Cystic Fibrosis – Other CF Related Disease

<table>
<thead>
<tr>
<th>Title of Guideline</th>
<th>Cystic Fibrosis Management Guidelines – Section 8 – Management of Other CF Related Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact Name and Job Title (author)</td>
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<td>Directorate &amp; Speciality</td>
<td>Directorate: Family Health – Children Speciality: Respiratory</td>
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</tbody>
</table>
1a meta analysis of randomised controlled trials | X |
2a at least one well-designed controlled study without randomisation | |
2b at least one other type of well-designed quasi-experimental study | |
3 well –designed non-experimental descriptive studies (ie comparative / correlation and case studies) | |
4 expert committee reports or opinions and / or clinical experiences of respected authorities | |
5 recommended best practise based on the clinical experience of the guideline developer | |
Consultation Process | Staff at Nottingham Children’s Hospital via the Guidelines E-mail process. |
Target audience | Staff at the Nottingham Children’s Hospital |

This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date.
Summary of changes for October 2018 update:

- CF-related diabetes section updated: use of glucojuice

Statement of Compliance with Child Health Guidelines SOP

This guideline refers to activities of only one specific team and consultation has taken place with relevant members of that team. Therefore this version has not been circulated for wider review.

Maria Moran, Clinical Guideline Lead
4th October 2018
Section 8 - Management of Other CF Related Disease

8.1 Abdominal pain
   (Jayesh Bhatt & Andrew Prayle)

8.2 Cystic Fibrosis Related Liver Disease
   (Jayesh Bhatt & Geoff Burnhill)

8.3 Management of Bleeding Oesophageal Varices
   (Jayesh Bhatt & Andrew Prayle)

8.4 Low Bone Mineral Density
   (Jayesh Bhatt & Aarti Mistry)

8.5 CF Joint Pain and Disease
   (Jayesh Bhatt & Andrew Prayle)

8.6 Cystic Fibrosis Related Diabetes
   (Jayesh Bhatt, Renu Khetan, Pooja Sachdev, Salma Ali & Jennifer Calvert)
Section 8 - Management of Other CF Related Disease

8.1 Abdominal Pain - Distal intestinal obstruction syndrome (DIOS)
8.2 Cystic fibrosis related liver disease
8.3 Management of bleeding oesophageal varices
8.4 CF Bone disease
8.4.1 Assessment of bone health
8.4.2 Treatment recommendations
8.5 Joint pain and disease
8.6 Cystic fibrosis related diabetes (CFRD)
8.6.1 Diagnosis of CFRD
8.6.2 Insulin
8.6.3 Oral hypoglycaemic agents
8.6.4 Complications will be screened for at annual review
8.6.5 Dietary management of Diabetes in Cystic Fibrosis
8.6.6 Dietary management if patient is generally well and in good nutritional status
8.6.7 Dietary management if patient is unwell and in poor clinical status
8.6.8 Dietary treatment of a ‘hypo’
8.6.9 Summary
8.1 Abdominal Pain

Recurrent abdominal symptoms are common despite adequate enzyme doses. The commonest symptom is abdominal pain and patients may not have infrequent stools despite constipation. The pain is often relieved by passing stools and responds to lactulose.

Distal intestinal obstruction syndrome (DIOS) - (previously called Meconium Ileus Equivalent)[2]

Intestinal obstruction may occur in CF patients, outside the neonatal period, due to the accumulation of viscid mucofeculent material in the terminal ileum and caecum. Patients with a history of meconium ileus, previous laparotomy and post lung transplant are at high risk of developing DIOS.[3] The pathophysiology is poorly understood. It may be related to inadequate dosage of pancreatic enzymes, poor compliance and episodes of dehydration, though why some patients suffer recurrent episodes is not always clear. It can also occur in those who are taking regular enzyme supplements and diabetes mellitus may be a contributory factor in some.[4] Clinical features are of abdominal pain, constipation, and poor appetite, with a palpable right iliac fossa mass. In children who have simple constipation, faecal loading is often felt in the left iliac fossa. In a recent adult case series, almost 50% of cases presented with generalised abdominal pain.[5] Vomiting is a late feature and it is important to intervene before vomiting occurs. A plain abdominal X-ray shows absence of the normal gas pattern, faecal loading with a granular or bubbly appearance in the right lower quadrant.

Management

- Patients who present early with a short history of abdominal pain and constipation can be managed with lactulose or movicol.
- When symptoms have been prolonged, or when abdominal examination reveals distension and a right iliac fossa mass, then admission is required and oral gastrograffin should be given. N-acetylcysteine can be also used as an alternative to gastrograffin. Oral granules or dilute injection solution (200mg/ml); orange or blackcurrant juice may be used to mask the bitter taste. Biochemistry should be checked. Adequate hydration and pain relief should be ensured. Nasogastric tube will need to be placed to ensure fluid and gastrograffin intake.
- When an appropriate dose of gastrograffin has been given, without the patient passing stool or when gastrograffin is not tolerated because of vomiting, then a prompt surgical review is indicated.
- Consider other diagnoses: Intussusception, appendicitis, fibrosing colonopathy. biliary tract or gallbladder disease, acute pancreatitis, urinary tract infection.
- Following an episode of DIOS, review to the CF specialist dietician is appropriate. The dietician will review and advise on: appropriate use of Pancreatic Enzyme Replacement Therapy, adequate fluid intake, fibre intake and regular meal pattern.
- Proton Pump inhibitors should be considered to improve the efficacy of enteric-coated enzyme preparations. In order to achieve a high intraduodenal enzyme concentration, the dissolution of these preparations in the duodenum can be optimized by increasing intraduodenal pH by adding a PPI.[4]
8.2 Cystic fibrosis related liver disease

