
Cystic fibrosis

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Advancement in treatment has resulted in a dramatic increase in life expectancy of patients with cystic fibrosis (CF) to well beyond 30 years of age in most centres. What was once a fatal genetic disease in childhood now sees over a third of its CF populations in adult clinics. The improved survival is multifactorial, but most attribute the reasons to more aggressive nutritional care along with better management of the gastrointestinal and pulmonary systems. Many of the nutritional and GI issues of paediatric patients remain similar when they become adults, except that there is the added psychosocial stress associated with this transition. This chapter aims to highlight the gastrointestinal and nutritional issues manifesting at the different stages of life from infancy to adulthood, and the recommended management.

Key words: cystic fibrosis; nutrition; malnutrition; transition of care.

The improvement in clinical care of cystic fibrosis (CF) patients has dramatically changed the disease from predominantly a paediatric entity to a disease spectrum starting in childhood, but expected to progress well into adulthood. Historically, more than 70% of infants died during the first year of life when CF was first described in 1938.¹ Recent data show that, in most developed countries, the median survival is now well over 30 years^{2,3}, while approximately half the CF populations are now adults. Much of this improvement has been attributed to the essential factor of better nutrition.^{4,5} As the projected survival continues to increase, primary care physicians need to expand their awareness of all gastrointestinal and nutritional aspects and manifestations of CF patients as they pass from childhood to adulthood.

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BASIS OF THE DISEASE

CF has remained one of the most common lethal genetic diseases in the general population. This autosomal recessive condition has an incidence of one in 2500³ live births for Caucasians, one in 15 000 among African-Americans, and one in 31 000 among Asians.⁶ The defective gene was cloned and characterized in 1989.⁷ The CF gene is located on the long arm of chromosome 7. It encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is an important cAMP-regulated chloride channel within epithelial cells lining the airways, intestines, biliary trees, pancreatic ducts, vas deferens and sweat ducts. A defect in the CFTR protein causes abnormal chloride transport, with decreased chloride secretions and increased sodium re-absorption. Abnormal chloride movement results in decreased fluid secretion, leading to viscid plugging of ducts and secondary dysfunction of the various organs involved. There are now over 1000 different mutations of the CFTR gene listed on the Hospital for Sick Children website.⁸ The most common mutation, $\Delta F508$, is found in more than 50% of the population. It consists of a deletion of phenylalanine at the 508th amino acid within the CFTR protein. With the large number of mutations being discovered, it was most practical to have these genotype mutations classified from class I to class V according to the functional effects and molecular fate of the CFTR mutation.⁹ This was summarized recently in terms of potential therapeutic approaches.¹⁰ Carriers of severe mutations (homozygous or compound heterozygous for class I to III mutations) have a more severe disease spectrum. The common end result is the lack of functioning Cl^- channels. As a result, these patients often have pancreatic insufficiency (PI).¹¹ The common defect, $\Delta F508$, belongs to the class II CFTR defects. Patients with one class IV or class V mutation will have some degree of residual CFTR function, and therefore often have pancreatic sufficiency and, in general, have less severe disease manifestations.

DIAGNOSIS

The diagnosis of CF has traditionally been made by the presence of the major classical clinical features, as well as by abnormal laboratory tests showing elevated sweat chloride of greater than 60 mmol/l. Gene mutation analysis is now used in borderline cases, and is also used as a prognostic indicator for predicting pancreatic function. The CF Consensus Panel published the consensus criteria for the diagnosis of CF in 1998.¹² The criteria have been updated to include newer testing methods such as nasal potential difference¹³, but most of the traditional criteria remain. The diagnosis of CF is based on the following:

1. the presence of one or more characteristic phenotypic features (see [Table I](#));
2. a history of CF in a sibling;
3. a positive newborn screening test (immunoreactive trypsin (IRT) if available);
4. laboratory evidence of a CFTR abnormality (elevated sweat chloride, or identification of two CFTR gene mutations known to cause CF, or abnormal nasal epithelial potential difference).

However, even with the existing diagnostic criteria, only approximately 71% of patients will be diagnosed by 1 year of age.¹² In certain parts of the world, neonatal testing for CF has been incorporated into newborn screening programmes by testing

Table 1. Phenotypic features consistent with a diagnosis of CF.

1. Chronic sinopulmonary disease manifested by:
 - a. Persistent colonization/infection with typical CF pathogens, including *Staphylococcus aureus*, non-typeable *Haemophilus influenzae*, mucoid and non-mucoid *Pseudomonas aeruginosa* and *Burkholderia cepacia*
 - b. Chronic cough and sputum production
 - c. Persistent chest radiograph abnormalities (e.g. bronchiectasis, atelectasis, infiltrates, hyperinflation)
 - d. Airways obstruction manifested by wheezing and air trapping
 - e. Nasal polyps; radiographic or computer tomographic abnormalities of the paranasal sinuses
 - f. Digital clubbing
2. Gastrointestinal and nutritional abnormalities, including:
 - a. Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
 - b. Pancreatic: pancreatic insufficiency, recurrent pancreatitis
 - c. Hepatic: chronic hepatic disease manifested by clinical or histological evidence of focal biliary cirrhosis or multilobular cirrhosis
 - d. Nutritional: failure to thrive (protein-calorie malnutrition), hypoproteinaemia and oedema; complications secondary to fat-soluble vitamin deficiency
3. Salt-loss syndromes: acute salt depletion, chronic metabolic alkalosis
4. Male urological abnormalities resulting in obstructive azoospermia (congenital bilateral absence of vas deferens)

From Rosenstein BJ & Cutting GR (1998, *Journal of Pediatrics* 132: 589–595) with permission.

levels of IRT in the blood during the routine newborn screening for other inheritable diseases. Abnormal IRT results are then followed by confirmation with mutation analysis or sweat chloride tests.¹⁴ Whether a newborn screening programme can change the long-term outcome in CF remains controversial. Neonatal screening may provide an opportunity to prevent malnutrition¹⁵, but longer-term follow-up is necessary before advocating universal screening. However, diagnosis beyond this age and into adulthood continues to be made, especially in persons with mild and less common mutations.

