University Library

A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Bolia, R;Ooi, CY;Lewindon, P;Bishop, J;Ranganathan, S;Harrison, J;Ford, K;van der Haak, N;Oliver, MR

Title:
Practical approach to the gastrointestinal manifestations of cystic fibrosis

Date:
2018-06-01

Citation:
Bolia, R., Ooi, C. Y., Lewindon, P., Bishop, J., Ranganathan, S., Harrison, J., Ford, K., van der Haak, N. & Oliver, M. R. (2018). Practical approach to the gastrointestinal manifestations of cystic fibrosis. Journal of Paediatrics and Child Health, 54 (6), pp.609-619. https://doi.org/10.1111/jpc.13921.

Persistent Link:
https://hdl.handle.net/11343/283984

Ooi Chee (Orcid ID: 0000-0001-7111-0926)

**Title Page**

**Title**

A Practical Approach to the Gastro-intestinal Manifestations of Cystic Fibrosis

**Type of Manuscript**

Review article

**Full names and affiliations of the authors**

**Rishi Bolia[1], Chee Y. Ooi[2], Peter Lewindon[3], Jonathan Bishop[4], Sarath Ranganathan[5], Jo Harrison[5], Kristyn Ford[6], Natalie van der Haak[7], Mark R Oliver[8]**

[1]Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Melbourne, Australia.

[2]School of Women and Children's Health, Medicine, The University of New South Wales, New South Wales, Australia; miCF Research Centre and Department of Gastroenterology, Sydney Children's Hospital, High Street, Randwick, New South Wales, Australia.

[3]Department of Gastroenterology, Lady Cilento Children's Hospital and Queensland Liver Transplant Service, South Brisbane, Queensland, Australia.

[4]Department of Paediatric Gastroenterology, Starship Children's Hospital, Auckland, New Zealand

[5]Department of Respiratory Medicine, Royal Children's Hospital, Melbourne, Australia; Infection and Immunity Theme, Murdoch Children's Research Institute, Melbourne, Australia; Department of Paediatrics, University of Melbourne, Australia.

[6]Department of Nutrition and Dietetics, Royal Children's Hospital, Melbourne, Australia

[7]Department of Nutrition and Dietetics, Women's and Children's Hospital, Adelaide, Australia

[8]Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Melbourne, Australia; University of Melbourne, Melbourne, Australia; Murdoch Childrens Research Institute, Parkville, Melbourne, Australia.

Author Manuscript

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jpc.13921

This article is protected by copyright. All rights reserved.

Author Manuscript

**Corresponding author**

Mark R Oliver

Department of Gastroenterology and Clinical Nutrition

Royal Children's Hospital Melbourne

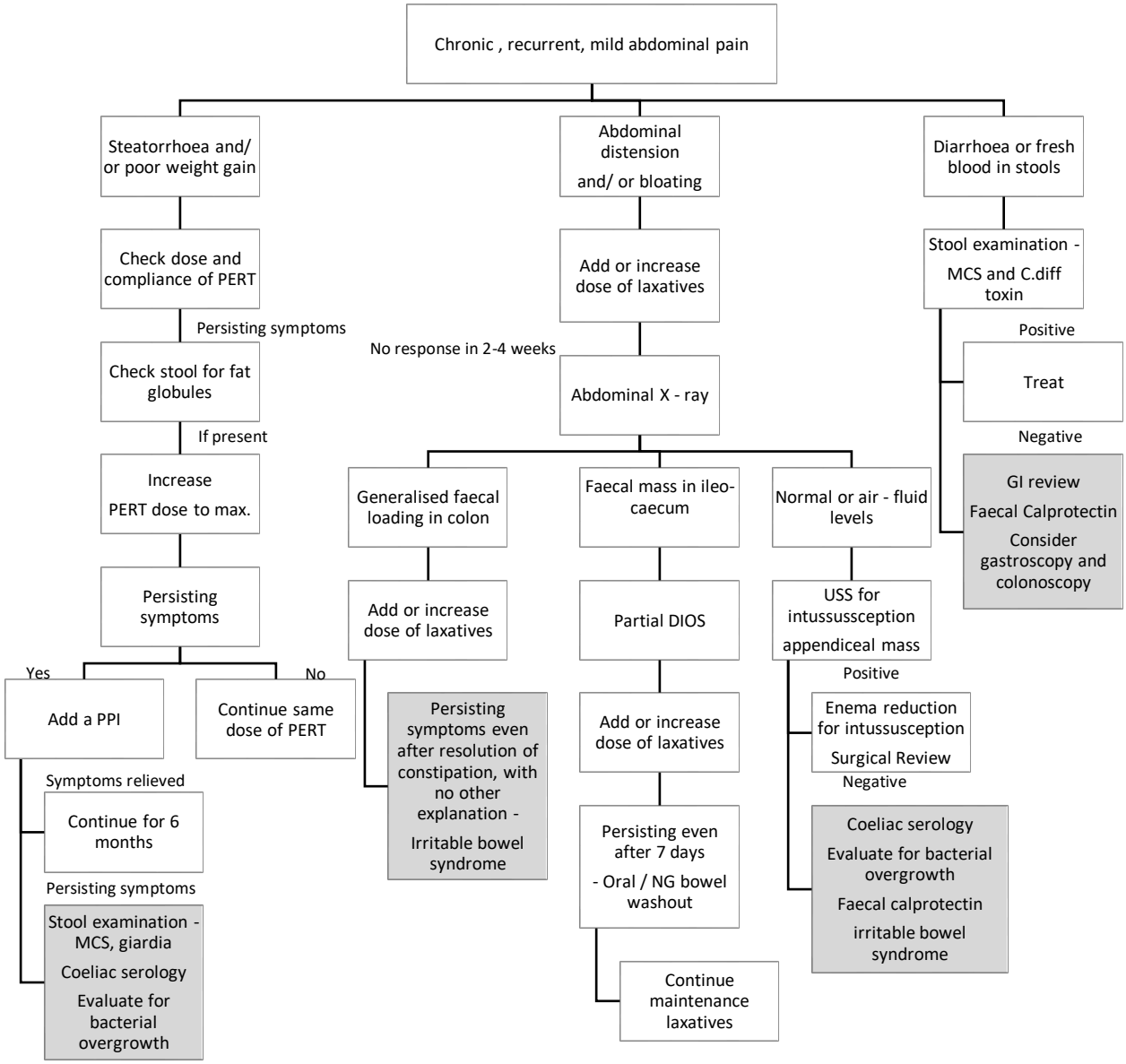
Ph. 613 93455060

Fax 613 93456240

Email – mark.oliver@rch.org.au

This article is protected by copyright. All rights reserved.