The CFTR (cystic fibrosis transmembrane regulator) is additionally expressed in the epithelial cells lining the intra and extra-hepatic bile ducts and gall bladder (though not in the hepatocytes or other cells of liver) and plays a significant role in ductal secretion. Absent or dysfunctional CFTR activity leads to dehydrated viscous secretions that may lead to obstruction of the bile ducts resulting in fibrosis and ultimately biliary cirrhosis; this process is usually asymptomatic. As patients with CF begin to have longer life expectancy, so the issue of CF-related liver disease becomes an increasing concern.

As in other liver diseases characterised by initial involvement of bile ducts and later impairment of hepatocyte function, the haemodynamic consequences of cirrhosis, mainly portal hypertension, are often prominent, whereas liver failure tends to be a late event. In infancy, presentation may be with bile duct obstruction (neonatal cholestasis) due to inspissated bile or with fatty change that may cause abdominal distension. Gallstones and cholecystitis can occur in later childhood. Recent best practice guidance for the diagnosis and management of cystic fibrosis–associated liver disease mentions a cumulative incidence of liver disease ranging between 27 and 35%, without incident cases after the age of 18 years. 5-10% of all CF patients will develop multilobular cirrhosis during the first decade of life and liver cirrhosis accounts for 2.5% of overall CF mortality. No specific CFTR mutations have been associated with the presence and severity of CFLD and environmental and modifier genes might play a role.

**Identification**

- Neonates who present with meconium ileus are more likely to develop CFLD (40% prevalence at 9yrs) as well as neonatal cholestasis and may benefit from closer monitoring of liver dysfunction and early commencement of ursodeoxycholic acid (see below).[6]
- Annual screening for CLFD is necessary to detect pre-symptomatic signs of liver disease and to initiate treatment with ursodeoxycholic acid. The presence of CFLD should be considered if at least two of the following are present[7]
  - **Clinical**: Hepatomegaly i.e. palpable liver edge >2cm below costal margin in mid-clavicular line or a palpable left lobe in epigastrium
  - **Biochemical**: Elevated transaminases (ALT, AST) and GGT above the upper normal limits on 3 consecutive tests over 12 months (excluding other causes of liver disease)
  - **Radiological**: Abnormal liver ultrasound[8]
    - Increased/heterogeneous echogenicity, irregular margins, nodularity
    - Portal hypertension
    - Biliary tract anomalies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age</th>
<th>Dosage</th>
<th>Doses/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose</td>
<td>&lt;7 years</td>
<td>10 ml</td>
<td>bd</td>
</tr>
<tr>
<td></td>
<td>&gt;7 years</td>
<td>20 ml</td>
<td>bd</td>
</tr>
<tr>
<td>Movicol Paediatric plain</td>
<td>&lt;6 years</td>
<td>1 sachet (max 4 sachets)</td>
<td>daily</td>
</tr>
<tr>
<td></td>
<td>&gt;6 years</td>
<td>2 sachets (max 4 sachets)</td>
<td>daily</td>
</tr>
<tr>
<td>Gastrografin</td>
<td>&lt;10 kg</td>
<td>25 ml in 100 ml water/ juice</td>
<td>single dose</td>
</tr>
<tr>
<td></td>
<td>&lt;25 kg</td>
<td>50 ml in 200 ml water/ juice</td>
<td>single dose</td>
</tr>
<tr>
<td></td>
<td>&gt;25 kg</td>
<td>100 ml in 400 ml water/ juice</td>
<td>single dose</td>
</tr>
<tr>
<td>N Acetylcysteine</td>
<td>&lt;7 years</td>
<td>2-3 g</td>
<td>single dose</td>
</tr>
<tr>
<td></td>
<td>&gt;7 years</td>
<td>4-6 g</td>
<td>single dose</td>
</tr>
</tbody>
</table>

Dr Jayesh Bhatt  Dec 2016 (minor update Oct 2018)
Management
Ursodeoxycholic acid and vitamin K are the mainstay of medical treatment in CFLD patients. Both medicines, when started, should be continued indefinitely. Nutritional support may also help to optimise care.

Ursodeoxycholic acid

The water-soluble bile acid ursodeoxycholic acid (UDCA) is widely used in the treatment in CF liver disease. This has been shown to improve liver function tests, biliary drainage, early ultrasonographic changes in the liver and even liver histology.[9]

Ursodeoxycholic Acid should be started if liver damage has been demonstrated by the above criteria. Additionally, evidence suggests that, in children who present with meconium ileus, there is significant benefit from early commencement (before 2yrs of age) of USDA.[10] Patients in this increased risk group had a significantly lower (0% vs 40%) of developing liver disease in the first decade compared to those treated with USDA later on.

