Consensus conference

Management of patients with cystic fibrosis

18-19 November 2002

Palais du Luxembourg - Paris

Topic 2: Compliance, nutrition, gastroenterology and metabolism
Guidelines (short version)
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INTRODUCTION

Management of cystic fibrosis focuses mainly on respiratory tract disorders. However, management also addresses other major manifestations of the disease such as malnutrition, digestive problems (including hepatobiliary disorders) and diabetes which contribute to the morbidity and mortality of the disease and can aggravate the pulmonary complications.

In the preamble to its responses, the jury emphasised the difficulties it encountered due to the absence of standardised epidemiological and clinical criteria in the literature and due to the very few studies of a high level of scientific evidence. Many forms of management have not been assessed within the context of cystic fibrosis per se and are used empirically on the basis of management of similar or identical manifestations with other causes.

Given the close inter-relationship between the various aspects of cystic fibrosis, and the fact that it affects many organs of the body, this disease needs to be managed by a specialist multidisciplinary team whose members work in close coordination. This imposes major constraints on the patient that impact on their quality of life and that of their family, and which encourage non-compliance with treatment.

Although there is no proof that poor compliance with treatment affects the course of cystic fibrosis, it does seem likely that it accelerates the disease either insidiously or by increasing the frequency and severity of acute exacerbations. The problem of compliance must therefore be tackled with patients early on, and then readdressed regularly. This important aspect of the disease should be borne in mind when planning treatment. The treatment protocol should be reduced to the absolute minimum required and attempts made to simplify drug regimens. The protocol should also take account of the individual’s desire to preserve some degree of quality of life, even though this might mean that treatment falls short of the ideal regimen. Psychological support should also be offered.

QUESTION 1

How does nutritional status affect the course of cystic fibrosis?

Malnutrition is very common at all stages of cystic fibrosis:

- **at the time of diagnosis**: up to 44% of patients are malnourished. The earlier the diagnosis, the lower the extent of malnutrition;
- **during neonatal screening**: 5-25%;
- **in infants**: 8-12% (poor growth), 11-13% (poor weight gain); early management could reduce malnutrition (grade C);
- **during childhood**: 9-17% (poor growth), 4-8% (poor weight gain) between 1 and 10 years;
- **during adolescence**: 8-21% (poor growth), 9-13% (poor weight gain);
- **in adults**: 8-38% (varies depending on age, severity, and criteria used for malnutrition).

Improved assessment of nutritional status can prevent malnutrition and its consequences. Studies suggest that it is rare for a serious nutritional deficiency to be fully overcome; this is a strong argument for early treatment of malnutrition (grade B).

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\[1\] A *grade A* guideline is based on scientific evidence established by a high level of evidence. A *grade B* guideline is based on presumption of a scientific foundation derived from studies of an intermediate level of evidence. A *grade C* guideline is based on studies of a low level of evidence. In the absence of specific scientific evidence, guidelines are based on agreement among professionals expressed by the jury. See: ANAES, *Guide d'analyse de la littérature et gradation des recommandations*. Janvier 2000. (Guide to literature analysis and grading of guidelines, January 2000)
MECHANISMS RESPONSIBLE FOR MALNUTRITION

Malnutrition is the result of a long-lasting negative nutritional balance related to a reduction in food intake and an increase in losses.

I. Factors that reduce food intake

- *Anorexia*: common from vomiting, coughing, airway plugging, inflammation, drugs, depression.
- *Digestive tract disorders*: gastro-oesophageal reflux, delayed stomach emptying, pain, constipation.
- *Restricted diet*.

II. Factors that increase losses

*Increased digestive losses*

- *Exocrine pancreatic deficiency* affects approximately 85% of patients. It may lead to malabsorption of half the protein and fatty acid ingested, and deficiencies of fat-soluble vitamins (A, D, E, K), B12 and zinc.
- *Intestinal insufficiency*: following intestinal resection.
- *Losses through sweating*: water, sodium and protein.

*Increased energy expenditure*. This is particularly related to impaired lung function, through increased respiratory muscle work, and inflammation (superinfection).

REPERCUSSIONS OF MALNUTRITION

Malnutrition leads to impairment of many functions:

- lung function;
- muscle mass and function;
- immune function;
- motor function of the digestive tract;
- cell and tissue repair function;
- growth, lung development, puberty;
- psychomotor, mental and intellectual development;
- bone mass (osteoporosis and osteomalacia);
- life expectancy.