Author Manuscript

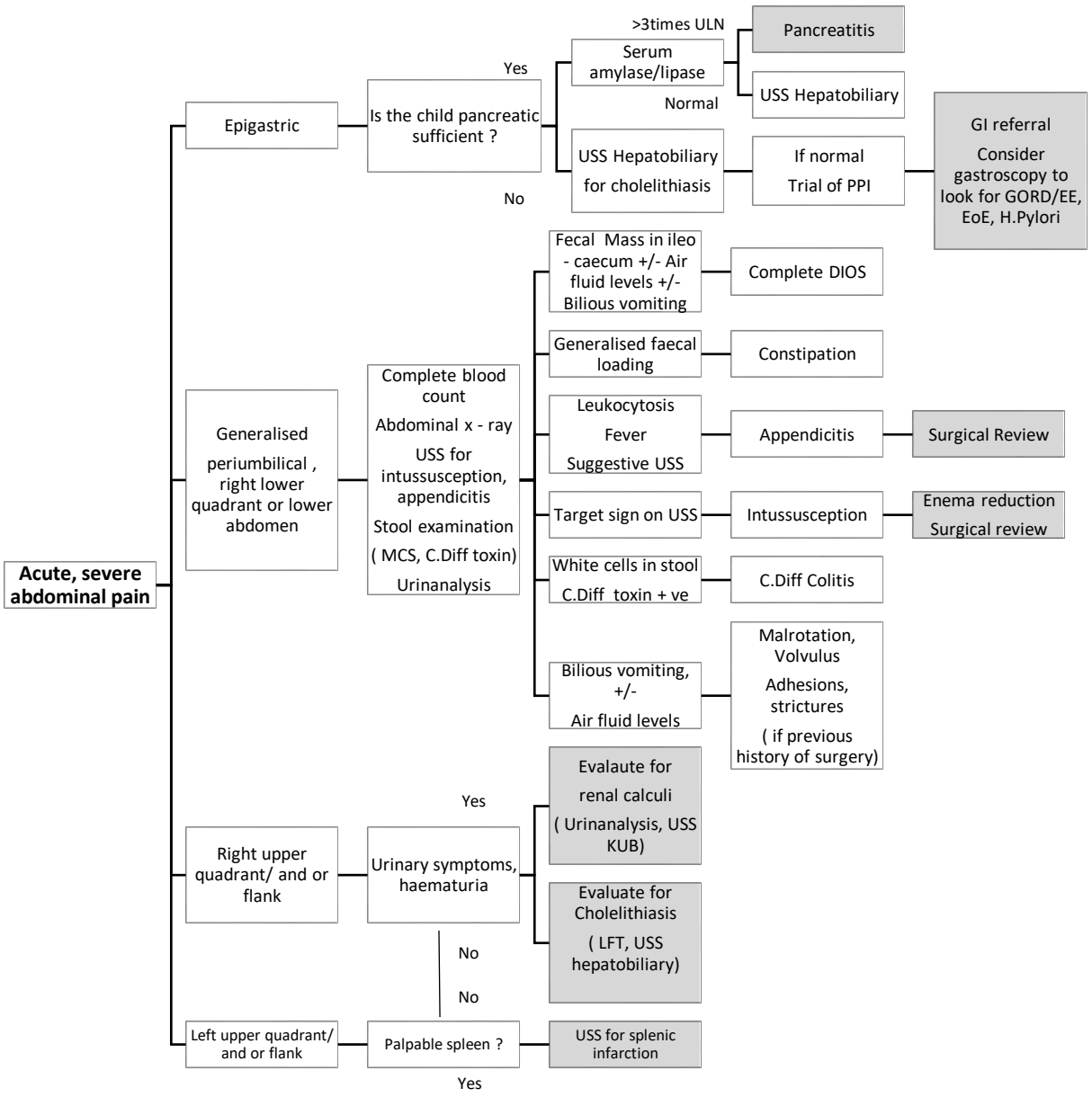



*PERT – Pancreatic Enzyme Replacement Therapy, PPI – Proton Pump inhibitor, USS – Ultrasound scan, MCS – Microscopy, culture and sensitivity

Refer

This article is protected by copyright. All rights reserved.