Dosage:

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>10-15mg/kg twice daily</td>
</tr>
</tbody>
</table>

Available as 150mg/5mL or 250mg/5mL suspension

Vitamin K

Vitamin K should be commenced if the prothrombin time is prolonged on two subsequent occasions

Dosage:

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12 years</td>
<td>5-10mg once daily</td>
</tr>
<tr>
<td>12-18 years</td>
<td>10-20mg once daily</td>
</tr>
</tbody>
</table>

Available as 10mg tablets of 10mg/5mL suspension

Nutritional Support

Malnutrition is a common problem in Cystic Fibrosis and can be further exacerbated by CFLD. Nutritional supplementation should be provided with advice from dieticians but the following points are recommended:[7]

- Increase energy intake to 150%
- Increase proportion of fat to 40-50% (carbohydrate should be avoided due to increased risk of CFRD)
- Provide protein supplements to 3g/kg/day
- Avoid salt supplementation in cirrhosis
- Prescribe fat soluble vitamins (A, E, D, K)

Referral to supra regional liver Unit

A referral should be made to the Supraregional Liver Unit at Birmingham Children's Hospital (Dr Indra Van Mourik) if any of the below criteria are present:
• Progressive hepatic synthetic dysfunction (albumin <30g/L, worsening coagulopathy)
or progression on liver ultrasound (bi-annual)
• Development of ascites and jaundice
• Intractable variceal bleeding
• Hepatopulmonary/Portopulmonary syndromes
• Severe malnutrition
• Deteriorating quality of life related to liver disease
• Uncertainty of diagnosis of CF liver disease

8.3 The management of bleeding oesophageal varices

Oesophageal varices may remain undetected until they bleed or patients with known varices may bleed unexpectedly.
Resuscitation of the patient with bleeding varices follows the usual rules of ABC.

1. If the bleed take place at Queens Medical Centre, activate the Nottingham University Hospitals major haemorrhage protocol (call 2222 and state major haemorrhage and give the ward location). The line used for activating the protocol needs to be kept free. Haematology / blood bank will call back on this line and will request patients details, weight, the name of the activating clinician (i.e. doctor activating the major haemorrhage protocol) and the name of a ‘Medical Coordinator’ who will thereafter be the sole clinician to liaise with blood bank (to prevent unnecessary duplication).
2. Patients will need high flow face mask oxygen.
3. Intravenous access should be achieved immediately (2 sites). Call for help from the anaesthetic team if necessary.
4. Take blood for group and cross match, clotting and platelets.
5. Administer colloid - 4.5% Human albumin solution 20 ml/kg until blood is available. If necessary give group specific uncross-matched blood initially. Correct shock but take care not to over-transfuse as this may precipitate re-bleeding.
6. Transfer the patient to Paediatric HDU/PICU.
7. Commence octreotide infusion (see below).
8. Correct thrombocytopenia (often secondary to splenomegaly from portal hypertension) and prolonged clotting (fresh frozen plasma 10 ml/kg and vitamin K 10 mg IV)
Octreotide
(dosage as per Nottingham PICU Pharmacopoeia; monograph version 1)

Children over 1 month: Initial IV loading bolus of 1 microgram/kg, followed by continuous infusion of 1 microgram/kg/hr.

If needed, increase up to a maximum of 3 micrograms/kg/hour (although anecdotally doses up to 5 micrograms/kg/hour have been used).

When no active bleeding has occurred for 24 hours, wean slowly to avoid rebound bleeding (i.e. halve rate every 6 hours and discontinue when dose is 25% of maximum dose used).

Administration instructions
Use only the 500 mcg/mL Hosperia brand. Draw up as per the table below

<table>
<thead>
<tr>
<th>Amount of drug to add to 50 mL Syringe</th>
<th>Dilute to 50 mL with 0.9% saline. Incompatible with dextrose containing solutions</th>
<th>1 mL/hr = 1 mcg/kg/h</th>
<th>Dose range: 1 – 3 mcg/kg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 micrograms x weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Octreotide is a somatostatin analogue[11] which stops bleeding from oesophageal varices by reducing pressure in the portal vein. When there is no active bleeding reduce dose over 24 hours. Patients with bleeding oesophageal varices should be discussed with the pediatric gastroenterology team to assess whether urgent endoscopy and injection of varices is indicated. All children should be discussed with the Liver Unit in Birmingham and, if necessary, transferred for assessment.

8.4 CF Bone Disease [1, 12]

People with CF may develop low bone mineral density (BMD) from either osteoporosis or vitamin D deficiency osteomalacia. Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. Osteomalacia is a disorder where there is an increase in the proportion of non-mineralised bone. Low bone mineral density (BMD) was first reported in CF patients in 1979.[13] It is now emerged as a common complication in the long term survivors of CF. The pathophysiology of low BMD in people with CF is related to the accelerated bone resorption and decreased bone formation. Low BMD in CF patients can lead to pathological fractures and kyphosis in adolescence, and exclusion from lung transplant.[14] In addition to causing pain and debilitation, rib and vertebral fractures produce chest wall deformities that reduce lung function, inhibit effective cough, and hinder airway clearance. Therefore, optimizing bone health is just as crucial as treating the lungs itself.
Recent research has focused on the impact of Vitamin D on Bone Mineral density and how best to optimize levels. Vitamin D has an important role increasing the absorption of intestinal calcium, stimulating osteoblastic activity and enhancing the production of osteoclasts.[15, 16]

Therefore, suboptimal levels in CF can reduced peak bone mass, but also impair glucose regulation and immune function. Recent Scandinavian studies demonstrate a positive correlation to the development of CF related diabetes, and the severity of CF lung disease due to the relative reduction in immune function with associated Vitamin D deficiency. These factors all impact on bone mineral density in CF, alongside many other interplaying factors. Therefore good all round CF care is essential in addressing all possible aetiological factors that can contribute to low BMD.[1]

8.4.1 Assessment of Bone Health

1. **Nutritional status**: Good nutrition is vital and should be optimised through frequent liaison with a specialist CF dietitian.

