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Surgical considerations in cystic fibrosis: what every general surgeon needs to know

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Abstract

Cystic fibrosis (CF) is a complex multiorgan disease, which often affects the gastrointestinal tract. With improved CF specific therapies and multidisciplinary management, patients with CF are now living longer with a median life expectancy of around 50 years. This increased life expectancy has resulted in corresponding increase in presentations of the CF patient with comorbid surgical conditions that were never important considerations. Investigations and management of these conditions, such as distal intestinal obstruction syndrome and colorectal cancer warrant good clinical understanding of the unique challenges that CF patients present including chronic immunosuppression, impaired respiratory function and their multi-organ dysfunction. The purpose of this review is to provide general surgeons with a contemporary update on the CF related surgical issues as they are likely to become increasingly involved in the care of these complex patients and form an integral part of the multidisciplinary team.

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease associated with complex multiorgan involvement. It is the most common lethal inherited disorder in high-income setting.[1] It is caused by deficiencies in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, an epithelial anion channel essential for the regulation of many mucosal surfaces' fluid and electrolyte homeostasis.[2] This results in a thick tenacious mucus on mucosal surfaces which leads to mucosal dysfunction from mucus plugging. The end result is mucosal dysfunction in the lungs, gastrointestinal tract, pancreatic duct and bile duct which in turn manifests clinically as recurrent lower respiratory tract infections, progressive respiratory impairment, distal intestinal obstruction syndrome (DIOS), progressive endocrine and exocrine pancreatic insufficiency as well as cirrhosis.

Although CF is the most common lethal hereditary recessive disorder, it is generally considered rare. In Australia alone, CF is thought to affect 3500 people.[3] With improved pharmacological and non-pharmacological respiratory therapies, the advent of CF specific multi-disciplinary teams and better nutritional support, the life expectancy of CF patients has improved markedly in recent decades.[3,4] The median age of survival is now approaching 50 years and the proportion of CF patients who survive well past adulthood has also increased dramatically.[5] With improved respiratory management and survival, the intestinal and pancreatico-biliary

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surgical management of *CF* patients has transitioned from principally the paediatric domain to also include the adult general surgeon. This contemporary narrative review provides a general overview in the pre-operative management of more common gastro-intestinal or hepatico-pancreatic issues for the general surgeon in CF patients. Subspecialty surgical conditions such as organ transplantation or other extra-abdominal surgical implications of CF are not included in this review. The European Society for Paediatric Gastroenterology and Nutrition (ESPGHAN) classifies the gastrointestinal manifestations of CF into three categories: intestinal, pancreatic, and hepatobiliary, this review will follow the same structure covering these three areas.[6]

Perioperative care

Independent of the presenting surgical pathology, common pre-operative considerations include optimization of CF lung disease (such as bronchiectasis and associated airway colonization, and pulmonary arterial hypertension and cor pulmonale with severe lung disease), CF related diabetes, sinus disease, adrenal function (for patients who are steroid dependent), and psychological sequalae related to their disease and the associated treatments.

Involvement of multi-disciplinary team with expertise in CF care including allied health is imperative.[5] Pre-operative respiratory 'tune up' comprising of twice daily chest physiotherapy, optimizing mucus expectoration and pre-emptive treatment with intravenous antibiotics to manage resistant respiratory microbiome is recommended.

Pre-operative nutritional optimisation is also important as previous studies have found malnutrition a prevalent problem even in community CF patients.[7] Baseline energy requirement is commonly higher in this cohort of patient because of chronic low grade sepsis and malabsorption. The need for supplemental glucocorticoids may compound the problem of the catabolic state, further increasing the need for supplemental enteral or parenteral nutritional support, even if the anticipated caloric shortfall is a limited period of time. In addition, CF related diabetes is common, and glycaemic optimisation needs early consideration, especially with peri-procedural fasting. Where possible, it is advisable to try to avoid interventions that increase the risk of respiratory complications. Minimizing the use of a nasogastric tube, minimally invasive techniques avoiding upper abdominal incisions and reducing the duration of surgery or anaesthesia is preferred. Regional anaesthesia techniques minimizing opioid use while optimizing post-operative pain management is also recommended.[7]