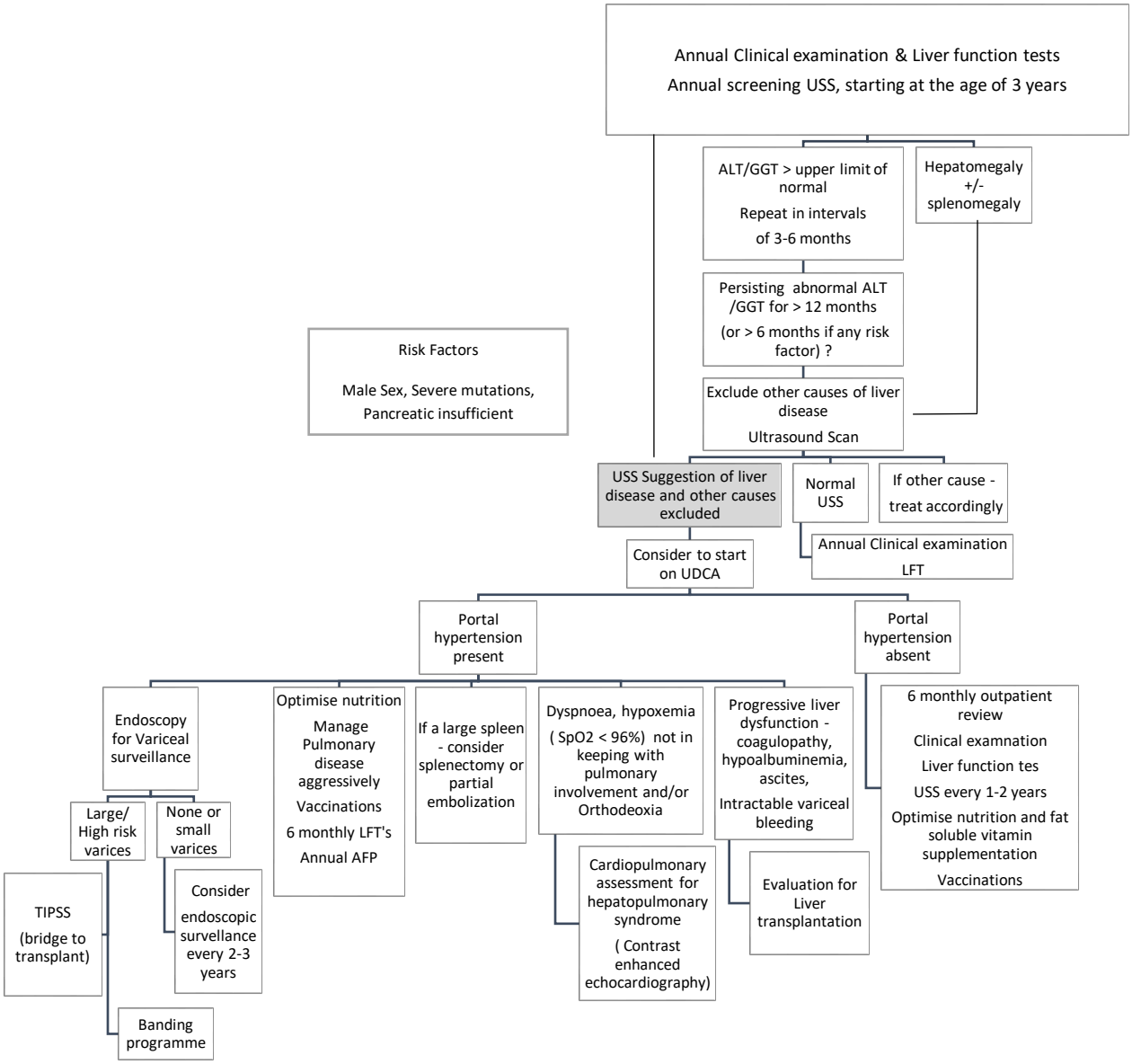
Author Manuscript




*USS – ultrasound scan, PPI – Proton pump inhibitor, EoE – Eosinophilic esophagitis, GORD/EE – gastro-oesophageal reflux disease/erosive esophagitis  Refer

This article is protected by copyright. All rights reserved.

Author Manuscript

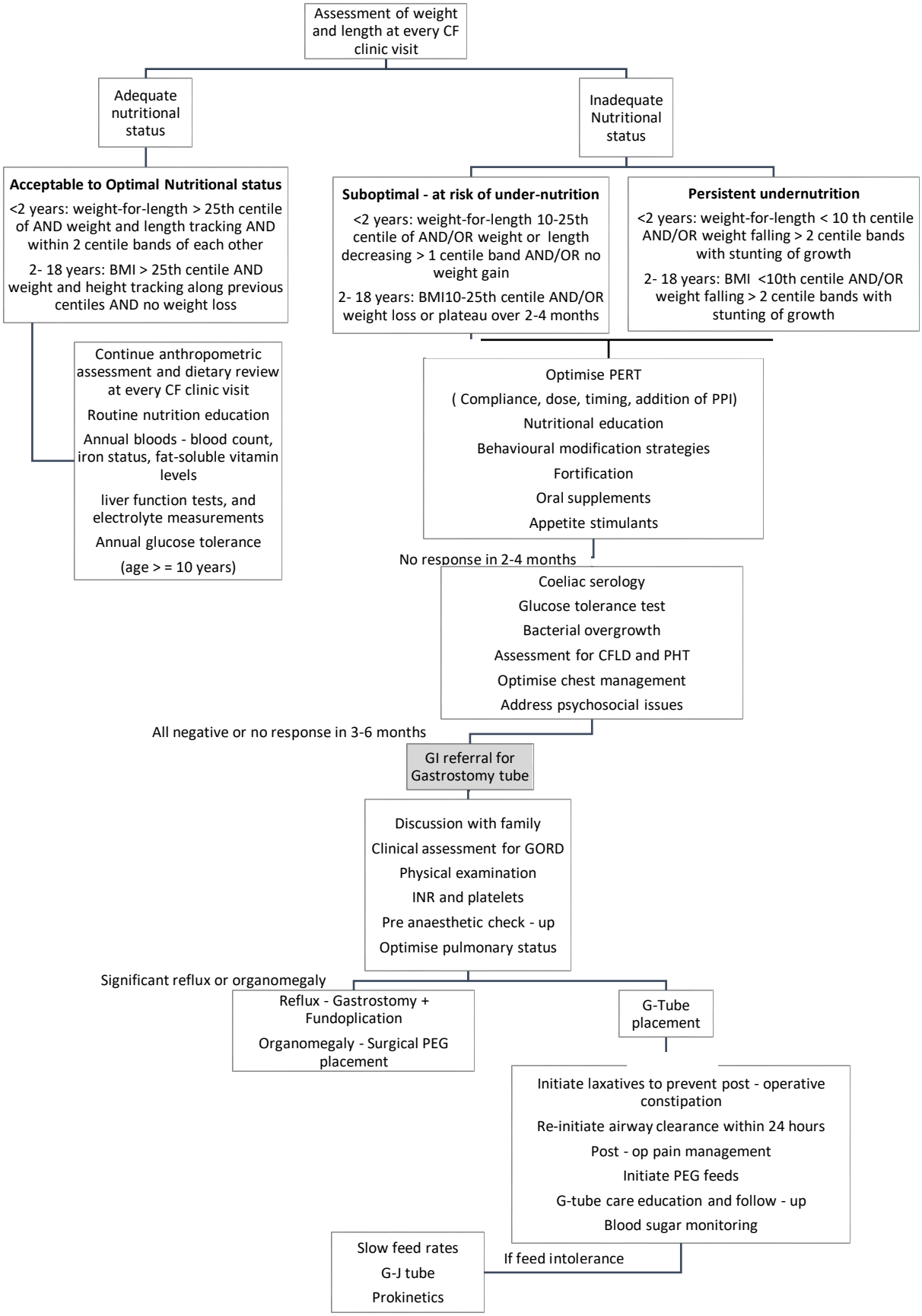



*UDCA- Ursodeoxycholic acid (20 mg/kg/day in two divided doses)

Refer

This article is protected by copyright. All rights reserved.

Author Manuscript




This article is protected by copyright. All rights reserved.

**Abstract**

Cystic Fibrosis (CF) is the most common, life-shortening genetic illness affecting children in Australia and New Zealand. The genetic abnormality results in abnormal anion transport across the apical membrane of epithelial cells in a number of organs including the lungs, gastrointestinal tract, liver and genito-urinary tract. Thus CF is a multi–system disorder which requires a multi-disciplinary approach.

Respiratory disease is the predominant cause of both morbidity and mortality in patients with CF. However, there are significant and clinically relevant gastrointestinal, liver, pancreatic and nutritional manifestations which must be detected and managed in a timely and structured manner.

The aim of this review is to provide evidence based information and clinical algorithms to guide the nutritional and gastrointestinal management of patients with CF.

**Key words –** abdominal pain, gastro – oesophageal reflux, CF – related liver disease, nutrition

Author Manuscript

This article is protected by copyright. All rights reserved.

Author Manuscript

## Introduction

Cystic fibrosis (CF) is the most common life-limiting, autosomal recessive inherited disease in the Caucasian population, affecting 1 in 2,500-4,000 live births[1]. It is caused by mutations in the gene encoding the chloride transporter, Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). CFTR is expressed at secretory epithelial cell surfaces, hence CF involves a number of organs including the gut, biliary tract, and pancreas in addition to the lungs. Almost 2000 CFTR gene mutations have been identified of which only approximately 200 have been characterised in terms of disease liability[2]. The Australian Cystic Fibrosis Data Registry for 2014 identified that more than 90% of patients had at least one copy of the p.F508del mutation and just over half were homozygous[3].