2. **Calcium** intake should be at current recommended level for age:

<table>
<thead>
<tr>
<th>Age</th>
<th>Calcium (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 6 months</td>
<td>210</td>
</tr>
<tr>
<td>7 - 12 months</td>
<td>270</td>
</tr>
<tr>
<td>1 - 3 years</td>
<td>500</td>
</tr>
<tr>
<td>4 - 8 years</td>
<td>800</td>
</tr>
<tr>
<td>9 - 18 years</td>
<td>1300</td>
</tr>
<tr>
<td>Adults</td>
<td>1300 – 1500</td>
</tr>
</tbody>
</table>

3. **Vitamin D** status should be assessed from diagnosis by measuring the serum level of 25-hydroxyvitamin D taken at annual assessment. Vitamin D supplementation should be individualised with the aim of achieving serum 25 hydroxyvitamin D (25OHD) levels between 30 and 60 ng/ml (75–150 nmol/L). Please refer to the Vitamin D treatment section for further guidance.

4. **Hormonal Status**- annual clinical assessment of pubertal staging using Tanner staging should ideally be conducted starting at 9 years in females and 10 years in males. Pubertal delay is defined in girls as no breast development by the age of 13 years or no menarche by 16 years. Pubertal delay in boys is defined as no testicular enlargement by the age of 14 years. Patients with delayed puberty should be referred to a paediatric endocrinologist and considered at increased risk of bone disease.

5. **Glucocorticoid exposure** the cumulative dose of glucocorticoids should be assessed annually. More frequent assessment of bone health is recommended in patients taking significant doses of prednisolone (>5mg /day >90 days /year)
6. **Bone density measurement**: DEXA scan (lumbar spine and proximal femur) may underestimate BMD in children with CF who have suboptimal growth and short, narrow bones.

- A DEXA scan should be performed from about 10 years of age and repeated every two years, determined by clinical need, to ensure that bone accrual is occurring at a satisfactory rate.
- The results for any individual should be compared to Z-scores (mean value for age and sex obtained from DEXA studies of the general population). T-scores (mean bone mineral density of the young adult normal reference population must not be used in children.
- “CF related low BMD” can be applied to children or adults with CF with a BMD Z-score below –2, (<2SDs below the age and gender matched mean reference value). **Z-scores may be unreliable in individuals of small body size.**

CXR at annual assessment should be examined for presence of vertebral fractures. If a fracture is present DEXA scan should be performed.

8.4.2 **Treatment recommendations**

This mainly consists of optimisation of clinically modifiable factors that are likely to affect bone health. Identifying those at more of risk through surveillance and reinforcing preventing measures.

1. Optimize nutrition

2. Exercise: encourage regular weight bearing exercise, as this will increase bone mineral content. Sunlight exposure should be encouraged and just a few minutes a day would suffice.

4. Calcium see above table: an increased calcium intake may improve BMD\textsuperscript{14}

5. There is not yet sufficient evidence to recommend universal vitamin K supplementation for bone health in CF, but consideration should be given to individuals with low BMD, liver disease and/or a prolonged prothrombin time.

6. Minimise the use of glucocorticoid therapy.

7. Optimisation of Vitamin D.[17, 18]
### Recommendations for Vitamin D Supplementation:

<table>
<thead>
<tr>
<th>Age</th>
<th>Starting Maintenance Therapy</th>
<th>Vitamin D Level (75-150nmol/l)</th>
<th>50-75nmol/l</th>
<th>30-50nmol/l</th>
<th>&lt; 30nmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3yrs</td>
<td>Abidec 0.6ml</td>
<td>continue</td>
<td></td>
<td></td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abidec 1.6ml</td>
</tr>
<tr>
<td>3-5yrs</td>
<td>Cholecalciferol 1000 units OD</td>
<td>continue</td>
<td></td>
<td>Increase to 3000 units OD or 20,000 once weekly</td>
<td>Acute regime</td>
</tr>
<tr>
<td>5-12yrs</td>
<td>Cholecalciferol 3000 units OD</td>
<td>Continue</td>
<td></td>
<td>Increase 6000 units OD or 20,000 twice weekly</td>
<td>Acute regime</td>
</tr>
<tr>
<td>&gt;12 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vitamin D levels do not need to be checked following an acute course. Restart previous maintenance therapy, if appropriate consider increasing their previous maintenance therapy. (Max 50,000 units once weekly)

*Patients who have; moderate to severe CF lung disease, pancreatic insufficient, CF liver disease, on long term steroids are high risk for CF bone disease. Have low threshold to increasing their maintenance and starting an Acute regime.

- Avoid the use of Multivitamins they don't provide appropriate daily dose of Vitamin D.
- Avoid use of AdCalD3, ONLY consider use in patients with low Calcium levels.

