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CURRENT TOPIC

# Nutritional management of the infant with cystic fibrosis

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Identification of the infant with cystic fibrosis by neonatal screening of blood immunoreactive trypsin has been undertaken in some regions for many years,[1] and molecular methods are increasingly being used for the genetic detection of affected children.[2] Several retrospective studies suggest that early detection of cystic fibrosis is beneficial in the long term[3 4]: improved nutritional status,[5] and decreased morbidity from respiratory infection follow treatment that begins soon after diagnosis.[6]

Detection of the cystic fibrosis gene[7] has not only made possible genetic screening of affected fetuses and carriers,[8] but may also offer a cure for this disease.[9] While exciting therapeutic prospects, such as manipulation of the abnormal gene product[10] and pharmacological interventions to correct defective chloride transport across epithelial cell membranes[11] are explored, there remains the challenge of caring for the infant with cystic fibrosis identified in the neonatal period. The major objectives of treatment are to prevent pulmonary infection and to ensure optimal growth and nutrition. Physiotherapy from diagnosis, a full course of immunisations, and prophylactic oral flucloxacillin[6] are all indicated.

In this review we discuss the nutritional management of the infant with cystic fibrosis identified soon after birth, in the light of our growing understanding of the pathophysiology of the disease in early life. There are three major reasons why nutrition of the infant with cystic fibrosis requires special attention (table 1).

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## Exocrine pancreatic insufficiency

The acinar to connective tissue ratio of the pancreas of the fetus with cystic fibrosis decreases progressively during the last trimester of pregnancy.[12] This is probably due to the primary defect of chloride impermeability of the exocrine pancreatic ductules[13]: acinar secretions become dry, proteinaceous, and viscous causing ductular obstruction. Inspissated secretions lead to ductular dilatation and formation of periductular fibrous connective tissue. Destruction of acinar tissue also begins well before birth, documented by a serial decline in blood immunoreactive trypsin values, and most children with cystic fibrosis have negligible levels by school age.[14] At birth the infant with cystic fibrosis has 50% less active secretory exocrine tissue than the healthy neonate. Although its functional reserve capacity is large, and clinically significant steatorrhoea and azotorrhoea do not occur until more than 90% of lipase and trypsin output is lost,[15] most infants with cystic fibrosis have measurable exocrine pancreatic deficiency.[16]

Deficiency of pancreatic lipase, colipase, phospholipase A2, bicarbonate, and bile salt secretion all contribute to fat malabsorption, and the infant with cystic fibrosis therefore relies largely on lingual lipase, an enzyme active at low pH. Preduodenal lipase activity in cystic fibrosis represents up to 90% of the total lipolytic activity in the acidic duodenal environment.[17] Pancreatic lipase, trypsin, and amylase are all inactivated below pH 5, and at this pH conjugated bile acids precipitate in aqueous solution and fatty acids are protonated prematurely, together further impairing micellar formation.

Immature hepatobiliary function, with diminished bile acid synthesis and a small bile acid pool tend toward 'physiological cholestasis' in the newborn.[18] Obstruction of the pancreaticobiliary system by inspissated secretions rarely occur in infancy,[19] but there may be increased intraluminal sequestration of bile acids in cystic fibrosis due to adsorption to dietary residues,[20] with a consequent further reduction in the size of the bile acid pool. A predominance of glycine rather than taurine conjugates (the former preferentially precipitated at acidic pH and significantly absorbed in the proximal small intestine),[21] exacerbates the deficient micellar solubilisation of fat. Moreover while both amino acids may be lost in the stool, only glycine can be endogenously synthesised.