SWEAT TEST

The sweat test is still the most useful tool in screening for CF. It should always be carried out in accordance with the guidelines of the National Committee for Clinical Laboratory Standards and only the quantitative test should be performed. This allows the chloride and sodium concentration of collected sweat to be measured. Results are usually then categorized as follows:

Less than 40 mmol/l: negative

40 to 60 mmol/l: borderline

Greater than 60 mmol/l: consistent with CF (or other diseases with a positive sweat test: metabolic conditions (glycogen storage disease type I, mucopolysaccharidosis, hypothyroidism, adrenal insufficiency), skin and sweat gland conditions (ectodermal dysplasia and atopic dermatitis), malnutrition, and methodological or calculation errors.¹⁶)

Table 2. Cystic fibrosis presentation in adulthood.

<i>Gastrointestinal/hepatic</i>
Recurrent acute pancreatitis
Cirrhosis
Gall stones
Portal hypertension with oesophageal varices
Jaundice
<i>Respiratory</i>
Recurrent chest infections
Chronic cough
Sinusitis
Nasal polyps
<i>Others</i>
Infertility
Heat prostration
Genetic screening of relatives with CF

Adapted from Mallia P (1999, *Hospital Medicine* **60**: 29–33).

The majority of CF patients have a sweat chloride level greater than 60 mmol/l, but infants with CF less than 3 months of age may have a borderline sweat chloride of 40 to 60 mmol/l.¹⁷ However, the consensus guidelines for diagnosis should always be followed, and the diagnosis of CF should be made through repeated positive elevation or genotyping.

Increasingly, patients with milder disease are presenting later for the first time in adulthood, and a wide spectrum of symptoms is being recognized. Clinicians need to be suspicious in adult patients with suggestive symptoms and not presume that CF is unlikely to present later in life (see [Table 2](#)). Some of the late diagnoses may have been due to normal or borderline sweat test results. Genotyping has helped to identify some of these patients as having newer, milder mutations and non- $\Delta F508$ mutations.¹⁸

THE EVOLUTION OF THE DISEASE IN CYSTIC FIBROSIS

Paediatric patients with CF usually present with gastrointestinal or nutritional manifestations during the newborn period or early infancy. Pulmonary symptoms, although present, do not tend to be the first presentation leading to diagnosis. [Table 3](#) categorizes the manifestations according to systems in the paediatric age group.

NUTRITION/PANCREAS

Pancreatic insufficiency

Most CF neonates have close to normal weight and length parameters at birth, but will begin to deteriorate by the time of diagnosis.¹⁵ The main contributing factor for

Table 3. GI/nutritional manifestations and presentations in childhood.*General*

Failure to thrive
 Malnutrition
 Hypoproteinaemia
 Micronutrient deficiency (e.g. fat-soluble vitamins)

Oesophagus

Gastro-oesophageal reflux
 Oesophagitis
 Oesophageal varices

Gallbladder/biliary tract

Microgallbladder
 Cystic duct atresia
 Distended gallbladder
 Cholelithiasis/biliary sludge
 Common bile duct stenosis

Hepatic

Neonatal cholestasis
 Hepatosteatosi
 Focal biliary cirrhosis
 Multilobular biliary cirrhosis
 Portal hypertension
 Liver failure

Pancreas/endocrine

Pancreatic insufficiency
 Acute pancreatitis
 CF-related diabetes

Intestine

Meconium ileus (MI)
 Complication of MI
 Volvulus
 Small-bowel atresia
 Meconium peritonitis
 Distal intestinal obstruction syndrome
 Rectal prolapse
 Crohn's disease, ulcerative colitis

the poor growth is PI. Pancreatic insufficiency is the hallmark of the typical CF patient, leading to maldigestion, malabsorption and failure to thrive. The majority of CF patients will have evidence of PI in the neonatal (~60%) and infancy periods (~85 to 90% of patients by 1 year).¹⁹ Multiple other factors contribute to the poor growth and malnutrition. The pathogenesis model of energy imbalance in CF has been proposed and used by the Toronto CF group for many years and has formed the basis of treatment.^{20–22} The model helps to define the independent variables which give rise to the growth failure or malnutrition. The principles can be applied to both paediatric and adult CF patients (see [Table 4](#)).

Table 4. Energy imbalance in cystic fibrosis.

Increased requirement	Reduced intake
<i>Increased intestinal losses</i>	iatrogenic fat restriction Reflux/oesophagitis Anorexia, vomiting Psychosocial factors Pancreatic insufficiency Abnormal bile salt metabolism Regurgitation from reflux Hepatobiliary disease
<i>Increased energy need</i> Pulmonary disease	
<i>Increased energy losses</i> CF-related diabetes mellitus	

Modified from Durie PR and Pencharz PB (1989, *Journal of the Royal Society of Medicine* **82**(supplement 16): 11–20) and Pencharz PB and Durie PR (2000, *Clinical Nutrition* **19**: 387–394).

Pancreatic insufficiency can be confirmed by 72-hour stool collection for faecal fat, along with a dietary fat intake record to calculate levels of fat malabsorption. Levels greater than 7% in children and adults or greater than 15% for young infants suggest fat malabsorption. Severe CFTR mutations also concur with PI. Treatment consists of oral pancreatic enzyme supplementation taken with feeds. Enzymes are available in tablet, powdered form, or capsules of enteric-coated micro-encapsulated enzyme. The dosage according to units of lipase is listed in [Table 5](#). Dosage should be aimed at controlling steatorrhoea but should avoid exceeding 6000 lipase units/kg per meal for periods longer than 6 months because of the risk of the patient developing fibrosing colonopathy.²³ This will be discussed in further detail below.