In cystic fibrosis, the causes and consequences of malnutrition form a vicious circle. Several studies (levels 2-4 scientific evidence) have shown that the disease becomes worse with malnutrition.

IS IT POSSIBLE TO DEFINE CRITERIA FOR MALNUTRITION?

There are no studies comparing nutritional criteria in cystic fibrosis. In the literature, the most commonly used criteria are weight and height.
I. Clinical criteria

- **Anthropometric criteria**
  - Weight in relation to height and age is a major criterion. Poor weight gain is the earliest sign of malnutrition. It is assessed as a percentage of ideal weight or by calculating body mass index (BMI).
  - Failure to gain height.
  - Cranial circumference is only useful in very young children. Monitoring of these parameters (growth and height scales) is essential. A good criterion of deterioration in nutritional status is weight, height or BMI that falls outside the expected range.

- **Body composition.** This gives the contribution of lean or fat body mass to failure to gain weight, and should be routinely monitored. Several measurement criteria are used such as triceps skin-fold thickness, mid upper arm circumference, mid upper arm muscle circumference, impedance, and dual photon absorptiometry.

- **Other variables.** State of the skin and hair, delayed puberty.

II. Biological criteria are those used in other types of malnutrition

- **Protein.** By decreasing sensitivity: retinol binding protein (RBP), prealbumin, and albumin levels.

- **Micronutrients.** Serum iron, blood zinc, vitamins A, D, E and K, plasma fatty acid and haemoglobin levels.

III. Bone mineral status

- Determination of dietary calcium intake,
- Assay of plasma 25-hydroxy-vitamin D,
- Measurement of whole bone mineral content and bone mineral density by dual photon absorptiometry.

**GUIDELINES**

Preventing malnutrition is a key factor in improving the prognosis for cystic fibrosis. Nutritional status should be assessed at neonatal screening and then as follows:
- clinical parameters every month in infants under 1 year, then every 3-6 months;
- energy and dietary calcium balance every 3-6 months;
- serum tests once a year;
- bone absorptiometry once a year from puberty.

**QUESTION 2**
Which strategy maintains optimum nutritional status?

**COVERING BASIC NUTRITIONAL REQUIREMENTS**

This concerns all patients from neonatal screening to adulthood with neither malnutrition nor a disorder leading to a reduction or increase in food intake.
I. Infants

Infants adjust their food intake spontaneously to their needs. Breast-feeding or standard milk formulas can be recommended for children with normal growth. Weaning begins at 5 or 6 months as commonly recommended.

Meconium ileus with intestinal resection often requires a period of parenteral nutrition, followed by continuous enteral nutrition.

II. Daily diet

The aim is to achieve an energy intake higher than the recommended daily intake (RDI) for age. An intake of 100-110% of RDI is generally sufficient to maintain normal nutritional status.
- The diet should comprise nutrients providing calories from carbohydrates and fats.
- Dietary habits that include these foods should be encouraged early on.
A dietician should be seen regularly from an early stage.
The benefit of high energy supplements before there are signs of deterioration in nutritional status has not been demonstrated.

III. Treatment of exocrine pancreatic insufficiency

Pancreatic enzymes [PE] are essential. In infants, the capsule should be opened and the microgranules given in a mildly acid drink.

The PE doses, in lipase units (LU), recommended in the marketing authorisation are:
- infants: 2 000-4 000 LU /120 ml of milk;
- children: 1 000 LU /kg at each meal, 500 LU /kg at each snack, not exceeding 100 000 LU /day;
- adolescents and adults: do not exceed 250 000 LU /day (10 x 25 000 LU capsules/day).
These doses should be adjusted for each patient. Patients may adjust the dose according to their fat intake. Doses may be increased in the event of diarrhoea or persistent digestive discomfort. If digestive disorders persist, PE efficacy may be enhanced by reducing gastric acid with H₂ blockers (grade C).

IV. Supplements

- **Sodium and water.** To satisfy increased requirements, particularly in summer, oral rehydration solution between feeds or salt capsules should be given.
- **Vitamins.** Fat-soluble vitamins A, D and E available as soluble multivitamin complexes, are recommended, at twice the usual dose (grade C). Vitamin K should be prescribed throughout the first year of life at a dose of 5-10 mg once a week, and also given during prolonged antibiotic treatment.
- **Trace elements.** Supplementation with iron, zinc, selenium and magnesium is needed if there is a confirmed deficiency.