The mutations have been grouped into 7 functional classes[2] with class 1-3, 6 and 7 most affecting the transporter while classes 4 and 5 contain milder mutations which result in some functional CFTR reaching the cell surface and thus some maintenance of chloride secretion. CFTR genotype does not accurately predict individual outcome[4]. The genotype-phenotype correlation varies depending on affected organ, with end-organ disease severity affected by environmental factors and/or modifier genes.

Gastrointestinal manifestations are very common in CF with all patients included in a recent study reporting at least one abdominal symptom within the preceding three months[5]. In another recent survey of the top 10 research priorities in cystic fibrosis, gastrointestinal symptoms were considered a major priority second only behind effective ways of simplifying the treatment burden of patients[6].

The aim of this article is to provide practical clinical algorithms to guide the management of children with CF from a nutritional, gastrointestinal and liver perspective. It is not intended to be a comprehensive review, but a guide on how to approach these common problems on a day to day basis. For a detailed overview of CF gastroenterological issues, the reader is referred to more exhaustive reviews[7-12].

The areas covered in this article are: (1) Abdominal pain, (2) CF-related liver disease, and (3) Nutritional assessment and intervention in a child with CF.

For this review a literature search in PubMed and Google Scholar was conducted (English language, up to August, 2017) using the terms relevant for each of the sections. Review articles, practice guidelines and consensus statements in these areas were also reviewed and relevant information extracted.

## Abdominal pain

This article is protected by copyright. All rights reserved.

Abdominal pain and discomfort is experienced by 21-60% patients with CF[13]. Although it is often periumbilical, mild to moderate and of short duration[5], a significant number of patients report pain which has a negative impact on daily functioning[14].

Abdominal pain in CF may be –

1) Directly / Intrinsically CF related

   *Distal intestinal obstruction syndrome (DIOS)* has an incidence of 6.2 episodes per 1000 patient years and is defined as the presence of abdominal pain and / or distension and a faecal mass in ileo–caecum, with (Complete DIOS) or without (Incomplete/impending DIOS) complete intestinal obstruction[15]. Severe genotype, pancreatic insufficiency, dehydration and history of meconium ileus are risk factors[15,16]. The management of DIOS is summarised in table 1.

2) Conditions more frequently reported in CF

   (i) *Constipation* is a significant issue with a prevalence of ~ 47% [17]. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) CF working group defined it as the presence of abdominal pain and/or distension or reduced frequency or increased consistency of bowel movements relieved by the use of laxatives[15].

   (ii) *Recurrent intussusception* is seen in ~ 1%, due to sticky, mucofaeculent material adherent to the intestinal epithelium acting as the lead-point. It is usually ileocolic, and most commonly presents with recurrent abdominal pain, though presentation may be asymptomatic.

   (iii) An older study suggested that children with CF have an increased risk of *Inflammatory bowel disease* (IBD) (7 times higher than general population)[18]. However, this has been challenged in recent years as many cases were reported before the description of fibrosing colonopathy[19] and dysbiosis. It is important to note the limitations of using faecal calprotectin to screen children with CF for IBD. Children with CF may have intestinal inflammation[11], resulting from an altered intestinal milieu that leads to an elevated faecal calprotectin, making it difficult to differentiate CF from milder forms of IBD[20,21].

   (iv) There are reports of an increased prevalence of *Coeliac disease* (2 – 3 fold higher than general prevalence) in children with CF[22], however the occurrence varies from country to country[23].

   (v) *Renal stones* are described in 3-6.3 % of patients with CF, a significantly higher prevalence than in age-matched controls without CF[24]. Possible reasons include

This article is protected by copyright. All rights reserved.

Author Manuscript

primary defects in calcium handling caused by mutation CFTR and lack of colonisation with Oxalobacter formigenes, an enteric oxalate-degrading bacterium.

(vi) Symptomatic *acute pancreatitis* is a significant problem in 10.3 -22 % of patients with CF who are pancreatic sufficient (~10-15% of all CF). Patients with genotypes associated with milder phenotypes are at greater risk[25,26].

(vii) *Cholelithiasis* is seen in 4-30% children with CF but is generally not symptomatic[27]. For symptomatic gall stones surgical referral is usually necessary.

(viii) *Small intestinal bacterial overgrowth* (SIBO) is reported in 37 – 56% patients with CF. Breath tests that have poor sensitivity and specificity in CF because of the post-antibiotic inability of GI flora to produce hydrogen [28,29]. Culture of a duodenal aspirate is the gold standard but is invasive and cumbersome to perform. If there is a high index of suspicion a clinical therapeutic trial for 14 days[30] is recommended. Clear clinical improvements in diarrhoea, appetite and bloating are grounds to consider repeat therapy in the event of symptom recurrence.

(ix) *Gastro-oesophageal reflux disease* (GORD) is up to four times more common in infants with CF compared with unaffected infants[31]. There is a lack of evidence based CF specific guidelines for the management of GORD, so initiation of treatment should be based on standard guidelines for the general population[32]

(x) There is a 10 - fold increase of Colorectal neoplasia in adults with CF as compared to the healthy controls.[33]

3) Treatments involved in CF care

(i) *Intestinal adhesions and strictures* can occur in patients who have undergone surgery for meconium ileus.

(ii) Despite high gastrointestinal colonization by *C. difficile* in patients with CF (32–50%)[34], *C. difficile* infection appears to occur infrequently. For symptomatic infection a 10-14 day course of oral metronidazole should be considered for mild to moderate presentations or oral vancomycin for severe cases.[35]

4) Causes unrelated to CF

(i) *Appendicitis* has an incidence rate of 1% to 2% in CF[36], lower than the 7% in the general population. The inspissated secretions might protect against appendicitis and chronic antibiotic use may mask symptoms. The diagnosis is often delayed until perforation and abscess formation has occurred.

This article is protected by copyright. All rights reserved.

Author Manuscript

(ii)*Functional abdominal pain* – The true prevalence of functional abdominal pain in CF is unknown. A prevalence of 6% was reported in a prospective pilot study.[37] Not unlike non-CF individuals with unexplained abdominal symptoms, the diagnosis of irritable bowel syndrome (IBS) should always be considered if Rome criteria are satisfied. In these cases IBS-specific therapies including behavioural and dietary treatments may be helpful.

Fig. 1 and 2 summarise the approach to children presenting in the outpatient setting (typically mild, recurrent, chronic pain) and those presenting to the emergency department (with acute, severe pain). However, it is to be remembered that there may be overlap between these clinical presentations. Children with CF who present to the emergency unit with acute abdominal pain should have all differential diagnoses considered as for a child without CF to ensure that serious conditions are considered. However, the conditions highlighted in the algorithm are more prevalent in the CF community and should be given greater consideration.