Protein–calorie malnutrition

The combination of increased losses from malabsorption and maldigestion, gastro-oesophageal reflux (GOR), and increased energy requirement contribute to severe protein–calorie malnutrition. In some infants, an acute Marasmic–Kwashiorkor-like presentation can occur.^{24–26} These infants often present with the constellation of growth failure, anaemia, hypoproteinaemia, oedema and even ascites. The anaemia is postulated to be on the basis of vitamin E deficiency causing haemolysis.^{27,28} The growth failure, oedema and low protein are reflections of severe protein–calorie malabsorption. This constellation is seen more often in pancreatic insufficient (PI) infants with delayed diagnosis and in those fed a soy-based formula.²⁹ It would be unlikely that older children and adults would be presenting in this fashion as older patients with malnutrition have a tendency to maintain their serum albumin levels until late into the disease process. Patients with protein–calorie malnutrition require tailored nutritional rescue along with pancreatic enzyme and vitamin supplementation. Hydrolysed or elemental formulas are not necessary as treatment of the malnutrition, unless there is co-existing cow's milk protein intolerance. Normal formulas at sufficient caloric intake

Table 5. Pancreatic enzyme treatment in cystic fibrosis.

<i>Starting dose</i>	
Infants	2000 to 4000 lipase units/120 ml formula or breast-feeding
Children < 4 years	1000 lipase units/kg/meal
Children > 4 years	500 lipase units/kg/meal
Snacks	half of mealtime dose
<i>Maximum dose</i>	
Avoid greater than 2500 lipase units/kg/meal	
<i>In persistent diarrhoea</i>	
Ensure compliance and proper administration of enzyme supplements	
Exclude dietary irregularities (e.g. 'grazing' behaviour or high-fat 'fast foods')	
Antacid treatment to allow appropriate release of enzyme	
Exclude concurrent diagnosis (e.g. bacterial and parasitic infections, <i>C. difficile</i> toxin-induced diarrhoea, coeliac disease, inflammatory bowel disease or bacterial overgrowth)	

Adapted from Borowitz DS et al (1995, *Journal of Pediatrics* **127**: 681–684) and Riedel BD (1997, *Pediatric Annals* **26**: 235–241).

levels along with adequate pancreatic enzyme replacement will provide adequate benefit for maintaining growth velocity and nutritional status.^{30,31}

Nutrition

Nutritional care is the key integral part of managing CF patients. Most infants are malnourished at the time of diagnosis.¹⁹ Careful assessment of the nutritional status is important in order to implement the necessary intervention. The nutritional deficiency in CF varies from mildly depleted body fat stores to frank protein malnutrition. Therefore, a standardized approach should be followed. The CF Consensus Committee has published a comprehensive report to assist in providing guidance for nutritional management in CF patients.³² The practice within the guidelines has been the routine care in the Toronto CF clinics for many years. Routine monitoring at intervals of 3 to 6 months will allow monitoring of growth and nutritional status. During each visit anthropometric measurements are performed. These include length, height, head circumference, midarm circumference (muscle store), and triceps skinfold thickness (fat store). Energy requirements are assessed by dietary intake record over 3 to 5 days, while 3-day faecal fat testing is performed yearly. For patients with impaired growth that is not responding to dietary manipulation, indirect calorimetry is performed when available to help guide the intake requirement. Yearly measurements of complete blood count, electrolytes, liver functions, albumin, vitamins A and E, calcium and phosphorus are performed. If there are any concerns with bone mineralization dual-photon absorptiometry is performed to assess bone density

because serum concentrations of calcium, and phosphorus, as well as alkaline phosphatase levels, do not reflect bone status.

The ideal anthropometric indicator for assessing nutritional status has always been controversial.³³ There are too many variables and confounders to be able to show convincingly that any one criterion is the most accurate. In our experience, the most useful measurement for the paediatric age group has been to express weight as a percentage of ideal weight-for-height, with normal ranging from 90 to 110%. The method for calculating this index is detailed in the appendix. Body mass index (BMI) curves do exist for children, but there is no consensus agreement on assessing malnutrition in children and taking into account genetic and ethnicity factors using BMI. In adults, however, BMI can be used more widely to indicate changes in nutrition. Nutritional intervention in CF malnutrition is well described.^{21,34} We use a BMI < 20 kg/m² as a cause for concern, and < 19 kg/m² to consider tube feeding. Supportive intervention and re-evaluation are necessary when a CF paediatric patient's weight-for-height ratio falls between 85 and 90%. Treatment should then be focused on improving caloric intake, minimizing malabsorption, and identifying any reversible psychosocial stressors. If these interventions are not successful within a 3-month period, or if the patient's percentage weight-for-height falls below 85% (defined as nutritional failure) of ideal, then more aggressive intervention such as nocturnal enteral feeding via a gastrostomy device should be implemented. Our centre has had encouraging success with enterostomy feeding in patients with nutritional failure.³⁵ Families often report after the use of enterostomy feeding on the positive impact on physical and psychosocial well-being in the patients as well as family members. In reality, the key goal is to maintain peak nutritional status, regardless of the methods used to maximize survival. A meta-analysis on 18 studies using various methods of nutritional intervention (including behavioural, enteral, supplemental and parenteral treatment) all showed benefit in producing weight gain.³⁶ In effect, we are using a combination of these methods and seldom use the parenteral route as it has the highest potential risk of adverse effects and limitations to life-style.