SITUATIONS CARRYING A RISK OF NUTRITIONAL DEFICIENCY

I. Risk situations

When nutritional status deteriorates, the following action should be taken:
- consultation with a dietician to assess and improve intake;
• medical examination to a) assess compliance; b) adjust dose of PE and micronutrients; c) look for associated risk factors (inflammation, bronchial superinfection, dysphagia, diabetes, cirrhosis, or portal hypertension); d) evaluate any psychological cause of anorexia.

II. Assisted nutrition

The benefit of assisted nutrition on nutritional and respiratory status has not been clearly demonstrated; it may reveal carbohydrate intolerance and gastro-oesophageal reflux.

• Nutritional supplements. Their efficacy has not been clearly demonstrated. They are expensive and not well accepted in the long-term. They have the disadvantage that they often replace normal oral food intake.
• Enteral nutrition. Its efficacy increases the earlier it is started. Nasogastric tubes are often poorly tolerated and gastrostomy is psychologically not well accepted.
• Parenteral nutrition is an invasive and expensive way of providing assisted nutrition. The benefit-risk ratio should be assessed.

GUIDELINES

Nutritional management in cystic fibrosis is too often based on empirical evidence and further studies are needed. It is often hindered by poor compliance, a complex problem which needs coordination between all members of the care team, the patient and the patient’s family. Compliance may be improved by making available preparations containing several active ingredients.

QUESTION 3

What diagnostic approach should be adopted when a patient with cystic fibrosis experiences abdominal pain?

In the absence of any underlying disorder, acute or chronic abdominal pain is a common reason for patients of all ages going to see a doctor. Diagnosis is based on history and careful clinical examination. Abdominal disorders should not be underestimated; they may be concealed in patients whose predominant problem is respiratory disease. History-taking helps to determine whether the pain is acute or recurrent, and how severe it is. This will guide the diagnostic strategy (Table 1).

Table 1. Diagnostic tests and examinations in abdominal pain

<table>
<thead>
<tr>
<th>Acute pain</th>
<th>Recurrent abdominal pain</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emergency</strong></td>
<td><strong>Upper gastrointestinal endoscopy</strong></td>
<td>Full clinical examination</td>
</tr>
<tr>
<td>Full clinical examination</td>
<td>Full clinical examination</td>
<td>Plain abdominal film</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>Upper gastrointestinal endoscopy</td>
<td>Laboratory tests and specific immunological tests</td>
</tr>
<tr>
<td>Plain abdominal film</td>
<td>± pH measurement</td>
<td>Abdominal ultrasound</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>Laboratory tests</td>
<td>± steatorrhoea</td>
</tr>
<tr>
<td>± lower digestive tract X-ray with contrast</td>
<td></td>
<td>± lower digestive tract X-ray with contrast</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± abdominal CT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± upper gastrointestinal endoscopy and colonoscopy</td>
</tr>
</tbody>
</table>
AETIOLOGY

The causes of abdominal pain and the tests to diagnose them are summarised in Tables 2 and 3.

I. Specific causes

- **Appendix mucocele** is obstruction of the appendix lumen by mucus. The ultrasound image shows an enlarged appendix with an obstructive lumen. It may be asymptomatic and should then be monitored by annual ultrasonography. When it is symptomatic, the signs are similar to those of appendicitis.

- **Distal intestinal obstruction syndrome (DIOS)** or meconium ileus equivalent is the obstruction of the ileocaecal region by impacted material and mucus. It manifests as pain in the right iliac fossa, abdominal distension and usually partial obstruction of the intestine.

- **Fibrosing colonopathy** (rare) has been reported in young children taking excessive doses of PE.

II. Common causes

- Pancreatitis (15% of patients)
- Gastro-oesophageal reflux (46-10%)
- DIOS (9% in children, 15% in adults)
- Constipation.

### Table 2. Causes of abdominal pain

<table>
<thead>
<tr>
<th>Acute pain</th>
<th>Recurrent pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendicitis</td>
<td>Gastro-oesophageal reflux</td>
</tr>
<tr>
<td>Acute intestinal intussception</td>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Appendix mucocele</td>
<td>Functional disorders, constipation</td>
</tr>
<tr>
<td>Volvulus</td>
<td>Distal intestinal obstruction syndrome</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Fibrosing colonopathy</td>
</tr>
<tr>
<td>Gallstones</td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>Other: gastroenteritis, urinary infection, tubal or ovarian disease</td>
<td>Intolerance to cow's milk protein</td>
</tr>
<tr>
<td></td>
<td>Crohn's disease</td>
</tr>
<tr>
<td></td>
<td>Cancer of the digestive tract</td>
</tr>
</tbody>
</table>