In poorly localized mild abdominal pain, a clinician should consider the adequacy of pancreatic enzyme replacement therapy (PERT), coeliac serology and stool examination for fat malabsorption and parasites. A trial of laxatives for 2-4 weeks can be tried. If there is no response, then clinical review and consideration should be given to other causes.

**Cystic fibrosis- related liver disease**

Cystic fibrosis–related liver disease (CFLD) is the third-leading cause of mortality in patients with CF (behind pulmonary disease and complications of lung transplantation) and is responsible for around 2.5%[38] of all deaths. Significant liver damage is detectable during post mortem in 72% of adult patients with CF[39]. However, clinically significant liver disease (defined by the presence of portal hypertension and/or macro nodular cirrhosis) occurs much less frequently with an incidence of 5-10% in the paediatric community and 1-2% in adult surveys of CF[40,41], with almost all cases detected in the first two decades of life. A characteristic of CFLD is early portal hypertension far in advance of hepatic cell dysfunction and often prior to evolution of cirrhosis[42].

The spectrum of hepatic involvement ranges from – hepatic steatosis (20-60%), to focal biliary cirrhosis (11- 70%) and multi-lobar cirrhosis (5-10%)[43,44]. Hepatic steatosis has been found to be associated with malnutrition, and essential fatty acid, carnitine or choline deficiency. However, steatosis is also found in patients with adequate nutritional status.

CF is also the cause for cholestasis in 0.7% of all infants with neonatal cholestasis.[45]

This article is protected by copyright. All rights reserved.

Author Manuscript

Author Manuscript

Forty to 50% of CF patients have intermittent elevations in AST, ALT or GGT that are not predictive of the development or presence of significant fibrosis.[46]

Hepatotoxic drugs and intercurrent infections may be causes for these intermittent elevations. The pathogenesis of CFLD remains poorly defined. Abnormal CFTR function in the apical membrane of the biliary epithelium leads to decreased bile fluidity and alkalinity, resulting in a sequence of inspissated bile accumulation, inflammation and progressive fibrosis. An alternative hypothesis is based on the premise of a 'leaky gut' in cystic fibrosis that predisposes to the translocation of bacterial factors into the portal circulation, which activate hepatic inflammation and fibrogenesis. More recently the role of a dysbiotic microbiome has been implicated in the steatosis and fibrosis of metabolic syndrome and in IBD related PSC, two conditions with similarities to the steatosis and cholangitis in CF again linking the gut to CF liver disease. The high rate of antibiotic usage in CF with a resulting reduction in microbial diversity and increase in inflammatory microbial signatures may have more of a role than previously thought, however this remains to be elucidated. It is not clear why some patients develop advanced liver disease while others do not and mechanisms including the role of bile salt stimulation of stellate cell recruiters and activators have been proposed[44] Non – cirrhotic portal hypertension has also been described in children with CF. [42, 47]

Male gender and mutations associated with a severe phenotype increase the risk of developing severe liver disease[48]. Non-CFTR genetic polymorphism studies revealed an increased risk of CFLD for patients carrying the alpha 1-antitrysin Z-allele[49].

Diagnosis and assessment of the severity of fibrosis in CFLD is challenging. Ultrasound of the liver in the early stages of CFLD may not reliably differentiate evolving fibrosis from steatosis. By the time changes develop, fibrosis may be advanced and severe[50]. Non – invasive tests like transient elastography[51] and aspartate aminotransferase to platelet ratio index[52] are promising tools which are not yet validated for surveillance. Liver biopsy is a prognostic indicator for the development of portal hypertension[53], but the lack of evidence relating to change in management has limited its widespread use.

Although consensus is lacking, diagnostic criteria for CFLD have been proposed by ESPGHAN -[38] (at least two of the following variables are needed): (1) hepatomegaly or splenomegaly; (2) a persistent (>12 months) elevation of serum alanine aminotransferase and / or GGT (level > upper limit of normal [ULN]) and exclusion of other causes of liver diseases (Table 2); or (3) abnormal liver ultrasound findings

This article is protected by copyright. All rights reserved.

Effective medical treatment for CFLD is not yet available. There is insufficient evidence to justify the routine use of ursodeoxycholic acid (UDCA) in cystic fibrosis[54]. However, there is some unconfirmed data to suggest that asymptomatic patients with early stage liver disease are more likely to benefit from its administration[55]. Moreover, patients with CF and no liver disease are known to have a greater endogenous bile enrichment with UDCA.[56]

Novel treatments that target the basic defects in the CFTR protein have emerged, but to date little is known about their effects on the hepatobiliary systems[1]. The indications for liver transplantation in CF are (i) gradual hepatic impairment unresponsive to standard treatment, (ii) intractable variceal bleeding or (iii) the presence of portopulmonary or hepatopulmonary syndromes. Impaired nutrition, poor pulmonary status, infections and uncontrolled diabetes should be optimised as they could have a negative impact and increase morbidity post-liver transplantation.

Combined liver-lung transplantation should be considered for patients with CF who have severely compromised lung function with frequent exacerbations of pulmonary infections, or who are colonisation with Burkholderia cepacia, non-tuberculous Mycobacteria or other multidrug-resistant organisms, or those who have severe pulmonary hypertension[57].

Fig. 3 summarises the approach to the diagnosis and management of CFLD in children

**Nutrition**

Nutrition is an important component of the care of children with CF[8]. A normal nutritional status is associated with better lung function and survival in children with CF.[58] Measurement of anthropometric parameters is a cornerstone of paediatric practice including the CF clinic and nutritional status monitoring plays an important role in the early detection of nutritional deficits.[59] High energy intakes (110%- 200% of energy needs for the general population) and a high fat diet are often required to achieve normal nutrition status[8] though meeting this is often difficult to achieve.

Inadequate nutritional status in CF is often multifactorial and when inadequate nutritional status is detected, there are a number of strategies that can be implemented to aid weight gain.

Individuals with CF and pancreatic insufficiency require Pancreatic Enzyme Replacement Therapy (PERT) with all fat containing food and fluids distributed according to fat content (Table 3).[8] PERT use including adherence, dose, distribution according to fat content, and timing should be reviewed regularly by an experienced dietitian, particularly when nutritional

This article is protected by copyright. All rights reserved.

Author Manuscript

Author Manuscript

status is a concern. While there is inconsistent and limited evidence to support the use of acid suppression medication to improve PERT efficacy[60], a short term trial may be considered once the above mentioned factors have been considered.

Routine nutrition education including encouraging a high energy, protein and fat diet, fortification of foods with additional energy sources and drinks naturally high in protein or energy to supplement intake outside of meal times is likely to assist in promoting weight gain and maintenance of adequate nutrition status in CF. During periods of undernutrition, these dietary intervention strategies may need to be intensified and increased and may include progression to oral supplements. While there is no clear evidence that the routine use of oral nutrition supplements in addition to food promotes weight gain in CF[61], these should be considered on an individual basis. The aim is that they should complement, rather than replace, normal food intake. To that end, the recommendation is that they are to be taken after a meal or as an in-between meal snack.