### Vitamin D Preparations and Dosages:

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Vitamin D IU</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivitamin</td>
<td>300</td>
<td>£1.50</td>
</tr>
<tr>
<td>Abidec 0.6ml</td>
<td>400</td>
<td>£2.20</td>
</tr>
<tr>
<td>Dalvit</td>
<td>400</td>
<td>£4.85</td>
</tr>
<tr>
<td>Vitamin A and D</td>
<td>400</td>
<td>£3.44</td>
</tr>
<tr>
<td>Adcal D3</td>
<td>500 nanograms</td>
<td>£3.89</td>
</tr>
<tr>
<td>Calchichew</td>
<td>500 nanograms</td>
<td>£7.21</td>
</tr>
<tr>
<td>Cholecalciferol</td>
<td>Variable preparations 3000, 20,000</td>
<td>£3.60</td>
</tr>
</tbody>
</table>

**Table to left:** Vitamin D preparations available.

**Table above:** Recommended age-related daily dose of Vitamin D. [1]
8. Antiresorptive agents

These agents can treat established osteoporosis mostly by decreasing bone resorption with some possible effects on bone formation. A recent trial of Alendronate has demonstrated its efficacy and safety in a small group of adult CF patients with low BMD.[19] Bisphosphonates are not licensed for use in children and although they appear to be relatively safe even when used for long periods in other paediatric bone disease, experience is limited. There are no published data reporting the outcome of bisphosphonate use in children with CF. However, bisphosphonates may be beneficial in children:

- with a history of fragility fracture
- and those listed for/post transplantation.
- Some authorities suggest bisphosphonates for children who have low BMD and continuing bone loss despite implementing general measures for optimising bone health.

Some children starting on bisphosphonates may develop severe bone pain and will require short course steroid therapy. Discuss with Consultant. Patients treated with bisphosphonates should be monitored with repeat DXA at 6-12 monthly intervals.

### Alendronic acid (Alendronate)

<table>
<thead>
<tr>
<th>ORAL</th>
<th>Adult dose 10 mg od. Once weekly dose of 70 mg may improve compliance.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets available</td>
<td>Adult dose 10 mg od. Once weekly dose of 70 mg may improve compliance.</td>
</tr>
<tr>
<td>5mg, 10mg and 70mg</td>
<td>Tablet should be taken in the morning</td>
</tr>
<tr>
<td>Administration</td>
<td>30 minutes before any food or drink and the patient needs to stay upright for 30 minutes after taking the tablet to ensure rapid passage down the oesophagus and stomach.</td>
</tr>
<tr>
<td>Contra-indications and warnings</td>
<td>Hypocalcaemia, abnormality of oesophagus or any factor which delays oesophageal emptying. Caution with upper GI disease as may cause irritation</td>
</tr>
</tbody>
</table>

Sex steroid replacement therapy should be considered in consultation with Paediatric endocrinologist in individual cases.

8.5 Joint Pain and Disease:

Arthropathy may be associated with cystic fibrosis in three ways.[20]

1. Cystic fibrosis arthropathy (CFA), a complication characteristic of CF. It affects large joints and is episodic. It can be quite disabling with sudden onset. There can be associated high swinging fevers and skin rashes. Most patients show a good response to NSAIDS. It follows a remitting and relapsing course and X-rays show no abnormality. There is no permanent damage in most cases.

2. Hypertrophic Pulmonary osteoarthropathy: It is insidious in onset and may begin as a continuous ache. The clinical picture may vary from a minimally swollen joint to tender, warm swollen joints/ symptoms are worse in cold weather. X-rays may show a periosteal reaction and some new bone formation. These changes can slowly progress and can result in permanent bone destruction. Symptomatic relief is with NSAIDS. HPOA may resolve if the underlying chest disease is intensively treated. Both these forms of arthritis can be worse with infective exacerbations.

3. Coincidental joint problems such as juvenile idiopathic arthritis.
8.6 Cystic fibrosis related diabetes (CFRD)[21]

CFRD occurs when progressive fibrosis and fatty infiltration of the exocrine pancreas leads to progressive disruption and destruction of endocrine cells. It is more common and develops at an earlier age in individuals who are pancreatic insufficient. Now as patients with CF are living longer, this is emerging as a major complication. CFRD is a distinct type of diabetes with features of both Type 1 and Type 2 diabetes. It differs from Type 1 in that onset is usually insidious; many individuals are asymptomatic at diagnosis and reliance upon clinical symptoms will result in failure to recognize CFRD in the majority of patients. In others the first sign may be a decline in pulmonary function, poor growth velocity, or delayed puberty. It differs from Type 2 diabetes in that weight loss despite nutritional intervention is often an early feature. Delaying the diagnosis can result in an unnecessary deterioration in both pulmonary function and clinical status.