*Table 1 Physiological disturbances leading to special nutritional requirements for infants with cystic fibrosis*

| | |
|---|---|
| Pancreas and liver | Pancreatic insufficiency from birth resulting in diminished enzyme secretion with maldigestion of fat, complex carbohydrate, and protein. Intraluminal sequestration of bile acids leading to reduction in bile salt pool and deficient solubilisation of fat |
| Small intestine | Defect in active and passive absorption related to abnormalities of absorptive cell membrane structure and function |
| Energy metabolism | Increased energy expenditure related to basic defect and respiratory infection |

## Small intestinal enteropathy

The small intestine may also be affected in cystic fibrosis, further contributing to poor

nutrition. Deficiencies of phospholipid and essential fatty acids may reduce the integrity of enterocyte cell membranes and impair the absorptive phase of fat assimilation.[22] Alteration of mucous glycoprotein structure and mucosal hydrolase and transport systems may affect the absorption of carbohydrates and amino acids. Decreased lactase activity, and altered passive permeability[23] may further contribute to deficient small intestinal function, accounting for nutrient losses as high as 50% of intake.[24]

Around 20% of infants with cystic fibrosis present with meconium ileus[25] and a few with atresias or perforation.[26] Although not all undergo gastrointestinal surgery, enteral nutrition may not be possible for prolonged periods and some infants require total parenteral nutrition, which in itself may diminish normal exocrine pancreatic secretory function and gastrointestinal function. Coeliac disease and gastro-oesophageal reflux are reported more commonly in cystic fibrosis,[27] and as well as pancreatic insufficiency, compromise of small intestinal function further contributes to malabsorption and poor nutrition in cystic fibrosis.

## Increased energy needs

Measurement of energy expenditure using indirect calorimetry and the doubly labelled water method suggests that infants with cystic fibrosis have an increased energy expenditure compared with normal infants of the same age, even in the absence of respiratory disease.[28 29] The cystic fibrosis transmembrane conductance regulator (CFTR), the putative gene product, contains multiple sites capable of protein kinase phosphorylation and ATP binding suggesting that ATP hydrolysis may be involved directly in the presumed transport function of CFTR and contribute to enhanced energy utilisation. The commonest cystic fibrosis gene mutation (δF508) results in the loss of a phenylalanine residue in the first nucleotide binding fold of the CFTR, and there is evidence that infants with two mutations within nucleotide binding folds have a greater energy defect than those who are heterozygous in this respect, or carry other mutations outside the nucleotide binding folds.[30] Such an intrinsic defect in energy metabolism, at a molecular level, has important implications for the nutritional management of infants with cystic fibrosis, and implies that they may require greater energy intakes to achieve normal growth.

Although many infants have signs of respiratory disease at diagnosis,[6 25] persistent pulmonary infection is uncommon in infancy. If the child is tachypnoeic or has other signs of respiratory distress he or she will be less able to achieve an adequate nutrient intake. This is in addition to the work involved in combating repeated microbial infections, mounting an inflammatory response, and replacing the protein and energy lost in sputum and faeces.[31 32]

## Nutritional management

A dietitian should work with the paediatrician to make a careful assessment of nutritional status at diagnosis. A clinical nurse specialist can also provide invaluable support and advice to the family at home during this time.[33] Although many infants are underweight at diagnosis, most achieve normal weight for age by 12 months.[6] Clinical evaluation comprises measurement of body weight, length, head circumference, mid upper arm circumference and skinfold thicknesses, all of which should be plotted on appropriate centile charts. Chest radiography should be performed and blood taken for full blood count and film, baseline liver function tests, and serum proteins. More specific laboratory nutritional assessment should include quantitative fat balance studies. In centres where this is not possible the stool fat output can be assessed using the 'steatocrit' method or by faecal fat microscopy,[34] and stool chymotrypsin can be measured as an index of exocrine pancreatic function.[35] Vitamin and mineral deficiencies can occur.[36] Serum concentrations of the fat soluble vitamins A, E, and D should be measured at diagnosis and thereafter annually. Trace elements are not routinely measured but this may be necessary in the severely malnourished child.

The choice of milk for the infant with cystic fibrosis depends on a number of factors, which include an understanding of pathophysiology of exocrine pancreatic insufficiency.