With the majority of adolescent and adult CF patients having a normal to lower normal range of BMI, and normal to thin body habitus, patients often have become accustomed to that particular body shape which they have grown up with. This is particularly the case when the slim body habitus has become culturally popular despite the health hazards. Health care providers need to be aware that eating disorders, such as anorexia nervosa, should always be part of the differential diagnosis when a patient is having difficulty maintaining or gaining weight.³⁷

Vitamins

Fat-soluble vitamin deficiency is a frequent finding in infants with pancreatic-insufficient CF. Deficiency in at least one fat-soluble vitamin deficiency was seen in up to half of newborn CF infants screened in the first 2 months of life.³⁸ Even when supplemented with standard multivitamins, for A, D, E and K (Scandipharm, Birmingham, AL), persistent vitamin deficiency may be seen on follow-up—that for vitamin E being the most frequent. Vitamins A and E are of the greatest concern, particularly in patients with liver disease, as correction may require high supplementary doses. Vitamin D deficiency is more of a concern in areas with poor sunlight exposure.³⁹ Using a sensitive marker for early vitamin K deficiency (PIVKA-II), we were able to demonstrate a biochemical deficiency as a common finding in CF children and adults⁴⁰, and the standard ADEKs dosage of these fat-soluble vitamins fails to correct half of the supplemented patients.⁴¹ With increasing knowledge of the role of vitamin K

Table 6. Daily fat-soluble vitamins recommendation in CF infants with pancreatic-insufficiency.

Vitamin A	5000 IU/day
Vitamin D	800 IU/day
Vitamin E	50 IU/day
Vitamin K	1 to 2.5 mg/day

Adapted from Ramsey BW et al (1992, *American Journal of Clinical Nutrition* **55**: 108–116).

deficiency in the development of osteoporosis⁴², and its relationship with the major bone protein matrix, osteocalcin, vitamin K deficiency is recognized to play a significant role in the bone pathology in CF patients. Although bone disease has not been shown to be an early consistent manifestation or presentation in CF until late childhood⁴³, there is increasing evidence that poor acquisition of bone mineral density in childhood is contributing to the prevalence of abnormal BMD in adult CF patients. Therefore, frequent and serial monitoring of all fat-soluble vitamin levels is warranted in pancreatic insufficient CF patients, and extra supplementation on top of the recommended multivitamin supplement should be given in cases with persistent deficiency (Table 6). At present, we do not routinely perform DEXA scans in CF patients, except in a study protocol to look for bone thinning, or in the more severely malnourished individuals.

Electrolytes

Infants and children with CF can lose salt in the form of sodium chloride, especially in a hot climate or at the time of illness involving fever or diarrhoea. Salt supplement at levels 2 to 4 mmol/kg/day of sodium chloride (approximately 1/4 teaspoon/day of table salt) should be given in these circumstances. Hypochloraemic alkalosis and dehydration can be the mode of presentation for some patients. Urine can be screened for low levels of chloride and sodium.

Pancreatitis

Pancreatitis may be the presentation in older children with CF.⁴⁴ It is usually seen in the pancreatic sufficient (PS) patients, because PI patients have over 90% destruction of the exocrine pancreas, which leaves no residual enzyme to produce inflammation. Acute abdominal pain in PS CF patients needs to have pancreatitis excluded. Conversely, children with acute pancreatitis need to have CF as well as CF mutation carrier status excluded, as CFTR mutations have now been discovered in a significant number of patients with what would otherwise have been considered to be idiopathic pancreatitis.⁴⁵

INTESTINE

Meconium ileus

Meconium ileus (MI) is one of the earliest intestinal manifestations of CF. It affects up to 15% of CF neonates and is essentially a disease seen in PI infants, although it has been

reported in non-CF neonates, particularly those with prematurity in an ICU setting.⁴⁶ Patients classically present soon after birth with symptoms of bowel obstruction due to inspissated meconium in the distal small intestine. Gastrograffin enemas⁴⁷ have been used extensively as diagnostic and therapeutic tools for the management of uncomplicated MI (no evidence of perforation or peritonitis) to relieve the obstruction. Approximately half of all MI is uncomplicated. For those who fail to improve on gastrograffin enemas, T-tube ileostomy with instillation of n-acetylcysteine or gastrograffin⁴⁸ has been tried with success as an alternative to conventional surgical decompression. Complicated MI, which includes meconium peritonitis from in utero perforations, gangrene, volvulus and atresia, always requires operative intervention. Complicated MI carries a higher early mortality rate⁴⁹, and a higher incidence, long term, of distal intestinal obstruction syndrome (DIOS) and surgical complications. However, the overall outcome for these patients in terms of survival, nutritional status and pulmonary functions appears to be similar to non-MI CF patients.^{49,50} Improved surgical techniques and intensive care nursing have significantly dropped the early mortality rate. Recently, a CF modifier locus for MI on chromosome 19 was described which gives some insight as to why MI occurs in only a small proportion of PI CF patients.⁵¹ The meconium plug syndrome is an entity which is distinct from MI and is seen more commonly in premature infants; it carries an excellent long-term prognosis.

DIOS

From the age of 5 to 15 onwards, DIOS (previously called MI equivalent) has an estimated prevalence of 15%. It presents as recurrent, crampy, abdominal pain with distension and occasionally vomiting, and decreased stooling suggestive of bowel obstruction. It is due to inspissated, adherent stool and mucus, which can be palpated as a tender mass in the right lower quadrant. In acute cases, the differential diagnosis should include intussusception and appendicitis. The treatment choice is the administration of a large volume polyethylene glycol-balanced electrolyte solution given orally or nasogastrically⁵², and maintenance treatment with mineral oil.

DIOS should be distinguished from constipation, which is also common in children with or without CF. DIOS is a condition affecting the distal intestine as opposed to constipation, which is a condition of the rectum and left side of the colon. The stool frequency is more affected in constipation, while the palpable stool should be mainly left-sided. Both conditions are obviously worsened by the intake of narcotic pain relievers and anti-cholinergics.