### Table 3. Main causes of abdominal pain in cystic fibrosis, and diagnostic examinations

<table>
<thead>
<tr>
<th>Cause</th>
<th>First line examination</th>
<th>Second line examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Plain abdominal film</td>
<td>Gastrograffin enema</td>
</tr>
<tr>
<td>Distal intestinal obstruction syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volvulus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Abdominal ultrasound</td>
<td>Gastrograffin enema</td>
</tr>
<tr>
<td>Acute intestinal intussception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocele</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallstones or kidney stones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Laboratory tests</td>
<td>Jejunal biopsy</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td></td>
<td>Test of treatment</td>
</tr>
<tr>
<td>Intolerance to cow's milk protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-oesophageal reflux</td>
<td>Test of treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PH measurement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upper gastrointestinal transit</td>
<td></td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>Upper gastrointestinal endoscopy ± biopsies</td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>Colonscopy + upper gastrointestinal endoscopy + biopsies</td>
<td></td>
</tr>
<tr>
<td>Ulcers</td>
<td>Urine tests</td>
<td>Urine microscopy and culture</td>
</tr>
<tr>
<td></td>
<td>Barium enema</td>
<td></td>
</tr>
<tr>
<td>Crohn's disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosing colonopathy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
GUIDELINES

A rigorous approach based on history and clinical examination is needed to reduce the number of invasive and irradiating tests in these patients who have to undergo many investigations and treatments. Effective sedation should be given for discomfort or pain.

QUESTION 4
What diagnostic and treatment strategies should be adopted for disorders of carbohydrate metabolism in cystic fibrosis?

Diabetes in cystic fibrosis is the result of non auto-immune destruction of the islets of Langerhans, leading to insulin and glucagon deficiency. It is preceded by a phase of glucose intolerance. In cystic fibrosis, it is always observed with exocrine pancreatic deficiency and is affected by genotype. Prevalence increases with age, reaching 50% at age 30. Patients 15 to 30 years old are particularly susceptible.

The clinical presentation is usually silent. More rarely, the following signs may be present: polyuria and polydipsia, poor weight gain, delayed growth and/or delayed puberty, deterioration of lung function, exacerbation of lung infection.

Diabetes enhances the morbidity and mortality of cystic fibrosis. Onset of retinopathy and diabetic nephropathy are due to increased life expectancy and duration of hyperglycaemia. Insulin therapy improves respiratory and nutritional status (grade 2).

In view of the epidemiological data, impaired glucose tolerance should be tested for routinely once a year after the age of 15 by an oral glucose tolerance test (OGTT) (patient fasted for 8 hours, dose of 1.75 g glucose/kg, maximum 75 g, glucose values fasting and after 2 hours). Earlier screening (at 10-15 years) should be considered in the event of poor weight gain or unexplained respiratory tract disorders.

DIAGNOSTIC CRITERIA

Diagnostic criteria are given in Table 4.

Table 4. Diagnostic criteria

<table>
<thead>
<tr>
<th></th>
<th>Fasting blood glucose (fasted 8 h)</th>
<th>“Random” blood glucose testing and clinical symptoms</th>
<th>Blood glucose 2 hours after challenge (OGTT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>≥ 1.26 g/L (7 mmol/L)</td>
<td>≥ 2 g/L (11.1 mmol/L)</td>
<td>≥ 2 g/L (11.1 mmol/L)</td>
</tr>
<tr>
<td>Impaired tolerance</td>
<td>Moderate fasting hyperglycaemia</td>
<td>Glucose intolerance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 1.1 g/L (6.1 mmol/L)</td>
<td>≥ 1.4 g/L (7.8 mmol/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 1.26 g/L (7 mmol/L)</td>
<td>&lt; 2 g/L (11.1 mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>&lt; 1.1 g/L (6.1 mmol/L)</td>
<td>&lt; 1.4 g/L (7.8 mmol/L)</td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT

Treatment is shown in Table 5.
Table 5. Treatment for diabetes in cystic fibrosis