Although organ transplantation is beyond the scope of this review, it is noteworthy that many patients with CF will also proceed to single-organ or multivisceral transplantation,[8] with ensuing immunosuppression considerations. Those with lung transplants are at higher risk of aspiration as the cough reflex is variably lost below the anastomosis.[9] They may also have impaired mucociliary clearance, and airway stenoses which can make peri-procedural ventilation more challenging.[10] Both this and the peri-operative analgesia management therefore warrant an early involvement of a consultant anaesthetist. Common strategies to minimize post-procedural respiratory complications include the use of volatile anaesthesia in high inspired concentrations of oxygen and the avoidance of potentially irritant vapours such as desflurane or isoflurane. The use of humidified inhaled gases and nebulised therapies peri-procedurally, the avoidance of nasal intubation where possible due to the high incidence of nasal polyposis, minimizing ventilatory pressures to reduce the risk of pneumothorax, ensuring normothermia (particularly with the diminished sweat thermoregulation and the increased pulmonary vascular resistance associated with hypothermia and hypercarbia), and sometimes intraoperative physiotherapy are all anaesthetic strategies worthy of consideration.[7] Longer acting sedatives are ideally avoided as are high doses of opiates with increasing the risk of constipation and DIOS. A proton pump inhibitor is also often used pre-operatively due to the increased incidence of gastro-oesophageal reflux disease (GORD),[8] and early mobilization/chest physiotherapy is encouraged including with positive expiratory pressure devices and incentive spirometry.[11] Many CF patients are also on a complex medication regime which needs peri-operative consideration.

Patients with severe cardio-respiratory disease (e.g. with a forced expiratory volume in 1 second (FEV1) less than 1 L) require early discussion with intensive care services as they are likely to require post-operative support including a period of postoperative ventilation and/or aggressive airway clearance regimes with adequate pain control and concurrent monitoring for DIOS.[7,12] Patients with CF-related portal hypertension often are high-risk general surgical candidates particularly if abdominal varices are present. Multi-disciplinary team (MDT) input and pre-operative optimisation including consideration of pre-operative elective transjugular intrahepatic portosystemic shunt placement, may be required.[13,14]

Intestinal manifestations

Distal intestinal obstruction syndrome

DIOS refers to a range of clinical conditions due to partial or complete small or large bowel obstruction from thickened inspissated secretions and reduced intestinal motility. Approximately 10% of neonates with CF develop meconium ileus,[6] and DIOS is thought to represent a later presentation of a similar obstructive syndrome and was previously known as 'meconium ileus equivalent' as meconium does not persist beyond infancy.[15]

DIOS can occur at any age but is most common in those over the age of 15 years and peaks at age 20–25 years. The internationally quoted incidence is variable but the incidence of DIOS seems to have increased, potentially due to the increased life expectancy but also increased awareness of DIOS in CF.[9] The risk of DIOS is related to the severity of the CFTR mutation, those leading to non-functioning proteins and pancreatic involvement portend a greater risk.[6,16] The effect of CFTR modulator therapy on DIOS risk is unclear, not least because severe constipation was listed as a serious adverse event leading to discontinuation of the study medication in several clinical trials.[17] Table 1 summarizes risk factors for DIOS. Most patients tend to have multiple risk factors for development of DIOS.

The presentation of DIOS is variable but often mimics a bowel obstruction with a fairly acute onset of central colicky abdominal

pain, nausea and bilious vomiting with clinical and radiographic features of obstruction. The key radiographic difference is the presence of variable segment of terminal ileum that is faecally loaded with a granular/speckled appearance (Fig. 1). In contrast to a bowel obstruction—bowel sounds are often normal instead of high-pitched or absent. Differentials for DIOS include constipation, an underlying colorectal malignancy, intussusception and a volvulus (see upcoming sections).