### HUMAN MILK

Breast feeding has been widely advocated for the baby with cystic fibrosis who is clinically well. It has several theoretical advantages: human milk has an optimal essential amino acid and fatty acid content, and the presence of taurine is particularly important because of its role in bile acid conjugation.[21] In addition human milk contains a range of protective factors, trophic factors, and digestive enzymes including amylase[37] and lipase that may compensate for diminished pancreatic secretion.[38] Fat and carbohydrate absorption are more efficient from human milk than from artificial formulas.[39]

Human milk, however, has a lower protein content than infant formulas and exclusive breast feeding has been associated with failure to thrive, and in a few cases with hypoproteinaemia, oedema, anaemia, and electrolyte depletion.[40] In spite of these potential but rare problems breast feeding should be encouraged as long as adequate intake is ensured.

### INFANT FORMULA

Infants with cystic fibrosis who are not breast fed can thrive satisfactorily on normal infant formula[41] with adequate pancreatic enzyme replacement therapy (see below). If infants fail to gain weight satisfactorily on infant formulas alone, glucose polymers such as Maxijul (Scientific Hospital Supplies, SHS) Polycal (Cow and Gate), or Caloreen (Clintec) can be added to the feed. Glucose polymers have a low osmolality and are added in 1 g/100 ml increments to provide a total of 12 g carbohydrate/100 ml of feed. If further energy

*Table 2 Recommendations for nutritional management for infants with cystic fibrosis, in conjunction with pancreatic enzyme supplements*

| | | |
|---|---|---|
| Energy | 120–150% of DRV | Feeds can be supplemented with glucose polymers |
| Protein | 100% DRV | |
| Fat | 45% of total energy requirements | Feeds can be supplemented with fat emulsions |
| Vitamin A | 4000–8000 IU | Given orally as a water miscible preparation (Abidec (Warner Lambert) 0·6 ml/day) |
| Vitamin D | 400–800 IU | |
| Vitamin E | 50–100 mg | |
| Vitamin K | Not routinely given | |
| Water soluble vitamins | Not routinely given | |
| Minerals | Not routinely given | |

DRV=dietary reference values.

supplementation is required, long chain lipid emulsions, such as Calogen (SHS), can be added to provide a total of 5 g fat/100 ml feed. Duocal (SHS), a combined fat and carbohydrate supplement, may be used as an alternative energy supplement which can be added to infant formula. Many infants with cystic fibrosis consume large volumes of infant formula (150–200 ml/kg or more),[41] despite apparently adequate enzyme replacement.

Infants who require surgery for meconium ileus may develop a temporary disaccharide intolerance and protein hydrolysate milks such as Pregestimil (Bristol Myers), Nutramigen (Bristol Myers), Peptijunior (Cow and Gate), and Prejomin (Milupa) can be used.[42] Pancreatic enzymes are still required with protein hydrolysate formulas, even though they contain a higher proportion of their fat as medium chain triglycerides.

Occasionally, a modular feed, such as comminuted chicken (Cow and Gate), with additional carbohydrate, fat, vitamins and minerals, may be necessary for infants who have undergone major surgery and fail to tolerate hydrolysed protein formulas.

## PANCREATIC ENZYME SUPPLEMENTS

Neither pancreatin powders nor enteric coated microsphere enzyme preparations are designed for administration with human milk. Pancreatin powders should be mixed with a little expressed breast milk and given at the beginning of each feed. Enzyme on the infant's lips may not only cause skin irritation, but also irritation of mother's nipple. Enteric coated preparations can be mixed either with expressed breast milk or formula, or with fruit puree and given from a spoon. They should never be added to feeds. The advantage of the enteric coated microspheres is that their enzyme contents are protected from hydrolysis in the stomach.[43]

## VITAMIN SUPPLEMENTS

Fat soluble vitamins A, D, and E should be given routinely from the time of diagnosis, as depletion of these micronutrients is detectable within a few months of birth.[44] Clinical signs of vitamin A deficiency include hyperkeratosis, failure to thrive, anaemia, and hepatosplenomegaly. Depressed serum concentrations may also be due to deficiency of retinol binding protein itself. Bone demineralisation can occur in children with cystic fibrosis but rickets is rarely seen, probably because dermal synthesis of vitamin D accounts for more than 80% of normal requirements.[45] Vitamin E is a powerful antioxidant and haemolytic anaemia has been reported in newly diagnosed infants.[46] Prolonged deficiency is associated with a peripheral neuropathy, although in cystic fibrosis this is usually associated with advanced hepatic disease. Clinically obvious vitamin K deficiency, presenting as haemorrhagic disease, is unusual in infants with cystic fibrosis and supplementation is not routinely undertaken unless there is evidence of liver disease.[19]