Fibrosing colonopathy

Although fibrosing colonopathy is not a true manifestation of CF but rather an associated iatrogenic condition, it is an association worth knowing and preventing. It was first described in 1994 by Smyth et al⁵³, followed by a larger series in 1997 by FitzSimmons et al⁵⁴, describing paediatric patients with severe submucosal fibrosis and stricture in the proximal large intestine requiring colectomy. The mechanism of developing fibrosing colonopathy is believed to be due to the exogenously administered pancreatic enzymes digesting the mucosal surface of the colon. Patients may develop abdominal pain, diarrhoea and haematochezia prior to stricture formation. The risk for development of fibrosing colonopathy is associated with the intake of high daily doses of pancreatic replacement enzymes. The risk is highest in children under 12 years of age or with a history of MI, DIOS or previous intestinal

surgery. A high-strength pancreatic-enzyme product was withdrawn from the market after these reports. There has been less reporting of the condition following more judicious usage of enzymes.

IBD

Reports of Crohn's disease^{55,56} and more rarely ulcerative colitis-like inflammatory bowel disease (IBD)⁵⁷ have been reported in children with CF. However, many were retrospective cases prior to the description of fibrosing colonopathy and some, but certainly not all, may actually be due to complications of high enzyme therapy. There does not appear to be an increase in prevalence of IBD with the increased awareness of fibrosing colonopathy.

Rectal prolapse

Rectal prolapse usually occurs after the first year of life and can be the presenting symptom of CF.⁵⁸ As a result, patients with recurrent rectal prolapse should have a sweat chloride test performed. Rectal relapse is associated with inadequate control of steatorrhoea and resolves with adjustment of pancreatic enzymes. When associated with concurrent constipation, agents such as mineral oil or lactulose should be added. The symptom is usually transient, and often resolves at 5 years of age. Not infrequently, patients may develop a method of self-reduction with pelvic floor muscles and do not require manual pressure on the prolapsed rectum. Surgery is rarely required.

OESOPHAGUS

Gastro-oesophageal reflux

Gastro-oesophageal reflux appears to be more common in CF infants under 6 months of age.⁵⁹ Physiotherapy with postural drainage⁶⁰ or severe lung disease may worsen the degree of reflux. Treatment with H₂ receptor antagonists or proton-pump inhibitors will treat symptomatic gastro-oesophageal reflux disease (GORD) and erosive oesophagitis, and can also aid in the efficacy of pancreatic enzyme treatment as the coated enzymes require an alkaline pH for their release. Antacid treatment will allow earlier release in the small intestine and a greater period of time for digestion and absorption. It will theoretically minimize the amount of enzyme entering the large intestine and decrease the risk of fibrosing colonopathy. The natural history of GOR or GORD is similar to that in non-CF populations in that symptoms will improve with age in most persons, but some patients will require ongoing or intermittent acid-lowering therapy.

HEPATOBIILIARY

The pathogenesis of different forms of liver disease in CF patients, for example, focal biliary cirrhosis and cholelithiasis, can perhaps be explained by the presence of CFTR expression only in bile duct cells (cholangiocytes) and gall bladder epithelium, and not in other cells in the liver.⁶¹ Abnormal CFTR functions in CF patients would naturally explain why the disease is focused around the ductular epithelium. Sokol and Durie had proposed a model of CFTR mutation causing bile duct injury and bile plugging

which, in turn, leads to stellate cell activation, collagen deposition and eventually biliary cirrhosis.⁶² However, no model could explain why significant liver disease does not develop in all patients with severe CF mutations.

The prevalence of significant liver disease in children with CF is estimated to be 13–25%.⁶³ The true prevalence may be higher, as Gaskin et al found 30% of CF patients had hepatomegaly.⁶⁴ The difficulty lies in the spectrum of liver disease that includes neonatal cholestasis, hepatomegaly and persistent enzyme elevation, to the more classical focal biliary cirrhosis. It may be that CF-associated liver disease represents a heterogeneous group of liver pathology and not simply a result of bile ductular inspissation and damage.

Neonatal cholestasis

Prolonged neonatal cholestasis was reported in the past to occur in about 35% of CF infants but recent data indicate that only 2% of CF infants had significant cholestasis.⁶⁵ The decline in incidence may be from improved care of MI, which was thought to be an association due to factors such as TPN, sepsis and abdominal surgery.⁶⁶ Exclusion of other causes of neonatal cholestasis is the priority in management. The overall prognosis is said to be favourable⁶⁶, but a small percentage of these patients will go on to develop biliary cirrhosis. There have been reports of cases of prolonged neonatal cholestasis that mimic biliary atresia, which can make the diagnosis difficult.⁶⁵ Our centre had a similar situation in which the liver histology was indistinguishable from extra-hepatic biliary atresia and a Kasai procedure was performed. Maximizing nutritional status and using the choleric agent ursodeoxycholic acid (UDCA) are the main treatment regimen. Although UDCA has been shown to be beneficial in improving bile flow⁶⁷ as well as biochemical and clinical parameters⁶⁸, there is no clear evidence that UDCA alters the long-term natural history of any form of liver disease in CF.

Hepatosteatosis

Steatosis or 'fatty liver' is a common finding in CF patients of all age groups. It can be a reflection of malnutrition or deficiencies of essential fatty acids, carnitine or choline. Development of CF-related diabetes in older teenage patients may also contribute to steatosis. Steatosis is suggested by the finding of a soft palpable enlarged liver, or the imaging finding of increased fat density on ultrasound or CT scan. There are no data to suggest that steatosis in CF progresses to the more serious focal biliary cirrhosis.