It is important to distinguish DIOS from a bowel obstruction due to the differences in management. However, the risk of bowel obstructions may also be increased by prior CF related surgery and adhesions such as resections for meconium ileus, stoma formation or closure) and more rarely, from malignancy. CF patients are at higher risk than the general population of developing colorectal, oesophageal, gastric, hepatobiliary, gallbladder, small intestinal cancers.[18–20]

The foundation of management involves rehydration, electrolyte replacement and aggressive aperient use in contrast to bowel rest or decompression strategies employed for mechanical obstruction. Current paediatric recommendations suggest managing DIOS with high doses of polyethylene glycol (PEG) at 2 g/kg, up to a maximum 80–100 g/day, or iso-osmotic PEG solution, 20–40 mL/kg/h, up to a maximum of 1 L/h, for a period of up to 8 h.[21] However there is a paucity of high quality randomized data to guide treatment of DIOS in adults thus a variety of published treatment strategies and regimes have been suggested.[22] This most often takes the form of osmotic aperients such as macrogol or PEG orally or via a nasogastric tube, rather than secretory and stimulating agents because of the underlying issue of inspissated faecal material. Gastrografin (sodium meglumine diatrizoate)orally/rectally and nasogastric lavage with a balanced electrolyte osmotic solution is often used though may be higher risk for complications including luminal perforation and necrotizing enterocolitis.[21,23] In patients at high risk of aspirating, oral Gastrografin is often avoided to prevent aspiration pneumonitis though can be used rectally.[24] Prokinetics are sometimes employed as an adjunct but there is a limited evidence base to support their use.[25] The efficacy of treating DIOS with high-dose pancreatic enzyme replacement is unproven.[20]

In more severe cases, endoscopic approaches have been described with colonoscopic instillation of Gastrografin, which has been reported to eliminate the need for surgical treatment in over 30%.[26] Surgical strategies have been employed including lavages (via enterostomies, temporary stomas and via an appendicostomy), and in rare cases resection.[27,28]

Table 1 Proposed DIOS risk factors in CF

1.	Severity of the CTFR mutation
2.	Previous episodes of DIOS (10-fold increase in risk)
3.	Meconium ileus at birth (44%–50% of cases)
4.	Alteration to pancreatic enzyme intake (up to 20% of cases)
5.	Dehydration
6.	Dietary changes (including binge eating patterns)
7.	Bed rest
8.	Constipating agents (such as opiates and tricyclic antidepressants)
9.	Organ transplantation (particularly lung transplantation, 10%–20% risk)
10.	Previous abdominal surgery
11.	The use of azathioprine
12.	CF-related diabetes (though with some controversy regarding this risk factor)

Intussusception

With improved survival, better cross sectional imaging and increased awareness, intussusception in CF is increasingly recognized. CF patients have up to ten fold increased risk of developing intussusception over the general population,[29] occurring in 1% of CF patients.[30]

The increased risk is likely multifactorial including impaired intestinal motility, increased intestinal thickness and the availability of lead points from inspissated secretions or faecal material, enlarged lymphoid follicles or even an underlying small bowel or colonic neoplasm.[31] The presentation can be somewhat variable