Behavioral modification strategies such as encouraging routine meals and snacks, setting rules and expectations around meal times, praise for eating well, self-monitoring of food intake, and setting energy targets for meals and snacks have been shown to be effective in achieving improved weight status in children, particularly when combined with nutrition education[62]. These should be considered in those with, or at risk of, undernutrition.

Appetite stimulants such as Cyproheptadine may improve appetite and result in weight gain in people with CF.[63] For children who have a chronic loss of appetite, appetite stimulants may be considered for a short duration of 4-6 months once other strategies to improve nutritional status such as PERT optimisation and nutrition education have been explored.

For people with CF and persistent suboptimal or undernutrition despite implementation of the strategies listed above, secondary causes like coeliac disease, CF-related diabetes etc. (Fig. 4) should be ruled out. CFRD may also cause feed intolerance by exacerbating gastrointestinal motility problems intrinsic to CF.

Following exclusion of alternate causes, supplemental enteral feeding should be considered for those failing non-invasive strategies, or earlier in those clearly at nutritional compromise or with recognized additional nutritional challenges such as emerging portal hypertension, feeding disorders and intestinal inflammation. Gastrostomy feeding should be initiated prior to the onset of significant lung disease[64] as aggressive enteral nutrition support is increasingly more challenging as lung function deteriorates, and is not usually successful in end-stage lung disease. Gastrostomy feeds are usually introduced gradually as tolerated and administered as a continuous infusion overnight via a pump to preserve appetite and oral

This article is protected by copyright. All rights reserved.

intake during the day. Supplementary bolus feeds (via gravity or pump assisted) during the day may be useful for those with poor appetite and/or inadequate oral intake[65]. A standard polymeric, age – appropriate enteral feed providing 30–60% of total estimated calorie requirements should be given. People with CF on enteral feeds should be reviewed regularly by a dietitian to assess progress towards goals, tolerance, adherence and ongoing need. Parenteral nutrition should be considered when enteral feeding is unsuccessful, or compounded by advanced lung disease where coughing and lung dysfunction compromise enteral delivery and tolerance not possible.

There is insufficient evidence to recommend routine supplementation of any complementary nutritional therapies (including probiotics, glutathione, garlic, ginseng, curcumin and coconut oil) to improve nutritional status or respiratory function in CF[8].

Fig. 4 outlines the approach to the nutritional evaluation and management in a child with CF.

**Conclusions**

Cystic fibrosis is a multisystem disorder which requires a multidisciplinary approach to care. Management of gastrointestinal manifestations is an integral part of holistic patient care. Timely recognition, proper evaluation, monitoring and therapy of these manifestations is key to alleviating the morbidity and mortality arising from them. It is to be remembered that this document cannot encompass every situation and is meant to provide general practical algorithms to achieve this goal. Recommendations are likely to change as more evidence becomes available.

**Acknowledgements**

We would like to thank the Gastroenterology and Cystic Fibrosis team at the Royal Children's Hospital, Melbourne for their inputs during the review process for this paper. We also extend our thanks to the RCH Foundation (Cystic Fibrosis Research Trust Auxiliary) for their support in awarding Dr Bolia a grant to write the guidelines.

**References**

1. AmaralMD.Novel personalized therapies for cystic fibrosis: treating the basic defect i n all patients. J Intern Med. 2015 Feb; 277(2):155-66.
2. De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. Lancet Respir Med. 2016;4(8):662-74.

This article is protected by copyright. All rights reserved.

Author Manuscript

Author Manuscript

3. https://www.cysticfibrosis.org.au/media/wysiwyg/CF-Australia/medical-documents/CFA_DataRegistryReport_2014_Final.pdf ( Accessed on 1 September 2017 )
4. Castellani C, Cuppens H, Macek M Jr et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. J Cyst Fibros. 2008;7(3):179-96
5. Tabori H, Arnold C, Jaudszus A et al. Abdominal symptoms in cystic fibrosis and their relation to genotype, history, clinical and laboratory findings. PLoS One. 2017;12(5):e0174463.
6. Rowbotham NJ, Smith S, Leighton PA et al. The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. Thorax. 2017 Aug 4 (Epub ahead of print)
7. Haller W, Ledder O, Lewindon PJ, Couper R, Gaskin KJ, Oliver M. Cystic fibrosis: An update for clinicians. Part 1: Nutrition and gastrointestinal complications. J Gastroenterol Hepatol. 2014;29(7):1344-55
8. Saxby N., Painter C., Kench A., King S., Crowder T., van der Haak N. and the Australian and New Zealand Cystic Fibrosis Nutrition Guideline Authorship Group (2017). Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand, ed. Scott C. Bell, Thoracic Society of Australia and New Zealand, Sydney.
9. Gelfond D, Borowitz D. Gastrointestinal complications of cystic fibrosis. Clin Gastroenterol Hepatol. 2013;11(4):333-42;
10. Ledder O, Haller W, Couper RT, Lewindon P, Oliver M. Cystic fibrosis: an update for clinicians. Part 2: hepatobiliary and pancreatic manifestations. J Gastroenterol Hepatol. 2014;29(12):1954-62
11. Ooi CY, Durie PR. Cystic fibrosis from the gastroenterologist's perspective. Nature Reviews Gastroenterology & Hepatology. 2016 13,175–185
12. Borowitz D, Durie PR, Clarke LL, Werlin SL, Taylor CJ, Semler J et al. Gastrointestinal Outcomes & Confounders in Cystic Fibrosis. J Pediatr Gastroenterol Nutr 2005;41:273-285
13. Lee AL, Rawlings S, Bennett KA, Armstrong D. Pain and its clinical associations in individuals with cystic fibrosis: A systematic review. Chron Respir Dis 2016;13: 102–117

This article is protected by copyright. All rights reserved.