Focal biliary cirrhosis/multilobular biliary cirrhosis

Focal biliary cirrhosis represents the pathognomonic lesion of CF-associated liver disease. The histological findings include focal areas of portal fibrosis, cholestasis, eosinophilic plugging and dilated ductules.⁶⁵ Focal biliary cirrhosis progresses with time to multilobular cirrhosis and eventually complications of portal hypertension. The disease is less common in the first decade of life, but is recognized more often in the teenage years.⁶⁹ Patients with biliary cirrhosis are often asymptomatic, with jaundice not developing until end-stage disease. Routine examination may reveal firm hepatomegaly or splenomegaly. Laboratory investigations may show elevation of serum transaminases, ALT, ALP or GGT. Serum bilirubin elevation is usually a late finding. Further evaluation with Doppler ultrasound to assess hepatic blood flow and

the presence of oesophageal varices should be arranged in patients with persistently elevated liver enzymes for 3 to 6 months.⁶² Endoscopic retrograde cholangio-pancreatogram (ERCP) is invasive and less useful for screening purposes because of the associated risks. Magnetic resonance cholangio-pancreatogram (MRCP) is becoming more readily available, and may represent a useful non-invasive method for assessing the biliary tree and gall bladder. Liver biopsy may be helpful when the sample is representative for assessing fibrosis. However, some clinicians consider a liver biopsy unwarranted as clinical outcome is not changed by the test, and no definitive therapy is available. UDCA therapy is used in biliary cirrhosis for many theoretical benefits, including possible nutritional improvement of essential fatty acids⁷⁰, retinal⁷⁰ and vitamin E⁷¹, but no long-term paediatric studies have been performed to prove true efficacy.

Portal hypertension/liver failure

Portal hypertension is a recognized complication of liver fibrosis in CF. The pace of development of portal hypertension is unpredictable. Although biliary cirrhosis develops in teenagers, the progression to portal hypertension is variable and may take years. In a retrospective study covering 26 years in 44 children with CF-associated cirrhosis, symptoms and signs from portal hypertension were surprisingly high. The mean age of diagnosis was 9 years of age, 86% had oesophageal varices, half of the patients bled during the second year of life at a mean age of 12 years, and liver failure occurred at a mean age of 15 years.⁷² However, this high frequency and early presentation of complications from portal hypertension have not been our experience. This may be a reflection of tertiary referral bias. As MI and DIOS have been reported to be risk factors for liver disease in CF, it remains to be seen whether improved management of both conditions will prolong further the timing of progression.

In our experience, the incidence of portal hypertension and variceal bleeding is low—under 5%. The rate of variceal bleeding depends on how extensively collateral vessels have developed over time. But in the case of oesophageal bleeding, our centre follows the management protocol proposed by Sokol and Durie⁶² for the treatment of any upper gastrointestinal haemorrhage: active resuscitation with appropriate blood products, correction of coagulopathy or thrombocytopenia, and infusion with intravenous octreotide and a proton-pump inhibitor. Upper gastrointestinal endoscopy is then performed to determine the source of bleeding, and band ligation or injection sclerotherapy is performed. Serial sessions of endoscopic treatment then follow over months until the oesophageal varices are eradicated. B-blockers have been used as long-term therapy in adults to decrease the risk of bleeding from portal hypertension.⁷³ These have not been used routinely in children due to the association with bronchospasm. Prophylactic variceal banding or sclerotherapy of patients with varices which are shown on Doppler ultrasound but which have never bled remains controversial. Prophylactic banding has been advocated by some clinicians because of the high incidence of bleeding in CF patients, and the possible increased risk secondary to chronic coughing from lung disease. Portosystemic shunting procedures (transjugular intrahepatic portosystemic shunts, portocaval or splenorenal shunts) remain possible options in some patients if medical management is ineffective.

Cholelithiasis

Cholelithiasis and biliary sludge are relatively common in paediatric and adult CF patients, with the incidence ranging from 1 to 10%. Most patients are asymptomatic,

with a tendency to report symptoms with increasing age.⁷⁴ CF patients have radiolucent gallstones that tend to be rich in calcium bilirubinate and proteins.⁷⁵ As a result, UDCA is not effective in dissolving these stones because cholesterol is not the main component.⁷⁶ Symptomatic patients should have a cholecystectomy (laparoscopic or surgical). It is recommended that an intraoperative cholangiogram and liver biopsy should be performed during cholecystectomy to assess the liver.

Biliary tract abnormality

Microgallbladder is a relatively benign condition with no apparent sequelae to patients. It is found on ultrasound in 20% of CF patients.⁶³ Bile duct stenosis, on the other hand, is a rare complication of CF. It is said to occur in less than 1% of CF patients, but Gaskin et al found that the majority of his CF cohorts with hepatomegaly or abnormal liver functions had abnormal stricturing of the common bile duct on hepatobiliary scan.⁶⁴ Bile duct dilatation is recommended for significant duct narrowing.

CYSTIC FIBROSIS-RELATED DIABETES

Cystic fibrosis-related diabetes (CFRD) is a distinct form of diabetes mellitus seen in pancreatic insufficient CF patients. CFRD is categorized differently to type 1 or 2 diabetes mellitus, although it shares features of both. It is an important complication of CF that needs to be screened for and managed appropriately as it is associated with nutritional failure, worsening lung disease, and early death.⁷⁷ The estimated prevalence of CFRD is 10–15%⁷⁸ and is increasing. The primary cause is insulin deficiency, but there is also a degree of insulin resistance.⁷⁹ The average age of onset is 18 to 21, but reports of CFRD in patients under the age of 10 have been published. It should be suspected in patients with polyuria, polydipsia, delayed puberty and growth failure, especially if there has been a decline in lung function. The pathology shows disruption of islet architecture and destruction of islets, along with amyloid deposits. At autopsy there has been found to be a discrepancy between the degree of beta cell destruction and the severity of CFRD, suggesting other factors play a role in pathogenesis.