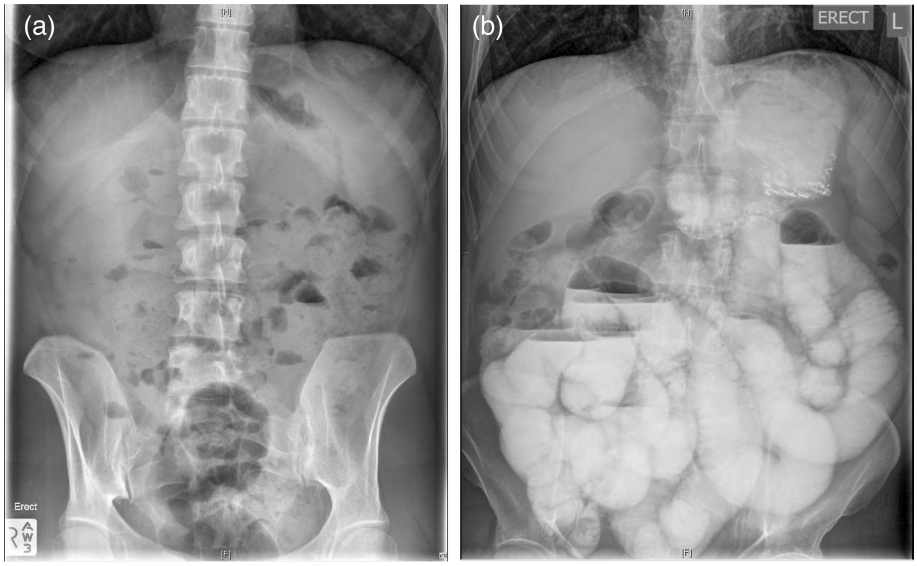

Fig. 1. Distal intestinal obstruction syndrome. (a) An erect abdominal radiograph in a patient who presented with obstructive symptoms and known cystic fibrosis; showing extensive faecal loading throughout the small and large bowel with faecalisation, some air-fluid levels—consistent with DIOS. (b) A subsequent erect abdominal radiograph in the same patient, with oral contrast (administered prior for a computerized tomography) showing small bowel distention, air-fluid levels, consistent with ongoing obstruction.

and may be acute but it is not uncommon for CF patients to have chronic intussusception with insidious symptoms.[30] A high index of suspicion and cross sectional imaging is required for early diagnosis. The ileocolic subtype seems markedly more common than colocolonic or small bowel (jejuno-jejunal and ileo-ileal) intussusception and relates to the point of invagination.[30] Generally patients may present with colicky abdominal pain, vomiting, a palpable mass, and/or rectal bleeding.[30] The diagnosis is made radiographically most often with computerized tomography (CT) and sometimes ultrasonography showing the pathognomonic 'bulls eye' or 'target sign' appearance (Figs. 2 and 3). In contrast to the non-CF population, adult intussusceptions may not routinely require a surgical approach unless recalcitrant or associated with perforation or ischaemia. Although air or water soluble contrast enema may treat the intussusception, it is less likely to be successful with chronicity, especially when it is not uncommon for these patients to have insidious symptoms.[30] Surgical resection will be necessary in patients with persistent intussusception, especially if there is any concerns for bowel integrity or an underlying lesion serving as the lead point.

Because of a possible association with underlying malignancy, an interval colonoscopy is usually recommended after resolution of intussusception.[30] The risk of malignancy may also be increased with concurrent immunosuppression used for organ transplantation.[32,33] Bowel preparation in patients with CF is also challenging because of inspissated faecal material. Extended osmotic preps with nutritional support are commonly required to permit adequate mucosal visualization at the time of colonoscopy.

Appendiceal disease

Appendicitis occurs less frequently in CF compared with the general population though may present atypically and mimic other CF-related intestinal conditions such as DIOS.[34] More rarely appendiceal abscesses may be seen.[35] Abdominal pain may also result from mucoid distention of the appendix which resolves after resection,[34] though such distention is often asymptomatic and only found at autopsy.[35,36]

Colorectal carcinoma

Individuals with CFTR mutations are highly susceptible for early-onset, aggressive colorectal tumour development, even heterozygous carriers of CFTR mutations are also at increased risk.[37,38] Patients with CF tend to present with larger and more aggressive colonic polyps compared with an age-matched non-CF population.[39] Colonoscopic surveillance at 1–3 yearly intervals has demonstrated a greater number of adenomatous polyps in patients with CF than non-CF populations which may suggest accelerated progression of polyps.[40] Low expression of CFTR protein is associated with poor disease-free survival in sporadic CRC.[39] In a recent study, up to 50% of patients with CF developed colonic adenomas by 40 years of age, and 3% had developed adenocarcinomas.[39,41]