Prevalence rates for CFRD are reported as 3% in 5-9 years, 11% between 10-19 years, with 50% aged more than 30 years being affected. Prevalence of impaired glucose tolerance is 20% of patients at 10 years, 50% at 15 years, 75% at 20 years, 82% at 30 years.[22] There is a clear association between diabetes and increased morbidity and mortality, with survival being significantly lower in patients with diabetes. Female patients with CFRD but without chronic Pseudomonas tend to have lower FEV₁ when compared to sex matched subjects with NGT[23] and a remarkably poorer prognosis as compared to all male subjects with CF and female subjects with CF but without diabetes.[24]

Prediabetic state may also be deleterious because a greater decline in pulmonary function and nutritional state was found as early as 6 years before the diagnosis of diabetes.[25]

Early diagnosis and aggressive treatment have played a major role in improving survival in patients with CRFD and previously noted gender differences in mortality have disappeared, and the gap in mortality between CF patients with and without diabetes has narrowed considerably.[26-31]

CFRD can occur at any age, including infancy, and its prevalence increases patients get older. Few individuals with CF have normal glucose tolerance and even when the fasting and 2-h oral glucose tolerance test (OGTT) glucose levels are normal, variable, intermittent post-prandial hyperglycemia can often be detected by continuous glucose monitoring (CGM). CF is associated with a progressive deterioration in glucose tolerance as individuals grow older, including indeterminate glycaemia (INDET mid plasma glucose >11.1) followed by impaired glucose tolerance (IGT) and finally diabetes.

CFRD may first present during situations where insulin resistance is increased, such as acute pulmonary infection or glucocorticoid therapy, or during high-carbohydrate food supplementation such as continuous nighttime drip feedings. Diabetes is common in the setting of lung transplantation, where pre-transplant patients are critically ill and thus quite insulin resistant, and where post-transplant patients receive diabetogenic medications such as steroids and calcineurin inhibitors. The prevalence of CFRD is higher in patients with liver disease.
8.6.1 Diagnosis of CFRD

The onset of CFRD is defined as the date a person with CF first meets diabetes diagnostic criteria, even if hyperglycemia subsequently abates. Distinguishing between CFRD with and without fasting hyperglycemia is not necessary. The use of hemoglobin A1c (HbA1c) as a screening test for CFRD is not recommended as it can be spuriously low. Thus, an elevated HbA1c is evidence of hyperglycemia, but a normal HbA1c does not exclude it.

When to screen?
1) An oral glucose tolerance test (OGTT) should be performed on patients aged 10 years or over annually (as a day case admission to the ward around their annual assessment). Children aged 5-9 should have HBA1c and random blood glucose and have OGTT if the random glucose is elevated or there is unexplained decline in pulmonary function or growth.

2) CF patients admitted with acute pulmonary exacerbation requiring intravenous antibiotics and/or systemic glucocorticoids should be screened for CFRD by monitoring fasting and 2-h post-prandial plasma glucose levels for the first 48 h of admission at least with the results discussed with the diabetes team.

OGTT
Though, the OGTT was designed for use in type 2 diabetes and involved only baseline and 120-min samples with the diagnostic cut-offs designed to forecast microvascular complications of diabetes rather than CF-specific outcomes such as decline in weight and lung function, it is still the most accepted means of diagnosing CFRD.27

Time 0:  (i) Take blood for glucose (samples should be taken in a grey top bottle)
          (ii) Administer glucose 1.75 g/kg or maximum 75g
          (iii) 75g glucose = 300ml Glucojuice (15g/60ml)
          (iv) Younger children: volume of Glucojuice = 300/75 × 1.75 × wt (Kg)

Time 120: Take blood for glucose (samples should be taken in a grey top bottle)

For the OGTT the patient should be fasted overnight. If possible they should remain seated or in quiet play throughout the test.

Interpretation of test done during a period of wellness:

<table>
<thead>
<tr>
<th>Category</th>
<th>Fasting glucose</th>
<th>2 hr plasma glucose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;7</td>
<td>&lt;7.8</td>
<td>All levels &lt;11.1</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>&lt;7</td>
<td>&lt;7.8</td>
<td>mid-OGTT levels &gt;11.1</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>&lt;7</td>
<td>7.8-11.1</td>
<td></td>
</tr>
<tr>
<td>CFRD FH-</td>
<td>&lt;7</td>
<td>&gt;11.1</td>
<td></td>
</tr>
<tr>
<td>CFRD FH+</td>
<td>&gt;7</td>
<td>&gt;11.1</td>
<td></td>
</tr>
</tbody>
</table>
Other ways to diagnose CFRD

- HBA1C>48 mmol/l
- Persistent random blood glucose readings >11.1 with symptoms
- Apart from the OGTT, the diagnosis of CFRD can also be made in CF patients with acute illness when fasting plasma glucose (FPG) levels ≥126 mg/dL (7.0 mmol/L) or 2-h post-prandial plasma glucose levels ≥200 mg/dL (11.1 mmol/L) persist for more than 48 h.

Role of CGM

CGM has been validated and proven to be useful in children and adolescents with CFRD, where it can help guide safe and effective insulin therapy. Its role in CF patients who do not have diabetes is less clear. CGM is not accurate enough to be used to make a diagnosis of diabetes.

Possible ACTION on results of screening OGTT:

- Normal glucose tolerance (BG at 120mins <7.8mmol/L): repeat OGTT in 1 year unless clinically indicated to do it sooner.
- Impaired glucose tolerance (BG at 120 mins between 7.8 and 11.1): consider repeat OGTT in 6 months and CGM if weight and pulmonary function are declining.
- Fasting hyperglycaemia alone (baseline 0 mins BG >7mmol/L): consider repeat OGTT in 6 months and CGM if weight and pulmonary function are declining.
- CFRD with or without fasting hyperglycaemia - commence insulin therapy

It is important to determine any factors that may have affected the OGTT result e.g. concomitant infection, use of steroid treatment etc. before a diagnosis of CFRD is made. Once diagnosis has been made, inform the diabetic team including the specialist nurse.