Annual screening has been recommended by the Consensus Group, with oral glucose tolerance tests (OGTT) to look at fasting and 2-hour glucose concentrations. The diagnosis of CFRD is made by the finding of a fasting glucose level greater than 7 mmol/l. There is a spectrum of impaired glucose tolerance in CF patients before they reach CFRD. Our policy is to screen adult patients yearly. We have performed annual OGTT in over 250 adult CF patients for the last 7 years and have found that patients can fluctuate for many years between degrees of glucose impairment and normal glucose tolerance. However, once a patient reaches the fasting hyperglycaemia stage it does not appear to reverse and insulin treatment is required. Our cohort has a male predominance, opposite to the findings in the consensus report. Although we have routinely screened only adult patients, the study on our paediatric population suggests that screening for CFRD from the age of 10 is worthwhile and will improve the pick-up rate on patients at risk.⁸⁰ Once identified, the care of CFRD should be focused on maintaining good nutritional status, with a multi-disciplinary approach that includes an endocrinologist and dieticians with expertise in advising on a special modified CF and diabetic diet. The diet aims to give a high-energy diet with 35–40% of total intake as fat. There is no restriction on total carbohydrate intake, and patients are advised to follow the routine of three meals and three snacks a day.⁷⁸

The importance of compliance with blood glucose monitoring, appropriate insulin dosing and maintenance of regular exercise routine are emphasized and encouraged, as each contributes to improving survival. Non-compliance is an important issue, especially in adolescents and young adults, as they may sense CFRD as an indicator of end-stage disease. Education and support is paramount to avoid rapid deterioration. Oral calorie supplements are given if nutritional failure is evident. Enteral tube feeding may be necessary in some patients but this can also precipitate diabetes mellitus in some patients.⁸¹ Of the 5% of our children and adult CF patients requiring enteral tube feeding, 16% developed CFRD. Patients receiving enteral tube feeding require careful monitoring.

TRANSPLANTATION

Lung transplants have become the standard care in CF patients. Survival is comparable to transplantation for other lung disease. The number of liver and lung transplantations for CF patients continues to increase each year. There has not been any paediatric CF patient requiring liver transplantation in our institution. The median age of liver transplant was 13 in a British series. Liver transplantation was shown to be an effective therapy in adolescent and young adult patients with CF complicated by portal hypertension and hepatic dysfunction. It is recommended before a critical stage of deteriorating lung function is reached. Liver transplantation can improve survival in end-stage liver disease as well as provide some beneficial effect on deteriorating lung function as a result of immunosuppressant therapy.⁸² Equally, lung transplantation has provided a significant survival benefit for patients with CF.⁸³ Care should be taken to ensure close monitoring of drug levels of anti-rejection therapy such as cyclosporin A, as inadequate pancreatic enzyme treatment and erratic absorption of medication can significantly lower the therapeutic levels, predisposing the patient to rejection. Multiple episodes of graft rejection within 2 months of lung transplantation were found to be associated with a high frequency of post-transplant lymphoproliferative disease (PTLD) in the subgroup of CF patients post-lung transplantation.⁸⁴

MALIGNANCIES

With increasing anecdotal reports suggesting increased risk of various cancers in CF patients, Neglia et al together with the CF and Cancer Study group performed a large retrospective cohort study of over 28 000 North American and European patients to look for the risk of malignancies in patients with CF.⁸⁵ There was not an increased risk of non-digestive tract tumours or haemopoietic malignancies as compared to the general population. However, there was an increased risk of digestive tract cancers, including cancers of the oesophagus, stomach, small and large intestine, rectum, liver, biliary tract and pancreas. Those in the age group 20–29 years have the highest number of gastrointestinal cancers. One explanation lies in the localization and expression of CFTR within the epithelium of the various at-risk digestive tract organs and their varying sensitivities to injury with abnormal CFTR expression. Another theory is that the tumours may be secondary to the effect of the CF disease process on the different digestive tract organs. For example, excessive GOR causing Barrett's oesophagus has been reported in patients with CF.⁸⁶ Barrett's oesophagus is a pre-malignant condition associated with the development of oesophageal adenocarcinomas. Similarly,

hepatobiliary tract tumours such as cholangiocarcinomas have been reported to be associated with gallstones, which are frequently found in CF patients.⁸⁷ The loss of protective antioxidants such as vitamin E and selenium as a result of malabsorption have also been postulated to have an additive role in the development of malignancies in CF. In our centre, we have seen increasing cases of digestive tract tumours such as colonic adenocarcinomas and hepatic tumours. We are currently in the process of developing protocols for cancer screening in adult CF patients as the development of cancer has a major impact on the CF patient's eligibility for organ transplantation.

CYSTIC FIBROSIS IN ADULTS

Many of the gastrointestinal, hepatobiliary and nutritional issues affecting the paediatric CF patient continue to play similar roles as the patient become an adult. Besides the neonatal complications such as MI, the disease is truly a continuum, with progression of adult symptoms at different rates depending on the phenotype. The philosophy of our management of CF patients remains the same, with the focus on maintaining good nutrition along with pulmonary function. The additional GI/nutritional manifestations in adult CF patients are listed in [Table 7](#).

TRANSITION CARE

Co-ordinated transfer

The process of the transfer of care from a paediatric to an adult setting has attracted much debate in chronic diseases, regardless of the underlying cause. In CF, there is a distinct lack of a standardized process for achieving this transition. In a survey of

Table 7. Additional GI/nutritional manifestations in adult CF patients.

<i>Oesophagus</i> Oesophageal adenocarcinoma
<i>Gallbladder/biliary tract</i> Cholangiocarcinoma
<i>Hepatic</i> Malignancy
<i>Intestine</i> Increased risk for adenocarcinoma in GI tract
<i>General</i> Organ transplantation issues
<i>Nutrition</i> Osteoporosis, osteopenia
<i>Nutrition/pancreas</i> Eating disorders

a hundred paediatric and adult CF programme directors, many reported having concerns over the transfer process.⁸⁸ The discussion of transition to adult CF clinics is possible only because of the excellent care delivered at the paediatric centres. The process should always be a co-ordinated effort, with every attempt made to ensure that the process is as smooth and efficient as possible. Timing is dependent on the developmental readiness and health status of the CF patient, and the capabilities of the receiving adult unit.⁸⁹ There is probably no 'perfect' time for transition. Around the world, clinics use different chronological cut-off marks for financial, social or health policy reasons. The age of transfer ranges from 15 upward. Ultimately, a target transition time needs to be set. We have adopted the 18 years or school-leaving period as our target. A transition clinic is arranged in the patient's 17th year at the Hospital for Sick Children's CF clinic. During this visit, the Chest specialist and CF Nurse practitioner from our adult centre will jointly review the patient to plan a co-ordinated transfer. The planning involves addressing the medical and psychosocial needs of the patient. It also allows the opportunity to begin the new trust and bonding with the new adult health care providers.