The mechanisms responsible for increased CRC risk in CF are unclear. However, CFTR plays critical roles in epithelial homeostasis in the gastrointestinal tract,[42] and acts as a tumour suppressor gene in the intestinal tract in mice with loss promoting tumour

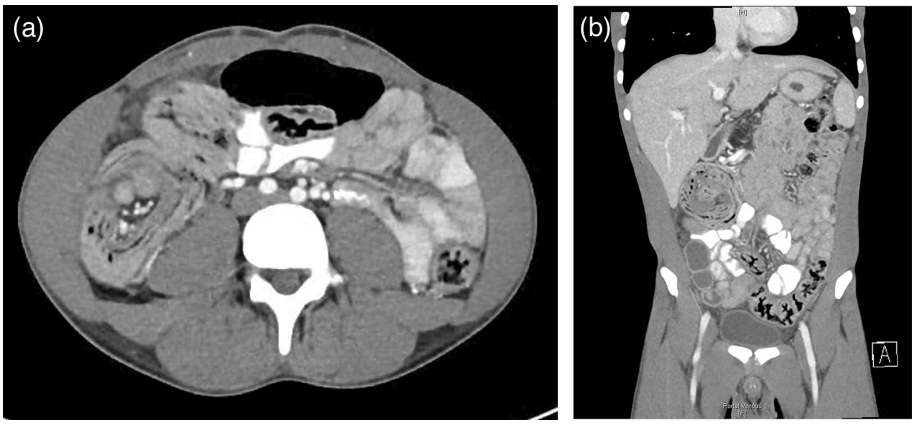

Fig. 2. Intussusception (CT). A computerized tomography of the abdomen & pelvis with IV contrast in the portal venous phase, showing intussusception of the caecum, appendix, and distal ileum into the ascending colon without an identified lead point. (a: Axial view, b: coronal view).

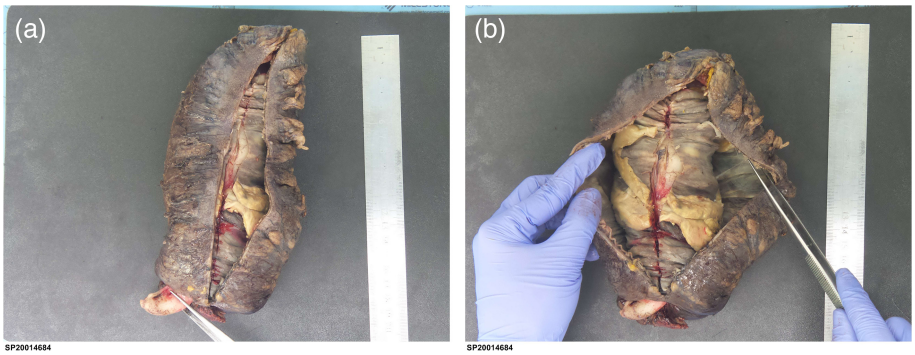

Fig. 3. The macroscopic histology for the patient in Fig. 2 with intussusception, with the distal ileum (held by the forceps in (a)) and appendix invaginated into the large bowel. The authors would like to acknowledge the kind contribution of Dr. Joo-Shik Shin in his assistance with Fig. 3.

formation.39 CF is now characterized as a hereditary colon cancer syndrome by the Cystic Fibrosis Foundation.[42]

Current colorectal cancer screening guidelines recommend that screening begin at age 40 years with continued rescreening every 5 years or sooner if adenomatous polyps are found. Patients with additional risk factors such as immunosuppression for solid organ transplantation should be considered for earlier screening, with current guidelines recommending commencing of screening colonoscopies at the age of 30.[42] The challenges of bowel preparation has already been discussed and this is particularly true for patients with a prior history of DIOS. PwCF generally require intensive bowel preparation to ensure adequate mucosal visualization, with three to four washes (minimum of 1-L purgative per wash).[42]