The decision to commence insulin therapy following OGTT and interpretation of CGM results will be taken following consultation with the Paediatric Diabetes Team. In the last year there has been the development of a joint clinic with the Paediatric Diabetes Team where patients with CFRD are reviewed on a 4 monthly basis. Shared care of patients with CFRD has been successful and will continue.

8.6.2 Insulin[21]

Insulin insufficiency is the primary pathologic feature of CFRD, and insulin replacement is the only recommended medical treatment. Insulin therapy stabilizes lung function and improves nutritional status in patients with CFRD. When patients are in their baseline state of health, insulin requirements tend to be modest because of the persistence of endogenous insulin secretion and perhaps because of decreased levels of glucagon (average insulin dose <0.5–0.8 units/kg/d in both adolescents and adults)

Patients with fasting hyperglycemia are generally treated with basal-bolus therapy, with an insulin pump or with a combination of long-acting basal insulin and rapid-acting insulin to cover carbohydrates and correct hyperglycemia. In patients with CFRD without fasting hyperglycemia, pre-meal rapid-acting insulin reversed chronic weight
loss and is now considered standard care. Because of the relation between nutritional status and survival in CF, the anabolic effects of insulin may be the most critical aspect of therapy. Thus, the goal is to provide as high an insulin dose as the patient can safely tolerate.

CFRD patients typically require 0.5–0.8 units insulin per kg body weight per day when they are in their usual state of health. Much more may be required during stress. Generally 0.25 u/kg per day of basal is needed, start with half this and increase gradually every couple of days if no issues with hypos. A common starting dose is 0.5 – 1 IU rapid-acting insulin for every 15 g of carbohydrate consumed. Insulin pens or syringes that deliver half units may be needed. The dose is adjusted by increments of 0.5IU per 15 g carbohydrate to achieve 2-h post-prandial blood glucose goals. Patients with CFRD without fasting hyperglycemia maybe managed with pre-meal insulin alone, or with basal alone (depending on patient factors, including eating habits)

- Pre-meal correction is usually started at 0.5 – 1 IU rapid-acting insulin for every 3 mmol/L above 11 mmol/L and adjusted as needed.

- Regular/soluble plus NPH (e.g., Humulin N, Protaphane, Novolin N, Insulatard, Isophane, etc) insulin will cover an overnight drip feeding and should be discussed with the diabetes dietitian.

Before starting insulin therapy; an insulin starter pack should be prescribed; and the patient should be reviewed by a member of the Paediatric diabetes team who will provide training on insulin administration.

Patients with CFRD may have increased insulin needs during acute infection secondary to worsening insulin resistance and these patients must be treated vigorously. Diabetic ketoacidosis is very rare in CFRD due to endogenous insulin production and should be treated according to the local protocol. If patients with CFRD are going for surgery and are on glargine, they may not necessarily need any other treatment. Blood glucose must be monitored more frequently at this time.

8.6.3 Oral hypoglycaemic agents

The use of oral agents, including insulin secretagogues (such as sulphonylureas) or insulin sensitizers (such as metformin or thiazolidinediones), is not recommended in CFRD.[32]

8.6.4 Complications will be screened for at annual review.

1) During clinic reviews patients will be screened for CFRD associated microvascular complications by checking blood pressure (every visit) and monitoring for development of hypertension secondary to renovascular disease.

2) Ophthalmology screening for detection of retinopathy will also be arranged annually with initial Ophthalmology referral to occur 5 years after diagnosis has been established. Because, there can be a lag in diagnosis and intermittent hyperglycaemia may predate this, referral will be made at diagnosis.

3) Urine for micro albuminuria annually
4) Annual lipid profile in pancreatic sufficient patients or if risk factors such as family history, obesity or immunosuppressive therapy are present.

5) Annual foot check for peripheral neuropathy

8.6.5 Dietary Management of Diabetes in Cystic Fibrosis

Once a diagnosis of CF diabetes has been made or a child is going to commence on insulin then the diabetes nurse and dietitian will become involved to provide specialist advice to children and families.

CF patients are often underweight, with reduction in both fat and protein stores. The degree they are underweight correlates inversely with survival. Progressive clinical deterioration and weight loss have been reported up to 4 years prior to the onset of overt diabetes. With appropriate insulin therapy and dietary management, body mass index and pulmonary function can be restored to levels found before the onset of diabetes. Patients with CFRD must therefore continue to follow an energy-dense diet because a low sugar, low fat, high fibre diet typically promoted in the management of Type 1 and Type 2 diabetes will not provide sufficient calories for the CF patient. A more liberal approach to management with minimal dietary restrictions is therefore recommended, and insulin regimens are adjusted to suit individual patients. However, it can be helpful to look at the timing and quantity of very high sugar foods to try to minimise the impact on glucose levels without compromising on calorie intake.

8.6.6 If the patient is generally well and in good nutritional status

Recommend regular meals/snacks to ensure an even and consistent distribution of carbohydrate throughout the day. Complex carbohydrates (bread, potatoes, pasta, rice, and cereals) should be a part of each meal in order to maintain stable blood sugars. Carbohydrates with high fibre content are to be encouraged in well-nourished children, but not necessarily with poorly nourished children, as energy intake may be compromised.