Special considerations

Burkholderia cepacia colonization in the lungs has been associated with a more rapid decline in lung function, and a significantly increased mortality.^{90,91} The organism can survive for long periods in respiratory droplets on environmental surfaces found in CF clinics.⁹² There is also evidence for person-to-person spread of *B. cepacia*, and simple isolation measures are effective in interrupting its spread.⁹³ For these reasons, documentation of most recent sputum growth before transfer, and providing separate clinics for positive and negative *B. cepacia* status, can prevent cross-infection.

Multidisciplinary approach

Although most CF care is focused around the pulmonologist—because lung disease is the number one cause of death—the major issues throughout the life of a CF patient evolve around the gastrointestinal and nutrition systems. Therefore, it is only sensible that any CF centre, paediatric or adult, should have a multi-disciplinary approach. The centre should provide a team with CF experience, with members including a pulmonologist, gastroenterologist/nutritionist, dieticians, nurse practitioner, physiotherapist, social worker and clerical support. The centre should be affiliated with the CF Foundation in order to promote patient utilization of the services provided by the Foundation. Our centre also has a strong affiliation with the research community. We have a large database of all data from patients seen in the paediatric and adult clinics, thereby providing a wealth of information and an active framework from which practice-based research can be conducted. Much of the basic science and genetics research has also benefited from our database, contributing significantly to the CF community.

Fertility

Parenting and fertility issues are important for men and women with CF but many patients are unlikely to introduce these issues; health professionals should be aware of the need actively to initiate discussion. CF in men is accompanied by congenital bilateral absence of the vas deferens (CBVAD). The resultant infertility can be treated

successfully with a combination of sperm aspiration and intracytoplasmic sperm injection (ICSI).⁹⁴

Pregnancy

Some female CF patients become pregnant and safely carry a child to term. To have the best possible outcome, women with CF should be encouraged to reach a certain ideal body weight prior to their conceiving.⁹⁵ Special attention should be made to the added energy requirements of pregnancy, and any loss of intake from morning sickness or vomiting. The RDA guidelines for vitamins and minerals should be followed, with attention to screening for any special needs, and supplementation implemented early for any deficiencies that develop. There are limited data on the impact of lactation on the health status of women with CF. A small study of five women with mild lung disease showed no adverse outcome when they were supervised closely with dietician support.⁹⁶

Psychosocial issues

Adolescence is the time of developing independence, but it can also be a time of development of rebellious behaviour. Regardless of the underlying disease, this is often a period when teenagers exhibit non-adherence with medication and treatment. Patients may experiment with substance abuse, including cigarette smoking and alcohol usage. Understanding these processes and sound social support may reduce the risk of a potential downhill spiral in their health.

It is good practice to allow adolescent patients to develop independence, during a clinic visit, by allowing them to be seen on their own and then giving the parents the option of joining the discussion afterwards. A cross-sectional survey of adolescent and adult CF patients found that autonomy (independence and responsibility for looking after one self) was a high priority.⁹⁷

Prognosis

The transition process is an essential component of high-quality health care. It is a major life event for young patients with a chronic disease. Poor transition can lead to potential adverse outcome that will influence long-term prognosis. [Table 8](#) lists

Table 8. Factors associated with poor prognosis.

Poor nutritional status
Poor physical fitness
Pancreatic insufficiency
Respiratory tract colonization/infections
Smoke exposure
Non-CF centre care
Poor socio-economic status
Female (teenage and young adult age period)

Adapted from Orenstein D et al (2002, *Journal of Pediatrics* **140**: 156–164).

the factors that are associated with poor prognosis. Some of these can be the result of a poor transition causing drop-out from a CF programme.

SUMMARY

CF as a disease has changed tremendously in the last three decades in terms of the quality of care that can be offered to patients. This care has improved survival through better understanding of the disease. The ideal CF care centres should have a multi-disciplinary approach, with careful transition to an adult CF centre at a target time for transition. The disease spectrum from the time of birth to adulthood is essentially a continuum. Besides neonatal conditions, such as MI and its complications, the care of paediatric and adult CF patients does not differ much. The main focus should evolve around maintaining good nutrition and ensuring smooth transition from paediatric to adult centres in order to minimize stresses during this major life event.

Practice points

- the disease spectrum of CF in children and adults is similar and should be considered as a continuum, except for neonatal conditions such as MI
- the spectrum of GI/nutrition problems in CF is diverse, and should always be considered as a potential differential diagnosis
- two abnormal sweat tests and the presence of characteristic phenotypic features of CF confirm the diagnosis of CF
- nutritional care is the key integral part of managing CF patients
- energy imbalance is the principle behind malnutrition in CF

Research agenda

- the genotype/phenotype correlation for various manifestations in CF needs further research to look for potential modifiers (similar to that described in MI)
- further extensive screening for CF-related diabetes and ongoing monitoring of treatment necessary to delineate the disease process and management
- the role of liver transplantation for patients with CF needs to be evaluated through multi-centre collaboration

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APPENDIX A

Table A1

Table A1. Calculation of weight as percentage of ideal weight for height.

1. Plot the patient's height or length on the growth chart to determine the height centile (use the third if centile plots below the third)
2. Determine the ideal weight for the corresponding height centile
3. Calculate the actual weight as a percentage of ideal weight for height: (actual weight/ideal weight for height) \times 100

Adapted from Ramsey BVW et al (1992, *American Journal of Clinical Nutrition* **55**: 108–116).

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