GORD

There is considerable heterogeneity in the prevalence of objectively measured GORD in CF patients, partly related to the variable patient cohorts, age, and techniques employed to diagnose GORD, but may approach 90% particularly following lung transplant.[43–45] This high prevalence is likely multifactorial; and related to low basal lower oesophageal sphincter (LOS) pressures with greater transient lower oesophageal relaxations, periodic increases in intra-abdominal pressure from coughing and straining, a high rate of hiatus hernia, hyperalimentation and a high-fat diet to offset malabsorption, peristaltic abnormalities, poor gastric emptying, and medications that contribute to LOS relaxation such as salbutamol and theophylline.[46,47] Lung transplant seems to portend a particular risk for GORD likely related to lung denervation, an impaired cough reflex, abnormal mucociliary clearance, and exacerbated gastric emptying function.[48]

Multiple studies have suggested that CF patients with GORD have more severe lung disease with lower pulmonary function and increased numbers of respiratory exacerbations, as well as an altered respiratory microbiology through acid and non-acid related effects.[28] Acid suppression therapy is often instituted for empirical management of respiratory issues thought to be related to GORD, or as an adjunct in the management of patients with poor response to enzyme therapy to reduce pH-related alterations of enteric-coated pancreatic enzyme activity.[28]

Though medical management with lifestyle modification and acid suppression medication remains the mainstay of management, surgical management may also be indicated if severe GORD symptoms persist despite medical therapy, if symptoms limit oral intake and cause weight loss, or if an oesophageal stricture forms.[49] Fundoplication has shown some success in paediatric populations: 28% of a cohort of 25 children were able to be weaned off from acid suppressive therapy post-fundoplication and showed an improvement in FEV1, though 48% subsequently developed symptoms of recurrent GORD and 12% had complications that required a subsequent surgical procedure.[50] In one retrospective cohort of 48 paediatric fundoplication patients, surgery slowed the decline in lung function, decreased exacerbations and led to improvements in weight.[51]

Several studies have suggested a poorer lung function and the development of obliterative bronchiolitis after lung transplantation associated with GORD,[52] and in some multiple reports have suggest a fundoplication has ameliorated a reversal of this decline and improved allograft function, as well as improved indirect markers of GORD and aspiration such as pulmonary lipid-laden macrophages.[53–55]

However the evidence poor in children is poor and mixed,[56] and there is even less to guide surgical decisions in adults—therefore such decisions should be as part of an MDT and personalized to the patient. Patients with CF also exhibit a higher rate of eosinophilic oesophagitis and coeliac disease than the general population, which may mimic GORD symptoms.[57]

Hepatobiliary manifestations

The CFTR gene is highly expressed throughout the entire biliary tree epithelia, most highly in the gallbladder,[58,59] leading to atypical biliary constituents (particularly bicarbonate). This leads to compensatory mucosal hyperplasia, increased susceptibility to inflammation and disruption of biliary circulation,[60,61] causing a spectrum of disease including microgallbladder, cholelithiasis, biliary tract ductal stones, intra- and extrahepatic biliary stenoses, sclerosing cholangitis, hepatic steatosis, nodular regenerative hyperplasia, focal biliary cirrhosis CF-related liver disease (multilobular cirrhosis) and portal hypertension.[62,63] Of note the hepatic changes are secondary in nature as CFTR is not expressed on hepatocytes.[64]

Cholelithiasis is particularly common from black pigmented stones and this is thought to result from either abnormal acidification of the bile and biliary stasis, or to a lesser extent cholesterol stones, particularly is malabsorption is present leading to enteral loss of bile acids.[64,65] Though asymptomatic cholelithiasis is common, symptomatic gallstone disease occurs in around 4% of adult pwCF,[63] and may be exacerbated by anatomical biliary variants such as biliary stenoses.[63] The clinical disease risk may depend on the specific genetic alteration implicated.[66] CF patients are also higher risk than the general population of hepatobiliary cancers particularly pancreatic cancer (particularly with concomitant immunosuppression use),[67] and if cirrhotic, hepatocellular carcinoma.[68]

CF patients are therefore likely to need endoscopic or surgical intervention, though such issues are managed conventionally though with consideration of the patient's comorbidities. In those who are not-operative candidates ursodeoxycholic acid (UDCA) has been attempted to manage cholelithiasis but with no success in one trial of 10 patients.[69] There is limited data about the use of lithotripsy in CF.

