerical data available for these outcomes, but the authors stated that there was no difference between treatment with high?dose or low?dose pancreatic enzymes. The overall certainty of the evidence was found to be very low.

Recently (Miles C et al, 2024) a retrospective study of children and adults with CF who were admitted with a primary diagnosis of constipation or DIOS between 1 January 2011 and 31 December 2022. ESPGHAN definitions for constipation and DIOS were retrospectively applied to all admissions to determine if the primary medical diagnosis met ESPGHAN criteria. The primary aim was to describe the characteristics of constipation and DIOS hospitalisations in a paediatric and adult CF service over a 12-year period. The secondary aims were to determine the proportion of constipation and DIOS presentations which met the ESPGHAN CF Working Group definitions and to describe management strategies of both conditions. During the 12-year study period, 42 hospitalisations for constipation were recorded in 19 patients, and 33 hospitalisations for DIOS were recorded in 23 patients. 88.10% of constipation episodes met ESPGHAN definitions, compared with 3.0% of DIOS episodes. Constipation and DIOS were primarily treated with polyethylene glycol (PEG). The use of sodium amidotrizoate meglumine enemas was significantly higher in the DIOS group (p=0.045). Those admitted with DIOS were significantly less likely to be recommended a weaning dose of PEG (p=0.018). The variation in diagnostic and therapeutic practice and data derived from this study highlight the need to enhance the translation and adoption of existing best-practice guidelines.

Several Authors (Modlin SE et al, 2019) evaluated the impact of osteopathic manipulative treatment (OMT) to improve bowel symptoms and prevent DIOS in 5 patients with CF by releasing myofascial restrictions found in the abdomen and somatic structures, with the intent to optimize the autonomic and lymphatic systems and improve range of motion. These preliminary findings support the use of OMT as a method for the management of chronic constipation and DIOS in the CF population.

Recently (Kormelink LN, Jacobs HR, 2025) a retrospective case series of 39 adults with CF who was prescribed linaclotide, a treatment approved for chronic idiopathic constipation and irritable bowel syndrome with constipation investigated the potential for use of this agent. The daily starting dose of linaclotide did vary with 18%, 72%, and 10% started on 72 mcg, 145 mcg, and 290 mcg respectively. Most patients (n = 30, 77%) reported experiencing no side effects. Of the total patients, 15% (n = 6) reported the medicine was not effective and 10% (n = 4) had to stop therapy due to adverse reactions. More than half of patients started on therapy were able to reduce baseline treatments for constipation. More research is needed to fully evaluate safety and efficacy of linaclotide for treating constipation in CF.

Unresolved questions

Ethical issues do not consent to perform randomized clinical trials in topic of DIOS.

Anedoctical reports and expert panel may help clinicians to define the best practice for the rare complication of FC and DIOS.

A follow-up in people that undergo new therapies as HEMT may clarify the progression of these complications.

Keywords

Fibrosing colonopathy;