Author Manuscript

14. Palermo TM, Harrison D, Koh JL. Effect of disease-related pain on the health-related quality of life of children and adolescents with cystic fibrosis. Clin J Pain 2006:22: 532–537
15. Houwen RH, van der Doef HP, Sermet I et al. Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS. J Pediatr Gastroenterol Nutr. 2010;50 (1):38-42.
16. Ooi CY, Jeyaruban C, Lau J, Katz T, Matson A, Bell SC et al. High ambient temperature and risk of intestinal obstruction in cystic fibrosis. J Paediatr Child Health. 2016;52(4):430-5
17. Van der Doef HP, Kokke FT, Beek FJ, Woestenenk JW, Froeling SP, Houwen RH. Constipation in pediatric cystic fibrosis patients: an underestimated medical condition. J Cyst Fibros. 2010;9(1):59-63.
18. Lloyd-Still JD. Crohn's disease and cystic fibrosis. Dig Dis Sci. 1994; 39(4):880-5.
19. Wilschanski, M, Durie, P. R. Patterns of GI disease in adulthood associated with mutations in the CFTR gene. Gut 2007, 56, 1153–1163.
20. Garg M, Leach ST, Coffey MJ et al. Age-dependent variation of fecal calprotectin in cystic fibrosis and healthy children. J Cyst Fibros. 2017 Apr 14. [Epub ahead of print]
21. Dhaliwal J, Leach S, Katz T, et al Intestinal inflammation and impact on growth in children with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2015;60:521-6.
22. Walkowiak J, Blask-Osipa A, Lisowska A et al. Cystic fibrosis is a risk factor for celiac disease. Acta Biochim Pol. 2010;57(1):115-8. Epub 2010 Mar 20.
23. Fluge G, Olesen HV, Gilljam M et al. Co-morbidity of cystic fibrosis and celiac disease in Scandinavian cystic fibrosis patients. J Cyst Fibros 2009:8:198–202
24. Gibney EM, Goldfarb DS. The association of nephrolithiasis with cystic fibrosis. Am J Kidney Dis. 2003; 42(1):1-11.
25. Ooi CY, Dorfman R, Cipolli M et al. Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. Gastroenterology. 2011; 140(1):153-61
26. De Boeck K, Weren M, Proesmans M, Kerem E. Pancreatitis among patients with cystic fibrosis: correlation with pancreatic status and genotype. Pediatrics. 2005; 115(4):e463-9.
27. Jebbink MC, Heijerman HG, Masclee AA, Lamers CB. Gallbladder disease in cystic fibrosis. Neth J Med. 1992; 41(3-4):123-6.

This article is protected by copyright. All rights reserved.

Author Manuscript

28. Schneider AR, Klueber S, Posselt HG et al. Application of the glucose hydrogen breath test for the detection of bacterial overgrowth in patients with cystic fibrosis--a reliable method? Dig Dis Sci. 2009; 54(8):1730-5.
29. Lewindon PJ, Robb TA, Moore DJ, Davidson GP.Bowel dysfunction in cystic fibrosis: importance of breath testing. J Paediatr Child Health 1998; 34(1):79-82
30. Rezaie A, Pimentel M, Rao SS. How to Test and Treat Small Intestinal Bacterial Overgrowth: an Evidence-Based Approach. Curr Gastroenterol Rep. 2016 ; 18(2):8.
31. Heine RG, Button BM, Olinsky A, Phelan PD, Catto-Smith AG. Gastro-oesophageal reflux in infants under 6 months with cystic fibrosis. Arch Dis Child. 1998; 78(1):44-8.
32. Davies I, Burman-Roy S, Murphy MS et al. Gastro-oesophageal reflux disease in children: NICE guidance. BMJ. 2015;350:g7703
33. Gory I, Brown G, Wilson J, Kemp W, Paul E, Roberts SK et al. Increased risk of colorectal neoplasia in adult patients with cystic fibrosis: a matched case-control study. Scand J Gastroenterol. 2014 Oct;49(10):1230-6.
34. Burke DG, Harrison MJ, Fleming C et al. Clostridium difficile carriage in adult cystic fibrosis (CF); implications for patients with CF and the potential for transmission of nosocomial infection. J Cyst Fibros. 2017;16:291-298.
35. Trubiano JA, Cheng AC, Korman TM et al. Australasian Society of Infectious Diseases updated guidelines for the management of Clostridium difficile infection in adults and children in Australia and New Zealand. Intern Med J. 2016; 46:479-93.
36. Shields, M. D. et al. Appendicitis in cystic fibrosis. Arch. Dis. Child.1991;66;307–310.
37. Munck A, Pesle A, Cunin-Roy C et al. Recurrent abdominal pain in children with cystic fibrosis: a pilot prospective longitudinal evaluation of characteristics and management. J Cyst Fibros. 2012; 11(1):46-8.
38. Debray D, Kelly D, Houwen R, Strandvik B, Colombo C. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. J Cyst Fibros. 2011; 10; S2:S29-36
39. Vawter GF, Shwachmann H. Cystic fibrosis in adults: an autopsy study. Pathol. Annu. 1979; 14: 357–82.
40. Colombo C, Battezzati PM, Crosignani A et al. Liver disease in cystic fibrosis: A prospective study on incidence, risk factors, and outcome. Hepatology. 2002; 36(6):1374-82

This article is protected by copyright. All rights reserved.

Author Manuscript

41. Scott-Jupp R, Lama M, Tanner MS. Prevalence of liver disease in cystic fibrosis. Arch Dis Child. 1991;66(6):698-701
42. Lewindon PJ, Ramm GA. Cystic Fibrosis – cirrhosis, portal hypertension and liver biopsy. Hepatology 2011;53(3):1065-6
43. Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. Hepatology. 1999; 30(5):1151-8
44. Lewindon PJ, Pereira TN, Hoskins AC et al. Role of Hepatic Stellate Cells and Transforming Growth Factor -$\beta_1$ in Cystic Fibrosis Liver Disease. Am. J. Pathol 2002;160(5):1705-1715
45. Shapira R, Hadzic N, Francavilla R, Koukulis G, Price JF, Mieli-Vergani G.Retrospective review of cystic fibrosis presenting as infantile liver disease. Arch Dis Child 1999;81:125-8
46. Flass T, Narkewicz MR. Cirrhosis and other liver disease in cystic fibrosis. J Cyst Fibros. 2013 Mar; 12(2): 116–124.
47. Witters P, Libbrecht L, Roskams T, De Boeck K, Dupont L, Proesmans M et al. Liver disease in cystic fibrosis presents as non-cirrhotic portal hypertension. 2017 Sep;16(5):e11-e13.
48. Stonebraker JR, Ooi CY, Pace RG, Corvol H, Knowles MR, Durie PR, Ling SC. Features of Severe Liver Disease With Portal Hypertension in Patients With Cystic Fibrosis. Clin Gastroenterol Hepatol. 2016;14:1207-1215.e3
49. Bartlett JR, Friedman KJ, Ling SC, et al. Gene modifier study group. Genetic modifiers of liver disease in cystic fibrosis. JAMA 2009; 302:1076–1083
50. Mueller-Abt PR, Frawley KJ, Greer RM, Lewindon PJ. Comparison of ultrasound and biopsy findings in children with cystic fibrosis related liver disease.J Cyst Fibros. 2008;7:215-21
51. Klotter V, Gunchick C, Siemers E et al. Assessment of pathologic increase in liver stiffness enables earlier diagnosis of CFLD: Results from a prospective longitudinal cohort study. PLoS One. 2017; 12: e0178784
52. Leung DH, Khan M, Minard CG et al. Aspartate aminotransferase to platelet ratio and fibrosis-4 as biomarkers in biopsy-validated pediatric cystic fibrosis liver disease. Hepatology. 2015; 62: 1576–1583
53. Lewindon PJ, Shepherd RW, Walsh MJ et al. Importance of hepatic fibrosis in cystic fibrosis and the predictive value of liver biopsy. Hepatology. 2011 Jan;53(1):193-201

This article is protected by copyright. All rights reserved.