Fat soluble vitamins should be provided from time of diagnosis at concentrations of at least twice dietary reference values: vitamin A 4000–8000 IU, vitamin D 400–800 IU, and vitamin E 50–100 mg/day.[47] Because there is no single vitamin preparation to provide all three vitamins in satisfactory quantities, multivitamin preparations with additional vitamin E are usually prescribed (table 2).

Infants most at risk from fat soluble vitamin deficiency are those with poorly controlled malabsorption, poor dietary compliance, liver disease, bowel resection, or after late diagnosis. The water soluble vitamins (B group and C) are not usually deficient but may be given as part of a multivitamin supplement.

## MINERALS AND TRACE ELEMENTS

Iron absorption is usually normal in infancy, and iron supplements are not routinely prescribed in the first year. Low serum concentrations of trace elements, including selenium and zinc, have been reported,[34] but supplementation is not recommended routinely in early life.

## ESSENTIAL FATTY ACIDS

Essential fatty acids are required for neurodevelopment and membrane synthesis and function and may be malabsorbed in the infant with steatorrhoea, and contribute to the enteropathy of cystic fibrosis (see earlier). Signs of essential fatty acid deficiency (desquamation, poor wound healing, thrombocytopenia) are rarely seen, and supplementation beyond that recommended for inclusion in modern standard formulas is probably unnecessary in infancy.

## ENERGY REQUIREMENTS

The finding of a raised resting and total energy expenditure in infants with cystic fibrosis, and excessive faecal losses, suggest that total energy requirements should be 120–150% of the dietary reference values. Despite improved pancreatic enzyme replacement therapy, faecal energy losses can be as high as 10–20% of energy intake. Most infants who ingest normal volumes of milk for their age will receive adequate protein for growth. Infants who do not thrive on human milk or infant formula will require energy supplemented feeds as discussed earlier.

## Other clinical problems and weaning

It is unusual for the infant with cystic fibrosis to require nasogastric or intravenous feeding. However, infants with cystic fibrosis who have undergone gastrointestinal surgery may initially need total parenteral nutrition using standard solutions, and those with extensive ileal resection may require parenteral vitamin $B_{12}$ replacement. Infants who have persistent diarrhoea or fail to gain weight despite seemingly adequate diet and pancreatic enzyme supplementation should undergo jejunal biopsy to exclude coeliac disease. This may occasionally also reveal partial or complete deficiency of lactase activity. Gastro-oesophageal reflux occurs more frequently in cystic fibrosis.[27] Treatment includes thickening of feeds, Gaviscon (Reckitt and Colman), and sometimes cisapride.

The infant with cystic fibrosis is often dissatisfied with breast milk or infant formula alone and solids should be introduced at 3 months of age to ensure an optimal intake of energy and protein. Parents are encouraged to give a normal to high fat intake to ensure adequate growth.

## Conclusions

Identification of the infant with cystic fibrosis in early life offers the opportunity to optimise nutrition from diagnosis. Although our understanding of the basic defect in cystic fibrosis, and the way in which it affects the clinical expression and natural history of the disease, is still incomplete, enough is known about the ontogeny of the pancreatic defect, and of the factors contributing to enhanced nutritional requirements, to treat early infancy as a critical period in the life of the infant newly diagnosed with cystic fibrosis. Optimising the nutritional status,[48] and anticipating his or her nutritional needs during childhood, has been shown to reduce morbidity and improve outcome of this chronic disease.[49] There is no doubt that improvement of nutrition in early life, along with other interventions, should play a central part in the management of the infant newly diagnosed with cystic fibrosis.[50]

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