Ordinary squashes and fizzy drinks may be used, if taken in moderate amounts and spread evenly throughout the day - preferably after meals. If blood sugar levels are difficult to control, it may be necessary to use low calorie/diet drinks (squash/fizzy drinks).

Sugar need only be restricted if consumed in large quantities throughout the day, or if quantities are inconsistent from day-to-day. Otherwise, allow sugar as usual. Sweet foods e.g. chocolate/sweets should be spread evenly throughout the day and taken preferably after meals. This will help avoid large swings in blood sugar levels. Difficulties in controlling blood sugar levels should be resolved by a multidisciplinary approach, with liaison between the diabetes and CF team members.

Meal planning should be individualised to account for lifestyle, activity level and food preference. Advice should be given about hypos and extra carbohydrate may be required before longer periods of physical activity. A reduction in fat is not recommended; but a change to mono/polyunsaturated fats may be advisable.

Nutritional supplements/enteral feeding should be continued as prescribed by the dietitian. Insulin therapy should be adjusted as appropriate. Pure glucose supplements e.g. Polycal/maxijuel etc. are not recommended.
8.6.7 If the patient is unwell and in poor clinical status

No dietary restrictions are required. Encourage small regular meals and snacks throughout the day. Nutritional supplementation (including glucose polymers if necessary) or enteral feeding, as prescribed by the dietitian, should be considered.

Adjust insulin therapy to suit diet. Please contact diabetes team to discuss if change of insulin therapy is needed during illness.

8.6.8 Dietary treatment of a ‘hypo’

As in type 1 diabetes, hypoglycaemia in CFRD is defined as blood glucose of less than 4mmol/L. This may result from extra exercise or more activity than usual, too much insulin, diarrhoea and/or vomiting or alcohol consumption. It is important to advise patients with CFRD and their families of the symptoms of hypoglycaemia. The child may ‘feel’ or ‘look’ different with symptoms such as increased hunger, sweating, pallor, irritability, feeling wobbly/shaky, tearfulness, experiencing headaches or tummy pain or behaving out of character or not feeling ‘quite right’. If children experience any such symptoms their blood sugar should be checked and if it is below 4mmol/L then treatment is required. Parents should also be warned that hypoglycaemia may occur without any symptoms.

To treat hypoglycaemia the child needs to be immediately given fast acting glucose as either 40ml Glucojuice or 3x glucose tablets or 100ml pure fruit juice. Glucojuice is now the first line treatment advised in hypoglycaemia in patient who are co-operative and able to swallow and Lucozade should no longer be advised. These doses should be halved for children less than 4 years and doubled in teenagers. Blood sugars should be checked 10-15 minutes later. If the blood sugar is still below 4mmol/L then another dose of fast acting glucose needs to be given. Once the blood sugar is >4mmol/L a carbohydrate snack should be given or the next meal bought forward. 10-15g carbohydrate such as 1 portion fruit, 200ml milk or 1 slice of bread should be adequate to maintain blood sugars above 4mmol/L once the fast-acting glucose has been used up.

<table>
<thead>
<tr>
<th>Age</th>
<th>Carbohydrate</th>
<th>GlucoJuice 15g/60ml bottle</th>
<th>Dextrose Tablets 3.3g per tablet</th>
<th>Gluco Tabs 3.6g per tablet</th>
<th>*Fruit Juice 10g/100ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 4yrs</td>
<td>5g</td>
<td>20ml</td>
<td>1.5</td>
<td>1.5</td>
<td>50ml</td>
</tr>
<tr>
<td>4-12 years</td>
<td>10g</td>
<td>40ml</td>
<td>3</td>
<td>2.5</td>
<td>100ml</td>
</tr>
<tr>
<td>13 years and over</td>
<td>15g</td>
<td>60ml</td>
<td>4.5</td>
<td>4</td>
<td>150ml</td>
</tr>
</tbody>
</table>
Parents and carers should be advised that in an uncooperative or unconscious child, correction of blood glucose using food or drink should not be attempted and instead they will need to administer Glucagon and call 999 for help. Blood glucose will need to be checked every 15 minutes over the following hour as the child may become hypoglycaemic again following glucagon administration.

The above information is outlined in an information leaflet provided by the Department of Diabetes and Endocrinology for type 1 diabetics entitled ‘hypoglycaemia’. The same leaflet should be given to children with CFRD so that they and their parents/carers have a written guide to the stepwise management of hypoglycaemia.

Finally, the onset and diagnosis of diabetes in patients with CF adds to the burden of monitoring and treatment and may have important psychological implications. Appropriate psychosocial support should be ensured.
8.6.9 Summary

Patients with CFRD should be seen at least 3 times a year by a specialized multidisciplinary team with expertise in diabetes.

Patients with CFRD should receive ongoing diabetes self-management education from the diabetes team. CF patients with CFRD should be treated with insulin therapy.

Patients with CFRD should perform self-monitoring of blood glucose at least three times a day. For many patients, four to eight or more times a day is appropriate, depending on meal pattern, exercise, intestinal concerns such as gastroparesis, and acute state of health.

HbA1c measurement is recommended quarterly for patients with CFRD to guide insulin therapy decisions.

For most patients with CFRD the HbA1c treatment goal is <7% (53mmol/mol) to reduce the risk of microvascular complications, bearing in mind that higher or lower goals may be indicated for some patients, and that individualization is important.

REFERENCES