<table>
<thead>
<tr>
<th>Target</th>
<th>Method</th>
<th>Strategy</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial blood glucose: 0.90-1.40 g/l (5-8 mmol/l)</td>
<td>Therapeutic patient education</td>
<td>Glucose intolerance: - nutritional advice - self-monitoring</td>
<td>Annual multidisciplinary assessment</td>
</tr>
<tr>
<td>Postprandial blood glucose: 0.90-1.80 g/l (5-10 mmol/l)</td>
<td>Self-monitoring: blood glucose</td>
<td>Diabetes: - symptomatic: insulin therapy - transient (corticosteroid therapy, infection): insulin therapy - asymptomatic: first choice insulin therapy, oral treatment possible</td>
<td>Quarterly HbA1c</td>
</tr>
</tbody>
</table>

**Diet:** predominantly carbohydrates with a low glucose index

*Insulin secretagogues:*
- glimepiride: 1-6 mg/day (1 dose)
- repaglinide: 2 mg x 3/day
- nateglinide

*Insulin therapy:*
- rapid-acting analogues: before every meal, 0.1 U/kg/meal
- intermediate-acting insulin: 1-3 injections/day, 0.19 U/kg/day, premixed allowed
- long-acting analogue: 1 inj./day

**QUESTION 5**

How should hepatobiliary disorders be managed in cystic fibrosis?

Hepatobiliary lesions are a result of obstruction of the ducts and cytotoxicity induced by hydrophobic bile acids. There is no specific genotype.

**HEPATOBIILIARY DISORDERS IN CYSTIC FIBROSIS**

Overall, 15-20% of patients develop clinically significant hepatobiliary lesions. Frequency increases markedly in adolescence and decreases after the age of 20. The increase is explained by increased survival.

I. Hepatic lesions

- **Focal biliary cirrhosis** is the most characteristic lesion. Frequency increases from birth and may reach 70% in adults.
- **Macronodular or multilobular cirrhosis** develops in a minority of patients. Frequency in adolescence is 5-20%. It causes more than 15% of deaths.
- **Steatosis** occurs in 20-60% of patients.
II. Biliary lesions

- **Neonatal cholestatic jaundice** (frequency <2%) is observed in more than half of the cases associated with meconium ileus and usually resolves without sequelae.
- **Microgallbladder** (30% of cases) is not generally accompanied by cholecystitis.
- **Gallstones** are rarely symptomatic.
- **Sclerosing cholangitis** is very rare.

**HOW SHOULD THEY BE DIAGNOSED?**

- As there are no predictive risk factors for progression to multilobular biliary cirrhosis, the clinical examination should routinely look for hepatomegaly and signs of portal hypertension (PHT).
- Once a year, liver enzymes and gamma-GT should be determined, and abdominal ultrasound of the liver should be performed to look for any parenchymal disorders (hyperechogenic liver of steatosis, varying size of liver nodules in multinodular cirrhosis), gallbladder disorders and PHT (Doppler). CT scan may be proposed when ultrasound is not conclusive.
- Gastric endoscopy should be performed if cirrhosis is suspected, and then repeated every 2 years.
- Liver biopsy cannot be recommended as part of screening (source of error by biopsy of healthy tissue).
- The indications for MR-cholangiography, which can detect early hepatobiliary lesions, are likely to be extended.

**TREATMENT**

I. Treatment of hepatobiliary disease

Ursodeoxycholic acid (UDCA) should be given for any presumed chronic liver disorder. The effective dose is 20 mg/kg /day, given as a long-term treatment. If any potentially hepatotoxic drugs are given, liver enzymes should be monitored closely.

II. Treatment of complications of cirrhosis

In children, no medical or endoscopic treatment has been validated for the primary prevention of haemorrhage in PHT.

- NSAIDs and aspirin may not be used.
- Beta-blockers are contraindicated because of their effect on the bronchi.
- Nitrates have not been evaluated in children.
- Endoscopic sclerotherapy of oesophageal varices is the first-choice treatment in active bleeding. The choice between sclerosis and ligation depends mainly on the experience of the endoscopist.
- A surgical shunt (portocaval shunt) may be indicated if endoscopic treatment fails. A selective splenorenal shunt may be the best procedure by limiting the risk of encephalopathy without compromising liver transplantation. Transjugular intrahepatic portosystemic shunt (TIPS) is a recent technique which is likely to find wider indications in paediatrics.
GUIDELINES

Screening for hepatobiliary disorders should be carried out from birth and treatment with UDCA should be started early. Ultrasound examinations should be performed regularly. PHT is life-threatening and should be controlled in the short term by endoscopic techniques, in the medium term by radiological (TIPS) or surgical shunts, and in the long term by transplantation.

The full French text of these guidelines is available on written request to:
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