Pancreatic manifestations

The CFTR protein at the apical domain of the pancreatic ductal cells, and mutations lead to variable rates endocrine and exocrine pancreatic insufficiency via a reduced luminal bicarbonate secretion and subsequently reduced alkalinization of the acinar lumen, impaired apical endocytosis, obstruction of proximal intralobular pancreatic ducts by inspissated protein plugs, and subsequent progressive ductal obstruction and fibrosis.[70] These changes may begin *in utero*.[71]

Pancreatitis develops in around 15%–20% of CF patients with pancreatic sufficiency typically during teens or early adulthood, but is rare among those with pancreatic insufficiency as sufficient pancreatic acinar tissue is required for obstructive ductal lesions to cause disease.[72–74] Therefore milder CFTR genotypes, or those associated with pancreatic sufficiency, are at increased risk of pancreatitis and a pancreatic insufficiency prevalence (PIP) score has even been suggested to categorize the risk of developing pancreatitis based on mild versus moderate–severe CFTR mutations.[75] Of the few pwCF developing pancreatitis, approximately 18% will only have a single episode, while 60% experience acute recurrent pancreatitis, and 22% advance to chronic pancreatitis.[76]

Pancreatitis risk is also increased with traditional risk factors such as alcohol or smoking, not least as they specifically affect CFTR function.[77,78] Additionally retrospective studies from the idiopathic pancreatitis in the general population have shown a high proportion one or two CFTR mutations (and/or variants)[79–81] including those not associated with CF,[82] though pancreatitis may be the initial presentation of milder CF and those with a cystic fibrosis transmembrane conductance regulator-related disorders.[83]

The presentation of pancreatitis in CF is variable in keeping with the high number of identified mutations[75] and may change with the increasing use of CFTR modulator therapies that reduce the risk of recurrent pancreatitis.[84] The initial management is conservative, though endoscopic, interventional and surgical management of pseudocysts and walled-off pancreatic necrosis is considered similar to the general population,[79] as are lifestyle measures such as smoking and alcohol cessation.[82] Medical management of hypertriglyceridemia is more common in CF than the general population.[85] Of note, a low fat diet in CF-associated pancreatitis is of unclear benefit, and generally not advised with concerns about exacerbating nutrition and nutrition-related pulmonary outcomes.[79]

In rare cases, pancreatic cystosis can occur whereby the normal pancreatic tissue is replaced by multiple macrocysts (i.e., >1 cm in size).[86] These are often asymptomatic and observed but may need endoscopic, interventional laparoscopic or open surgical drainage, particularly for large symptomatic cysts that may present with mass effect and haemorrhage.[79,87] As above, pwCF are also at higher risk of pancreatic cancer than the general population which may need surgical intervention, though the absolute risk remains low.[88]

There is a paucity of data on optimal surveillance strategies in cystic fibrosis for pre-malignant pancreatic lesions such as intraductal papillary mucinous neoplasms.

Conclusion

Surgical management of patients with CF needs to be individualized given the complex multiorgan involvement and unique CF specific presentations including DIOS. Furthermore, with the more widespread use of CFTR modulators and the aging CF population, the clinical presentation, comorbidities and possible complications of CF patients may change over time. Best practice currently involves multidisciplinary care, and increasingly general surgeons will need to be an integral part of this team to facilitate optimal care of CF patients.

Author contributions

John D. Chetwood: Conceptualization; formal analysis; investigation; methodology; project administration; writing – original draft; writing – review and editing. **Anastasia Volovets:** Conceptualization; supervision; writing – review and editing. **Sheila Sivam:** Supervision; writing – review and editing.

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Conflict of interest

None declared.

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