Author Manuscript

54. Cheng K, Ashby D, Smyth R. Ursodeoxycholic acid for cystic fibrosis related liver disease (Cochrane review). Cochrane Database Syst Rev 2014; 12:CD000222.
55. Siano M, De Gregorio F, Boggia B et al. Ursodeoxycholic acid treatment in patients with cystic fibrosis at risk for liver disease. Dig Liver Dis. 2010; 42(6):428-31.
56. Smith JL, Lewindon PJ, Hoskins AC, et al. Endogenous ursodeoxycholic acid and cholic acid in liver disease due to cystic fibrosis. Hepatology 2004;39:1673-1682
57. Staufer K, Halilbasic E, Trauner M, Kazemi-Shirazi L. Cystic fibrosis related liver disease--another black box in hepatology. Int J Mol Sci. 2014;15(8):13529-49
58. E.H. Yen, H. Quinton, D. Borowitz. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. J Pediatr 2013; 162:530-535
59. Turck D, Braegger CP, Colombo C et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clin Nutr. 2016;35(3):557-77
60. Ng SM, Francini AJ. Drug therapies for reducing gastric acidity in people with cystic fibrosis. Cochrane Database Syst Rev. 2012;18;(4):CD003424.
61. Smyth RL, Rayner O. Oral calorie supplements for cystic fibrosis. Cochrane Database Syst Rev 2014;11:CD000406
62. Stark LJ, Opipari-Arrigan L, Quittner AL, Bean J, Powers SW. The effects of an intensive behavior and nutrition intervention compared to standard of care on weight outcomes in CF. Pediatr Pulmonol 2011;46:31e5
63. Chinuck R, Dewar J, Baldwin DR, Hendron E. Appetite stimulants for people with cystic fibrosis. Cochrane Database Syst Rev 2014;7:CD008190
64. Ledder O, Oliver MR, Heine RG, Graham J, Volders E, Robinson PJ. Clinical audit results in earlier nutritional intervention in malnourished children with cystic fibrosis with improved outcome. J Paediatr Child Health. 2015;51(10):988-93
65. Schwarzenberg SJ, Hempstead SE, McDonald CM et al. Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines. J Cyst Fibros. 2016;15(6):724-735.

**Key Points**

**1.** Cystic fibrosis children commonly experience abdominal pain and discomfort. Although the majority of patients describe their pain as mild and of relatively short duration, a

This article is protected by copyright. All rights reserved.

Author Manuscript

significant number of patients have pain which is severe or of long enough duration to potentially have a negative impact on daily functioning

**2.** With increased life expectancy over the past two decades, hepatobiliary complications have become increasingly more common, with liver disease being the third leading cause of death among CF patients

**3.** Malnutrition is both a frequent feature and a comorbidity of cystic fibrosis, with nutritional status strongly associated with pulmonary function and survival. Nutritional management is therefore an important component of care in CF patients.

**Multiple Choice Questions**

1. **All of the following are risk factors for distal intestinal obstruction syndrome (DIOS) except:**
   A. Pancreatic insufficiency
   **B.** History of meconium ileus
   **C.** History of DIOS
   **D.** Cystic fibrosis related liver disease
   **E.** Dehydration

Answer is **D**

The majority of patients with DIOS are pancreatic insufficient, with less than 10% of DIOS patients

being pancreatic sufficient. A previous history of meconium ileus is also a strong risk factor. Almost half of the DIOS patients in a large European study had presented with meconium ileus at birth, as opposed to a frequency of 15% in the general CF population. 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. Dehydration precipitated by intercurrent illnesses, such as respiratory exacerbation and hot weather might induce DIOS. Presence of cystic fibrosis related liver disease is not a risk factor.

2. **Which of the following is not true about Cystic fibrosis related liver disese (CFLD):**

A. There is a strong correlation between CFTR genotype and patients who develop severe CF-related cirrhosis
B. Liver disease is the third leading cause of death among CF patients.

This article is protected by copyright. All rights reserved.

C. The complications of CFLD arise mostly from portal hypertension
D. There are no proven therapies to prevent the development or progression of CFLD
E. Although many patients with CF will have elevated aminotransferase levels, only 5%-10% percent of CF patients develop severe CF-related multilobular cirrhosis

Answer is **A**

Liver disease is the third leading cause of death among CF patients. Only 5%-10% percent of CF patients
develop severe CF-related multilobular cirrhosis. There is no known correlation between CFTR genotype and
patients who develop severe CF-related cirrhosis, though there are known genetic modifiers such as the SERPINA1 Z allele. The complications of CFLD arise mostly from portal hypertension and include hypersplenism, esophageal and gastric varices, and ascites. Liver failure and severe coagulopathy present very late in the course of the disease.

**3. Which of the following is not true about nutrition in CF :**

A. Behavioural modification strategies and nutrition education are valuable components of standard CF care
B. Levels of fat soluble vitamins (with associated tests to aid interpretation) should be routinely tested
C. Practitioners should screen for both under- and over- nutrition in the CF population.
D. Oral nutrition supplements should be considered on an individual basis as they are unlikely to result in improvements to BMI, nutritional intake or pulmonary function
A. Most infants with CF are unable to maintain adequate growth while breastfeeding.

Answer is **E**

It is becoming increasingly common to see people with CF who are overweight. Practitioners should screen for both under- and over- nutrition in the CF population. Most infants with CF are able to maintain adequate growth while breastfeeding. The benefits of exclusively breastfeeding a CF baby for the first 6 months include a decreased use of intravenous antibiotics for the first two years of life. Fat-soluble vitamin status should be routinely reviewed. Low fat-soluble vitamin levels can be an early indicator of pancreatic insufficiency. Research indicates that behaviour modification strategies are to be considered at a young age, before disruptive eating and mealtime behaviours become an ongoing issue.

This article is protected by copyright. All rights reserved.

Author Manuscript

There is also evidence to support the ongoing use of these strategies throughout childhood. Oral nutrition supplements are unlikely to result in any improvement in outcomes such as BMI, nutritional intake or pulmonary function in adults and children with CF over and above the use of routine dietary advice and monitoring alone

Author Manuscript

**Figure legends**

Fig. 1 Approach to abdominal pain in a child with CF in the outpatient clinic (Mild, chronic, recurrent pain)

Fig. 2 Approach to abdominal pain in a child with CF in the emergency department (Acute, severe pain)

Fig. 3 Approach to liver disease in a child with Cystic Fibrosis

Fig. 4. Nutritional assessment and intervention in a child with Cystic Fibrosis

This article is protected by copyright. All rights reserved.

Author Manuscript

This article is protected by copyright. All rights reserved.